


# Determinants of child asthma: the bedding environment

Leigh Frances Trevillian

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This is to confirm that, unless otherwise stated, this thesis is entirely my own original work,  
conducted through the National Centre for Epidemiology and Population Health of The Australian  
National University

A handwritten signature in black ink, appearing to read 'Leigh Trevillian', written in a cursive style.

Leigh Trevillian

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## Abstract

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This epidemiological thesis explores the determinants of child asthma, focusing on the infant and child bedding environment. Three previous studies provided the datasets central to this thesis: (i) The 1988-1995 Tasmanian Infant Health Survey was a prospective birth cohort conducted to investigate the aetiology of sudden infant death syndrome; (ii) The 1997 Childhood Allergy and Respiratory Health Survey was a follow-up of children who as infants participated in the Tasmanian Infant Health Survey; and (iii) The 1995 cross-sectional Childhood Asthma Survey included all children turning 7 years of age in Tasmania.

In this thesis, bedding items used in infancy were found to be associated with adverse respiratory health in childhood. Infant sheepskin and plastic mattress covers were associated with subsequent house dust mite sensitization. Infants using cocoons were at a greater risk of wheeze in childhood. In the cross-sectional study, positive associations with increased wheeze were found between children either sleeping in the bottom bunk-bed or with their current use of an electric blanket. An adverse association was also found with synthetic quilt use on frequent wheeze and post-exercise lung function among children who slept supine but not among children who did not sleep supine. The main contribution to new knowledge from this thesis is the finding that wheeze risk in childhood at age 7 years increased linearly with increasing numbers of potentially high house dust mite-rich bedding items at one month of age. This composite bedding effect was further modified by the indoor environmental factors of bedroom heating, recent bedroom painting and absence of bedroom carpet. When two or more of these environmental factors were present the bedding-wheeze effect was markedly exacerbated with increasing composite bedding in infancy.

Bedding is an easily modifiable environmental factor. This thesis provides new knowledge on the role of bedding in early life in asthma. This has important implications for both future work and current public health recommendations regarding infant and child bedding and the prevention of asthma.

## Publications arising from this thesis

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### Published papers

Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. An association between plastic mattress covers and sheepskin underbedding use in infancy and house dust mite sensitization in childhood: a prospective study. *Clin Exp Allergy* 2003; 33(4):483-9.

This paper is based on the contents in Chapter 4.

Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. A prospective association between cocoon use in infancy and childhood asthma. *Paediatric and Perinatal Epidemiology* 2004; July 18(4):281-289.

This paper is based on the contents in Chapter 5.

Ponsonby AL, Dwyer T, Trevillian L, Kemp A, Cochrane J, Couper D, Carmichael A. The bedding environment, sleep position, and frequent wheeze in childhood. *Pediatrics* 2004; May 113(5):1216-22.

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Trevillian LF, Ponsonby AL, Dwyer T, Kemp A, Cochrane J, Lim LL-Y, Carmichael A. The infant sleeping environment and asthma at 7 years: a prospective cohort study. *Am J Public Health* 2005; 95(8):(In press).

This paper is based on the contents in Chapter 7.

# Table of Contents

---

Acknowledgments .....	iii
Abstract .....	iv
Publications arising from this thesis .....	v
Table of Contents .....	vi
List of Tables .....	xvi
List of Figures .....	xix
Abbreviations .....	xx
Prologue .....	1
Chapter 1 .....	4
The biological and immunological basis of allergic sensitization and asthma .....	4
1.0 Preface .....	4
1.1 The History of Asthma .....	4
1.2 Definition of Asthma, Atopy and Allergy .....	5
1.3 The genetic epidemiology of asthma and associated traits .....	6
1.3.1 Gene-environment interactions .....	7
1.3.2 Asthma phenotypes .....	7
1.3.2.1 Paediatric asthma phenotypes .....	8
1.4 Atopic and non-atopic asthma .....	9
1.5 Pathogenesis of Asthma .....	10
1.5.1 Immunopathogenesis of Asthma .....	12
1.5.2 Timing for the development of the immune response .....	14
1.5.3 Immunologic mechanisms for the influence of microbial agents on the prevention of allergic disease .....	14
1.5.4 Immune deviation or immune modulation .....	16
1.6 Conclusion .....	17
1.7 Post-script .....	17
Chapter 2 .....	18
Epidemiological review of child asthma .....	18
2.0 Preface .....	18
2.1 Prevalence of Asthma .....	18
2.1.1 Asthma prevalence studies in Australia in the 20 <sup>th</sup> century .....	21
2.1.2 International comparisons of asthma prevalence in the 20 <sup>th</sup> century .....	21
2.1.3 Asthma prevalence studies in the 21 <sup>st</sup> century .....	25

2.2 Putative risk factors for asthma.....	26
2.2.1 HDM Allergens .....	26
2.2.1.1 HDM allergen and sensitization.....	27
2.2.1.2 Mite Allergen Exposure as a risk factor for sensitization .....	28
2.2.1.3 Mite allergen sensitization as a risk factor for asthma.....	28
2.2.1.4 HDM allergen exposure as a cause for asthma .....	29
2.2.1.5 Allergen exposure and the clinical severity of asthma.....	31
2.2.1.6 Disease misclassification and the role of HDM allergen in asthma severity ....	33
2.2.1.7 Improvement in asthma with reduction of allergen exposure .....	34
2.2.1.8 Primary prevention of allergen exposure.....	35
2.2.2 Other allergens.....	36
2.2.3 Atopy .....	37
2.2.4 Air Pollution .....	38
2.2.4.1 Outdoor air pollution.....	38
2.2.4.2 Indoor air pollution.....	39
2.2.5 Environmental Tobacco Smoke.....	39
2.2.6 Heredity .....	41
2.3 The Hygiene Hypothesis.....	41
2.3.1. Large family size; sibship; and birth order .....	42
2.3.2 Day Care Centres.....	45
2.3.3 Early respiratory infections and subsequent atopic disease .....	46
2.3.4 Intestinal flora and antibiotics .....	47
2.3.5 Immunizations .....	49
2.3.6 Endotoxins: a rural versus urban lifestyle .....	51
2.4 Risk and Protective Environmental Factors not within the Hygiene Hypothesis .....	53
2.4.1 Breastfeeding .....	53
2.4.2 Diet.....	55
2.4.3 Socioeconomic variations.....	56
2.4.3.1 Australian indigenous population .....	57
2.4.3.2 USA urban minority population.....	59
2.4.4 International variations and westernization.....	60
2.4.4.1 Migrants .....	61
2.4.5 Pre and perinatal risk factors.....	62
2.4.5.1 Gestational age, low birth weight and premature birth .....	62
2.4.5.2 Head circumference at birth .....	63

2.4.5.3 Sex differences .....	64
2.4.5.4 Parental ages at birth .....	64
2.4.6 Obesity and physical activity .....	64
2.5 Environmental Factors inconsistent with the Hygiene hypothesis.....	65
2.5.1 Respiratory syncytial virus.....	65
2.5.2 Parasites .....	65
2.6 Conclusion.....	67
2.7 Post-script.....	69
Chapter 3 .....	70
Thesis study design and methodology.....	70
3.0 Preface .....	70
3.1 Thesis Aim and Hypotheses .....	70
3.2 The Study Datasets .....	71
3.2.1 The Tasmanian Infant Health Survey .....	71
3.2.1.1 Study measurements .....	73
3.2.2 The 1995 Childhood Asthma Survey.....	75
3.2.2.1 Study measurements .....	78
3.2.3 The 1997 Childhood Allergy and Respiratory Health Survey.....	79
3.2.3.1 Study measurements .....	80
3.2.4 Type I and Type II errors .....	81
3.2.4.1 Type I error .....	81
3.2.4.2 Type II error .....	81
3.2.5 Ethics .....	82
3.3 Theoretical Study Design Issues .....	82
3.3.1 Design aspects of a prospective cohort study .....	83
3.3.2 Design aspects of a cross-sectional study.....	85
3.3.3 Measures of effect or association.....	86
3.3.3.1 Cohort studies.....	86
3.3.3.2 Cross-sectional studies .....	88
3.3.4 Confounding.....	88
3.3.5 Multivariate analysis .....	89
3.3.5.1 Multiple logistic regression.....	89
3.3.5.2 Multiple linear regression .....	90
3.3.5.3 Generalized linear models .....	91
3.4 Postscript.....	92



Chapter 4 .....	93
The association between underbedding, mattress and bed, and allergic sensitization and respiratory health .....	93
4.0 Preface .....	93
4.1 Introduction .....	93
4.2 Methods .....	96
4.3 Statistical Methods: The 1997 CARHS .....	97
4.3.1 Exposure variables .....	97
4.3.2 Outcome variables .....	97
4.3.3 Statistical methods to examine HDM sensitization .....	98
4.3.3.1 The Cox proportional hazards model .....	98
4.3.3.2 Confounder identification .....	99
4.3.3.3 Proportional hazards model .....	100
4.3.3.4 Population attributable fraction .....	100
4.3.4 Statistical methods to assess respiratory symptoms .....	100
4.3.4.1 Lung function tests .....	101
4.4 Results: The 1997 CARHS .....	101
4.4.1 Characteristics of the study population .....	101
4.4.2 Potential predictors of HDM sensitization .....	105
4.4.3 Prospective association between underbedding and HDM sensitization .....	107
4.4.4 Prospective association between underbedding and asthma .....	109
4.4.4.1 The prospective association between mattress type and wheeze .....	111
4.4.4.2 Infant underbedding and child lung function .....	112
4.4.5 Family history .....	115
4.5 Statistical Methods: The 1995 Childhood Asthma Survey .....	115
4.5.1 The Infant cohort study with 1995 follow-up .....	115
4.5.2 The cross-sectional 1995 Childhood Asthma Survey .....	116
4.6 Results: the 1995 Childhood Asthma Survey .....	116
4.6.1 The Infant cohort study with 1995 follow-up .....	116
4.6.1.1 Characteristics of the study population .....	116
4.6.1.2 Prospective associations between underbedding and asthma .....	118
4.6.2 The cross-sectional 1995 Childhood Asthma Survey .....	118
4.6.2.1 Characteristics of the study population .....	118
4.6.2.2 Current underbedding and mattress type and respiratory symptoms .....	121
4.6.2.3 Current electric blanket and sheepskin use and respiratory symptoms .....	121

4.6.2.4 Bed type and respiratory symptoms.....	123
4.7 Discussion .....	126
4.7.1 Exposure to sheepskin .....	127
4.7.2 Exposure to plastic mattress liner.....	128
4.7.3 Exposure to different mattress type.....	131
4.7.4 Exposure to different bed type.....	132
4.7.5 Exposure to electric blanket .....	133
4.8 Conclusion.....	135
4.9 Post-script.....	136
Chapter 5 .....	138
Infant cocoons and sleeping bags: allergic sensitization and respiratory health .....	138
5.0 Preface .....	138
5.1 Introduction.....	138
5.2 Methods.....	141
5.3 Statistical Methods: the 1995 Childhood Asthma Survey .....	142
5.3.1 Exposure variables.....	142
5.3.2 Outcome variables .....	142
5.3.3 Generalized linear modeling.....	142
5.3.4 Discrete-time proportional hazards modeling .....	143
5.3.5 Matched cohort analysis.....	144
5.3.6 Population attributable fraction.....	146
5.4 Results: the Infant Cohort Study with 1995 follow-up .....	146
5.4.1 Characteristics of the study population.....	146
5.4.2 Univariate analysis .....	147
5.4.2.1 Cocoon use and its association with childhood wheeze.....	147
5.4.3 Confounder identification.....	147
5.4.3.1 Cocoon use and family history .....	150
5.4.3.2 Cocoon use and maternal smoking.....	150
5.4.4 Univariate analysis of sleeping bag use and its association with childhood wheeze .....	150
5.4.5 Multivariate analysis of cocoon use and its association with childhood wheeze...	151
5.4.5.1 Generalized linear models .....	151
5.4.5.2 Matched cohort analysis .....	152
5.4.5 Age of onset of wheeze.....	154
5.5 Statistical Methods: the 1997 CARHS .....	154

5.5.1 Exposure variables.....	154
5.5.2 Outcome variables .....	154
5.5.3 Study population and method of analysis.....	155
5.5.4 Lung function tests .....	155
5.5.4.1 Simple linear regression.....	155
5.6 Results: the 1997 CARHS .....	156
5.6.1 Cocoon use, HDM sensitization and child wheeze.....	156
5.7 Discussion .....	157
5.7.1 Selection bias.....	158
5.7.2 Measurement bias.....	158
5.7.3 Confounding.....	159
5.7.4 A causal role for cocoon and childhood wheeze .....	160
5.7.5 Possible biological and physical mechanisms for the observed results.....	160
5.7.6 Generalizability of the study findings.....	161
5.8 Conclusion.....	162
5.9 Post-script.....	163
Chapter 6 .....	164
The association between childhood sleep position, bedding and respiratory health.....	164
6.0 Preface .....	164
6.1 Introduction.....	164
6.2 Methods.....	166
6.3 Statistical Methods.....	166
6.3.1 Exposure variables.....	166
6.3.1.1 Child bedding.....	166
6.3.1.2 Usual sleep position.....	167
6.3.2 Outcome variables .....	167
6.3.2.1 Respiratory wheeze and measures of lung function.....	167
6.4 Statistical methods: the 1995 Childhood Asthma Survey .....	168
6.4.1 Logistic regression .....	168
6.4.2 Matched case-control analysis .....	169
6.4.3 Multiple logistic regression modeling.....	169
6.4.4 Lung function tests .....	170
6.5 Results: the 1995 Childhood Asthma Survey.....	170
6.5.1 Characteristics of the study population.....	170
6.5.2 Univariate analysis .....	172

6.5.2.1 Sleeping environment and other characteristics associated with frequent wheeze or sleep position .....	172
6.5.2.2 The relation between overbedding composition and frequent wheeze by usual sleep position.....	174
6.5.3 Confounder identification.....	175
6.5.4 Multivariate analysis.....	175
6.5.4.1 The relation between overbedding composition and frequent wheeze by usual sleep position.....	175
6.5.4.2 The relation between pillow composition and frequent wheeze by usual sleep position .....	176
6.5.5 Lung Function.....	177
6.6 Discussion .....	178
6.6.1 Measurement bias.....	179
6.6.2 Causal inference .....	180
6.7 Conclusion.....	183
6.8 Post-script.....	183
Chapter 7 .....	184
Combined bedding, allergic sensitization and respiratory health .....	184
7.0 Preface .....	184
7.1 Introduction.....	184
7.2 Methods.....	189
7.2.1 Sources of data .....	189
7.2.2 Exposure variables.....	189
7.2.2.1 Selection and classification of bedding items.....	189
7.2.2.2 Composite bedding classifications .....	190
7.2.2.3 Classification of home environmental factors.....	191
7.2.2.4 Validation of exposure variables .....	192
7.2.3 Outcome variables .....	194
7.3 Statistical Methods.....	194
7.4 Results: the Infant Cohort Study with 1995 follow-up .....	195
7.4.1. Characteristics of the study population.....	195
7.4.2 Risk of childhood wheeze associated with increasing numbers of bedding items in infancy.....	198
7.4.3 Bedding and home environmental factors .....	200
7.4.3.1 Risk potentiation of composite bedding effect by room heating .....	203

7.4.3.2 Risk potentiation of composite bedding by bedroom painting .....	205
7.4.3.3 Risk potentiation of composite bedding in the absence of bedroom carpet ..	205
7.4.3.4 Risk potentiation of composite bedding in the presence of environmental tobacco smoke or home gas appliance use.....	208
7.4.3.5 Risk potentiation of composite bedding in the presence of one or more environmental factors.....	208
7.4.4 Composite bedding and age of onset of asthma .....	210
7.4.5 Role of home environmental factors on composite bedding and age of onset of asthma .....	213
7.4.6 Summary of findings from the Infant cohort study with 1995 follow-up.....	215
7.5 Results: the 1997 CARHS .....	215
7.5.1. Characteristics of the study population.....	215
7.5.2 Risk of HDM sensitization associated with increasing numbers of bedding items in infancy.....	217
7.5.3 Risk of childhood wheeze associated with increasing numbers of bedding items in infancy.....	217
7.5.4 The effect of composite bedding classification in infancy and changes in lung function.....	219
7.5.5 Bedding and home environmental factors .....	219
7.6 Results: the 1995 Childhood Asthma Survey.....	221
7.6.1. Characteristics of the study population.....	221
7.6.2 Risk of childhood wheeze associated with increasing numbers of bedding items in childhood.....	221
7.6.3 Bedding and home environmental factors .....	221
7.7 Discussion .....	225
7.7.1 Overview of results.....	225
7.7.1.1 The Infant cohort study with 1995 follow-up and the 1997 CARHS.....	225
7.7.1.2 The 1995 Childhood Asthma Survey.....	226
7.7.2 Reported findings from the Infant cohort study with 1995 follow-up that support causality .....	226
7.7.2.1 Possible biological mechanisms for the bedding-wheeze effects.....	227
7.7.2.2 Possible biological mechanisms for the bedding-wheeze effects and home environment interactions.....	228
7.8 Conclusion.....	231
7.9 Post-script.....	232

Chapter 8 .....	233
Key findings and implications for public health policy and future research directions .....	233
8.0 INTRODUCTION .....	233
8.1 KEY FINDINGS OF THIS THESIS AND THEIR IMPLICATIONS .....	234
8.1.1 Underbedding, mattress and bed type.....	234
8.1.1.1 Sheepskin .....	234
8.1.1.2 Plastic mattress covers .....	234
8.1.1.3 Implications of the sheepskin and plastic mattress cover associations: the current public health recommendations for bedding and asthma.....	235
8.1.1.4 Bunk beds and electric blanket .....	235
8.1.1.5 Allergen-specific determinants of atopy .....	236
8.1.1.6 The use of frequent wheeze as marker of allergen-induced airway disease and disease misclassification.....	236
8.1.2 Synthetic bedding exposure, sleep position and increased risk of asthma.....	237
8.1.2.1 Infant cocoons.....	237
8.1.2.2 Synthetic quilts and sleep position .....	237
8.1.3 Composite bedding and environmental interactions .....	238
8.2 FUTURE RESEARCH IN CHILD ASTHMA: A FOCUS ON BEDDING.....	238
8.2.1 Personal allergen measures.....	239
8.2.2 Bedding changes over time .....	239
8.2.3 Composite bedding measurements .....	241
8.3 Conclusion .....	241
Bibliography.....	242
Appendix 1 .....	285
1995 Childhood Asthma Survey Questionnaire. ....	285
Appendix 2 .....	291
1997 Childhood Allergy & Respiratory Health Study Questionnaire.....	291
Appendix 3 .....	298
Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. An association between plastic mattress covers and sheepskin underbedding use in infancy and house dust mite sensitization in childhood: a prospective study. Clin Exp Allergy 2003; 33(4):483-9. ....	298

Appendix 4 .....	306
Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. A prospective association between cocoon use in infancy and childhood asthma. <i>Paediatric and Perinatal Epidemiology</i> 2004; July 18(4):281-289.....	
	306
Appendix 5 .....	316
Ponsonby AL, Dwyer T, Trevillian L, Kemp A, Cochrane J, Couper D, Carmichael A. The bedding environment, sleep position, and frequent wheeze in childhood. <i>Pediatrics</i> 2004; May 113(5):1216-22. ....	
	316
Appendix 6 .....	324
Trevillian LF, Ponsonby AL, Dwyer T, Kemp A, Cochrane J, Lim LL-Y, Carmichael A. The infant sleeping environment and asthma at 7 years: a prospective cohort study. <i>Am J Public Health</i> 2005; 95(8):(In press). ....	
	324

## List of Tables

---

Table 2.1 Worldwide changes in asthma prevalence in children and young adults until 1999 .....	20
Table 3.1 Component scores for model predicting infants at high risk of SIDS in Tasmania.....	72
Table 4.1 Characteristics of the Study Population in the 1997 CARHS.....	103
Table 4.2 Unadjusted risk ratio for infant underbedding, mattress and potential predictors of HDM sensitization* in the 1997 CARHS .....	106
Table 4.3 The prospective association between sheepskin, plastic mattress cover and foam mattress use in infancy and child sensitization to house dust mite in the 1997 CARHS....	109
Table 4.4 The prospective association between underbedding and cot type and respiratory symptoms in the 1997 CARHS .....	110
Table 4.5 Prospective association between foam mattress use in infancy and childhood respiratory symptoms in the 1997 CARHS .....	111
Table 4.6 Unadjusted differences in mean spirometric values between children with different bedding combinations in infancy in the 1997 CARHS.....	113
Table 4.7 Adjusted differences in mean spirometric values between children with different bedding combinations in infancy in the 1997 CARHS.....	114
Table 4.8 Characteristics of the study population in the Infant cohort study with 1995 follow-up	117
Table 4.9 The prospective association between underbedding and cot type and respiratory symptoms in the Infant Cohort Study with 1995 follow-up .....	119
Table 4.10 Characteristics of the study population in the cross-sectional 1995 Childhood Asthma Survey .....	120
Table 4.11 Association between underbedding and mattress use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey.....	122
Table 4.12 Association between electric blanket and sheepskin use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey.....	123
Table 4.13 Association between bed type in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey .....	124
Table 4.14 Association between bunk-bed use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey.....	125
Table 5.1 Confounder sets by strata for the Infant cohort study with 1995 follow-up for the assessment of infant cocoon use and subsequent wheeze.....	145
Table 5.2 Additional characteristics of the study population in the Infant cohort study with 1995 follow-up .....	146



Table 5.3 Cocoon use in infancy and asthma symptoms by number of wheeze episodes for the Infant Cohort Study with 1995 follow-up .....	147
Table 5.4 Identification of potential confounders: unadjusted relative risk for selected factors and infant cocoon use and recent wheeze in the Infant cohort study with 1995 follow-up.....	148
Table 5.5 The association between cocoon use in infancy and asthma symptoms in childhood in the Infant cohort study with 1995 follow-up.....	151
Table 5.6 Matched cohort analysis for the Infant cohort study with 1995 follow-up.....	153
Table 5.7 Association between cocoon use in infancy and wheeze in childhood for the 1997 CARHS .....	156
Table 5.8 Unadjusted mean difference (95% CI) in spirometric values for children using a cocoon in infancy in the 1997 CARHS .....	156
Table 6.1 Distribution of sleeping environment characteristics and respiratory wheeze in the 1995 Childhood Asthma Survey .....	171
Table 6.2 The univariate association between sleeping environment, child characteristics and frequent wheeze or supine sleep position.....	173
Table 6.3 The univariate association between overbedding composition and frequent wheeze by sleep position.....	174
Table 6.4 The risk of frequent wheeze for various combined sleep arrangements compared to sleeping supine under a feather quilt in nested case-control study.....	177
Table 6.5 Change in FEV1 post-exercise by wheeze frequency and sleep arrangement.....	178
Table 7.1 Results from 23 published studies of the analysis of household factors associated with higher indoor HDM allergen levels.....	187
Table 7.2 Guidelines for interpretation of kappa.....	193
Table 7.3 Characteristics of the study population in the Infant cohort study with 1995 follow-up.....	197
Table 7.4 Prospective association between infant composite bedding classifications and childhood wheeze in the Infant cohort study with 1995 follow-up .....	199
Table 7.5 Potentiation of composite bedding effects on wheeze by infant bedroom heating in the Infant cohort study with 1995 follow-up.....	204
Table 7.6 Potentiation of composite bedding effects on wheeze by recent infant bedroom painting in the Infant cohort study with 1995 follow-up.....	206
Table 7.7 Potentiation of composite bedding effects on wheeze by absence of bedroom carpet in the Infant cohort study with 1995 follow-up.....	207
Table 7.8 Age of onset of reported symptoms for children with asthma in the Infant cohort study with 1995 follow-up.....	212
Table 7.9 Characteristics of the study population in the 1997 CARHS.....	216

Table 7.10 Prospective association between infant composite bedding combinations and HDM sensitization in childhood in the 1997 CARHS.....	217
Table 7.11 Prospective association between Infant composite bedding combinations and childhood wheeze in the 1997 CARHS.....	218
Table 7.12 Unadjusted differences in mean spirometric values between children with different composite bedding classification in infancy, recent wheeze, frequent wheeze and night wheeze in the 1997 CARHS.....	220
Table 7.13 Adjusted differences in mean spirometric values between children with different composite bedding classification in infancy, recent wheeze, frequent wheeze and night wheeze in the 1997 CARHS.....	220
Table 7.14 Characteristics of the study population in the 1995 Childhood Asthma Survey.....	222
Table 7.15 Association between Child Composite Bedding Classification and Childhood Wheeze in the 1995 Childhood Asthma Survey.....	223
Table 7.16 Potentiation of composite bedding effects on wheeze by home environmental factors in the 1995 Childhood Asthma Survey.....	224

## List of Figures

---

Figure 1.1 Early and late pathophysiological respiratory airway responses to allergen.....	11
Figure 1.2 The development of the immune response .....	13
Figure 2.1 Prevalence of wheeze, eczema and rhinitis in the previous 12 months among Australian schoolchildren (1993-94) .....	23
Figure 2.2 Venn diagrams showing the interrelation between wheeze, eczema and rhinitis in the previous 12 months* in Australian schoolchildren (1993-94) .....	24
Figure 2.3 Relation between sensitization, exposure to allergens, and development of asthma..	30
Figure 3.1 The relationship between the Tasmanian Infant Health Survey and the 1995 Childhood Asthma Survey .....	77
Figure 5.1 Infant Cocoon.....	141
Figure 5.2 Age of onset or wheezy breathing by cocoon use in the Infant cohort study with 1995 follow-up.....	154
Figure 6.1 Schematic representation of a hypothesised mechanism involving close proximity of bedding to the child's airway.....	182
Figure 7.1 Graphical representation of unadjusted odds ratios for recent wheeze and the six-level composite bedding classification in the three Tasmanian data sets .....	191
Figure 7.2 Difference of potentiation of composite bedding effects on recent wheeze by environmental factors in the Infant cohort study with 1995 follow-up.....	201
Figure 7.3 Relationship between the number of environmental factors (bedroom heating, recent bedroom painting, absence of bedroom carpet) and potentiation of composite bedding- wheeze effect by bedding combination B <sub>0</sub> , B <sub>1</sub> and B <sub>2</sub> in the Infant cohorts with 1995 follow- up .....	209
Figure 7.4 Age of onset of wheezy breathing by composite bedding use at 1 month of age in the Infant cohort study with 1995 follow-up .....	211
Figure 7.5 Mean age of onset of asthma or wheezy breathing by bedding combinations and environmental factors in the Infant cohort study with 1995 follow-up.....	214
Figure 7.6 Diagrammatic model of the possible biological mechanisms underlying the bedding- wheeze effects and home environment interactions.....	230

## Abbreviations

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ACT	Australian Capital Territory
AHR	Airway hyperreactivity
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
BCG	Bacillus Calmette Guerin
BHR	Bronchial hyperresponsiveness
BMI	Body mass index
CARHS	Childhood Allergy and Respiratory Health Survey
CI	Confidence interval
CS	Caesarian section
D	Dermatophagoides
Der p	Allergen of Dermatophagoides pteronyssinus
Der p 1	Group I allergen of Dermatophagoides pteronyssinus
ETS	Environmental tobacco smoke
FEV1	Forced expiratory volume in one second
GIT	Gastro-intestinal tract
HDM	House dust mite
Hib	Haemophilus influenzae type b
IFN- $\gamma$	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IL-2	Interleukin -2
ISAAC	International Study of Asthma and Allergies in Childhood
L	litres
LRTI	Lower respiratory tract infection
MMR	Measles, mumps and rubella
NO <sub>2</sub>	Nitrogen dioxide
OR	Odds ratio
PAF	Population attributable fraction
PEFR	Peak expiratory flow rate
POR	Prevalence odds ratio
PRR	Prevalence rate ratio
RCT	Randomized controlled trial
RR	Relative risk
RSV	Respiratory syncytial virus
sd	Standard deviation
SIDS	Sudden infant death syndrome
SPT	Skin prick test
TIHS	Tasmanian Infant Health Survey
TNF- $\beta$	Tumour necrosis factor
UK	United Kingdom
URTI	Upper respiratory tract infection
USA	United States of America
vs	versus
WHO	World Health Organization

***“I have no magic cure. Asthma has many aetiological aspects and should be treated according to the various causes that bring it about”. (1)***

Moses Maimonides (1135-1204), one of the greatest physicians of Western Islam and court physician to the Sultan of Egypt and Syria.

### **THE CURRENT STATUS OF CHILD ASTHMA**

At the end of the 20<sup>th</sup> century, the prevalence of asthma in children and young adults was reported to be increasing world-wide by 5% - 6% each year (2); although there is recent evidence that this may have leveled off or declined in some countries, including Australia (3-5). Notwithstanding, the prevalence of child asthma in Australia is amongst the highest in the world (6) and recent surveys conducted by the Australian Bureau of Statistics show that 14% - 16% of Australian children have a diagnosis of asthma that remains a current problem (7).

The reported changes in the prevalence of asthma have occurred too rapidly to be in response to changes in genetic variants. Modifications in the pattern of exposure, and changes in susceptibility, to various environmental factors in large portions of the population may be important (6). Epidemiological studies have explored the putative role of environmental risk factors (for example, allergens, tobacco smoke, and air pollution) as well as the loss of possible protective factors over time, such as early infections and diet. These current putative risk factors cannot fully account for either the worldwide increase in prevalence or the international variations in asthma prevalence that have been observed (8). The aetiology of asthma is still unclear, and further research is required to better understand the environmental determinants of child asthma.

### **THE FOCUS OF THIS THESIS**

To date, the infant bedding environment and its role in the aetiology of child asthma is not well understood and research has focused on allergens, house dust mite (HDM) (9) and feather (10), and, to a lesser extent, bacterial endotoxin (11) content in individual bedding items. Few prospective studies have examined the associations between bedding and HDM sensitization and wheeze (12, 13). For infants and young children, a high proportion of indoor time is spent within this one environment (14, 15) with close proximity to the bedding items. Thus, the bedding

environment may be a key factor in child asthma. The aim of this thesis is to identify home environmental risk factors for HDM sensitization and child asthma, focusing on infant and child bedding and the bedding environment. My research provides the opportunity to identify factors that may play a causal role in child asthma, that can be modified in infancy, or in the early years of life, by exploring the relationship between the bedding environment with asthma development.

My analyses have been carried out on pre-existing data obtained from three studies previously undertaken by the Menzies Centre for Population Health Research in Tasmania, Australia: (i) The 1988-1995 Tasmanian Infant Health Survey (TIHS) was a prospective birth cohort conducted to investigate the aetiology of sudden infant death syndrome (SIDS); (ii) The 1997 Childhood Allergy and Respiratory Health Survey (CARHS) was a follow-up of children who as infants participated in the TIHS; and (iii) The 1995 cross-sectional Childhood Asthma Survey included all children turning 7 years of age in Tasmania.

Although the datasets existed and some findings on the home environment and bedding had been reported, I was approached by my chief supervisor, Anne-Louise Ponsonby, to undertake further work because the studies were under-utilised. The detailed analyses of the bedding items and home environmental factors identified in this thesis, and their associations with HDM sensitization and asthma had not been previously undertaken. The relationship between composite bedding arrangements, their interactions with home environmental factors and respiratory health has not previously been assessed and is a major focus of the work for this thesis. In addition, this thesis undertakes comparisons of bedding-wheeze and bedding-HDM associations across each of the three datasets, assessing the consistency of the reported findings. A range of different methodological and statistical approaches have been applied in my analyses. Apart from Chapter 6, I have provided the principle contribution to the design approach for the analyses, the analyses and the reporting of the findings of each Chapter in this thesis. In Chapter 6, I principally undertook only sections of the analysis and reporting.

## **CHAPTER OUTLINE**

Chapter 1 presents an overview of the history and definition of asthma, the genetic epidemiology of the disease and its immunopathogenesis. The evidence for potential environmental risk factors, and, their role in the development of asthma in the postnatal environment is overviewed in Chapter 2. The role of bedding and possible effect modifiers are discussed in detail in the

introduction and discussion sections of each relevant Chapter. This approach was utilized because the findings in these Chapters are best interpreted and discussed with reference to previously reported findings.

Chapter 3 outlines the aim and hypotheses of this thesis, and describes the design features of the three Tasmanian studies and their applicability in asthma studies.

Chapters 4, 5, 6 and 7 focus on the analyses of the two cohort and one cross-sectional studies with the presentation, discussion and implications of the findings. Chapter 4 reports the results of associations between underbedding, mattress and bed types, and allergic sensitization and respiratory health. Chapter 5 presents the prospective associations between the use of cocoons and sleeping bags in infancy and the development of child wheeze and HDM sensitization. In Chapter 6, findings are reported of an association between child sleep position, bedding and respiratory health. Chapter 7 describes the relationships between composite bedding, bedding-environment interactions and child asthma.

The final chapter, Chapter 8, summarises the key findings of this thesis, and discusses their implications for public health policy and future research directions.

## Chapter 1

# The biological and immunological basis of allergic sensitization and asthma

---

## 1.0 PREFACE

Epidemiological evidence suggests that the worldwide prevalence of asthma has increased significantly over the past 30 years with the greatest increase among children and adolescents (16). It now affects between 1% and 20% of the population, with the highest rates occurring in the USA, Australia, New Zealand and North-west Europe (17). Half of the cases present before the age of two years and more than 92% before the age of nine years (18). Public health programs are challenged to develop prevention programs based on an identification of the factors that have caused these increases. Critical to primary prevention programs, whereby the intervention precedes disease development, is an understanding of both the genetic and immunological basis of allergic sensitization and asthma. This Chapter will define asthma and discuss its pathogenesis.

## 1.1 THE HISTORY OF ASTHMA

The clinical manifestations of bronchial asthma have been known since antiquity; asthma-like symptoms were first recorded 3,500 years ago in an Egyptian manuscript called Ebers Papyrus (1300 BC). But almost 2,000 years elapsed between the first known description of the disease and its recognition as a distinct medical entity. The word "asthma" first appeared in Homer's epic poem, the Iliad, and is derived from the Greek verb "azein" or "azo" meaning to pant or laboured breathing. Asthma was first described as a clinical entity 500 years following Homer's Iliad, in the Hippocratic (460-370 B.C.) writings, "Corpus Hippocraticum" (19), where the word was used to denote all types of dyspnoea that became more common with increasing age. Hippocrates recognized the spasmodic nature of asthma and considered asthma had "its own nature" arising from external causes such as moisture, occupation and climate.

The first comprehensive book on asthma, "A Treatise of the Asthma" by Sir John Floyer (20) was published in 1698 where he considered the immediate cause of asthma was "straitness, compression, or constriction" of the bronchi. By observing the reactions of patients to both the



smoky London air and potent odors, Floyer was able to note that elements of the environment could trigger asthma attacks. In addition, he observed that exposure to airborne house dust plays an essential role in asthma (20), but it was only more recently that the Pyroglyphidae family (in particular the genus *Dermatophagoides*) were isolated by Voorhorst, in 1964, as the main source of allergen in house dust (21). By the late 19<sup>th</sup> century, physicians believed that asthma was a disease which had a specific set of causes, clinical consequences, and requirements for treatment, despite the diversity of individual experiences.

## 1.2 DEFINITION OF ASTHMA, ATOPY AND ALLERGY

The definition of asthma has become more complex as understanding of its pathophysiology has increased. However, despite this increased complexity, the basic characteristic feature of reversible airflow obstruction, by which one recognizes or diagnoses the disease, has changed little over recent years.

The 1959 CIBA Guest Symposium (22) was an important milestone in respiratory epidemiology. The definitions for a number of chronic lung diseases derive from this meeting. Asthma was defined as "...a widespread narrowing of the bronchial airways, which changes in severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease" (22). This definition still forms the basis of the current definition of asthma which remains based on pathology and its functional consequences: "Asthma is a chronic disorder of the airways that is characterized by reversible airflow obstruction and airway inflammation, persistent airway hyperreactivity (AHR), and airway remodeling" (23).

The term "atopy" was first introduced in the early 1920s (24) to designate some phenomena of hypersensitiveness in man and included the clinical characteristics of "bronchial asthma". Today, atopy is defined as a personal or familial tendency to produce immunoglobulin (Ig) E (IgE) antibodies directed to epitopes expressed on the molecules of common environmental allergens such as domestic mites, animal proteins, pollens and fungi (25), and to develop related disorders such as asthma, rhinoconjunctivitis, or eczema/dermatitis (26). Allergy is a hypersensitivity reaction initiated by immunological mechanisms. It can be antibody, (IgE-mediated allergy or humoral), or cell-mediated (non IgE-mediated allergy). The term "atopy" is used if the allergy is IgE-mediated (26).

In accordance with a recent joint statement (27), high-risk infants are defined as “infants with a well-defined increased risk of developing allergic disease: that is, infants with at least one first degree relative (parent or sibling) with a documented allergic disease”. However, in some studies “high-risk” has been defined as double parental heredity or single heredity (parents or sibling) combined with elevated cord blood IgE (28).

### **1.3 THE GENETIC EPIDEMIOLOGY OF ASTHMA AND ASSOCIATED TRAITS**

The genetic aetiology of asthma has been increasingly emphasized as a means of better understanding its pathogenesis with the ultimate goal of improving preventive strategies, diagnostic tools and therapies. However, the significant increase in the prevalence of atopy-related disorders over the past decades cannot be explained by changes in gene frequencies. It is probable that various pre-existing genetic factors interacting with a dramatically changing environment (decline of infectious diseases, change in diet, immunizations, and others) have rendered a large percentage of the population susceptible to asthma and atopy (29).

Asthma, eczema and the atopic state are familial (30) with multiple twin and family analyses strongly implicating a genetic basis for atopy-related traits (31). Studies of twins have reported that concordance rates for asthma are significantly higher in monozygotic twins than in dizygotic twins (32-35), whether reared apart or together (36). The estimated heritability for twins, under the multifactorial threshold model, ranges from 36% (33) to 75% (32). As the sum of population attributable fractions can exceed 100% (37), these findings do not indicate environmental influences to be insignificant. Furthermore, epidemiological studies suggest that maternal phenotype, more than paternal phenotype (38), influences the development of atopic disease in childhood (39). The inheritance of asthma, however, does not follow the classical Mendelian patterns that are characteristic of single-gene disorders (31, 40). Complex genetic disorders, such as asthma, exhibit multifactorial traits, the dissection of which is hampered by phenocopy, incomplete penetrance, and genetic heterogeneity (41). The genetics of asthma and other atopy-associated phenotypes is complex and is reflected by an increasingly large number of chromosomal regions showing (weak to moderate (41)) evidence for linkage, as well as various genetic variations in multiple candidate genes that are associated with asthma and associated phenotypes (29).

Linkage studies (genome-wide searches and candidate gene region analyses) have identified multiple chromosomal regions related to asthma and atopy (29), with markers in 19 chromosomal regions having shown some evidence of linkage to asthma, atopy or related phenotypes in multiple independent genome-wide searches (42). Thus, it has been clearly established that no single gene or even a small number of genes exert a decisive influence in determining susceptibility to asthma (43). Asthma appears to be essentially a polygenic disease in which many genetic variants determine small changes in immune responses or in the manner in which the airway responds to the environment (44).

### **1.3.1 Gene-environment interactions**

Environmental factors, therefore, play a key role in the pathogenesis of atopic asthma (45) and it is postulated that onset of disease and its clinical course are determined by gene-environment interactions. Those persons, in whom asthma develops, are both genetically susceptible and receive an appropriate environmental stimulus (46). Across the range of asthmatics in the population, the relative influence of genes and environmental factors probably varies (46), generating the hypothesis that individuals with different asthma-related genotypes will have different sensitivities to environmental exposures (47). Chapter 2 provides a review of epidemiological studies, and discusses the environmental exposures that may play a role in the development of asthma.

### **1.3.2 Asthma phenotypes**

The current definition of asthma describes its pathophysiologic basis and a single uniform phenotypic definition of asthma does not exist. There is no quantitative marker specific for asthma and no gold standard against which to validate the diagnostic usefulness of physiologic measures, such as bronchial hyperreactivity (48). This is in contrast with other complex diseases in which quantitative traits, or a series of measurable “biomarkers” have assisted in identifying susceptibility genes, for example prostate-specific-antigen in prostate cancer.

Asthma is, however, associated with a number of quantitative “intermediate” phenotypes (49), such as elevation of the total serum IgE and nonspecific airway responsiveness to inhaled spasmogens such as histamine or methacholine. Bronchial hyperresponsiveness (BHR) is

associated with asthma and atopy, as observed by the close association of serum IgE levels, BHR and asthma in asymptomatic children (46). As the atopic state underlies a considerable portion of childhood asthma (46, 50) other measures of the allergic phenotype, such as total serum eosinophil counts, skin prick test (SPT) responses to common allergens and specific IgE measures, are also studied as intermediate phenotypes (46). The asthma-associated quantitative phenotypes of atopy, elevated blood eosinophil counts, and increased airways responsiveness are also highly heritable (50). Asthma and all of its associated quantitative phenotypes are characterized by heterogeneity. Although the evidence suggests that the commonly measured asthma-associated pathophysiological factors are under some genetic control, the degree of genetic control and the extent to which most of these traits are genetically distinct from each other and from asthma is still unclear (50).

The pathogenesis of asthma is extremely complex, and it is conceivable that alterations in the regulation of many different immune and non-immune pathways may give rise to the same common final pathway: namely recurrent, reversible bronchial obstruction associated with chronic airway inflammation and BHR (43). Evidence suggests some of the intermediate phenotypes associated with asthma (in particular serum IgE) are caused by an oligogenic background modified by strong environmental factors (50). Clinical severity is one means of delineating subgroups of asthma (51). The classic distinction between extrinsic (atopic) and intrinsic (non-atopic) asthma considers measurements of atopy. Other clinical sub-phenotypes may be defined clinically as nocturnal asthma, aspirin-induced asthma, or based on inclusion criteria such as age of onset or smoking (51).

### **1.3.2.1 Paediatric asthma phenotypes**

Epidemiological studies suggest that, at least in the case of childhood asthma, the disease may have different phenotypic expressions at different ages, as assessed by their risk factors and prognosis (52). There are at least three distinct paediatric phenotypes which may each have a different aetiology and this has to be considered when searching for causes of asthma. These different phenotypes have been described as follows:

- (i) *Transient early wheezing*, characteristically resolving by age 3 years, and not associated with a family history of asthma or allergic sensitization (53). The primary risk factor is reduced pulmonary function (for example, from congenitally smaller airways) (53, 54).

Other risk factors include prematurity (55), maternal smoking during pregnancy and postnatal exposure to tobacco smoke (56), and exposure to siblings and other children at day care centres (57).

- (ii) *Non-atopic wheezing* associated with a viral infection-induced bronchial obstruction during ages 2 - 3 years and resolving in most children by 13 years of age (58). This is most frequently caused by the respiratory syncytial virus (RSV), and is not associated with an increased risk for allergic sensitization (58). Early age (under 2 years) of onset of wheeze is a poor predictor of continuing asthma in later childhood (59-61).
- (iii) *Atopic wheezing/asthma*. More than half of all cases of persistent asthma start before age 3 years, and 80% begin before age 6 years (58). Among school-aged children with persistent asthma, the onset of symptoms before age 3 years is associated with increased severity of the disease and increased BHR and is frequently associated with atopy (58).

## 1.4 ATOPIC AND NON-ATOPIC ASTHMA

Although asthma is multifactorial in origin, atopy is the strongest identifiable predisposing factor for the development of asthma, and there is considerable information regarding both its genetic and environmental risk factors. In comparison little is known, however, about the genetic basis for non-atopic asthma, though some data are available on environmental risk factors (smoking is of prime importance; but, viral infection, exercise, chronic sinusitis and gastro-oesophageal reflux may all be relevant) (62). Non-atopic asthma may also constitute around 50% of adult asthma (62) and is often severe. Although the aetiology is less well defined, similar inflammation is present in the lungs of non-atopics and atopics and the same drugs treat both diseases (62). Non-atopic asthmatics show negative SPTs to allergen provocation and there is no clinical or family history of allergy. Previous studies have shown that serum IgE concentrations are within the normal range and there is no evidence of specific IgE antibodies directed against common allergens (63). There is a preponderance of females with onset of symptoms in later life, and the association of nasal polyps and aspirin sensitivity occurs more frequently in the non-atopic form of the disease (63).

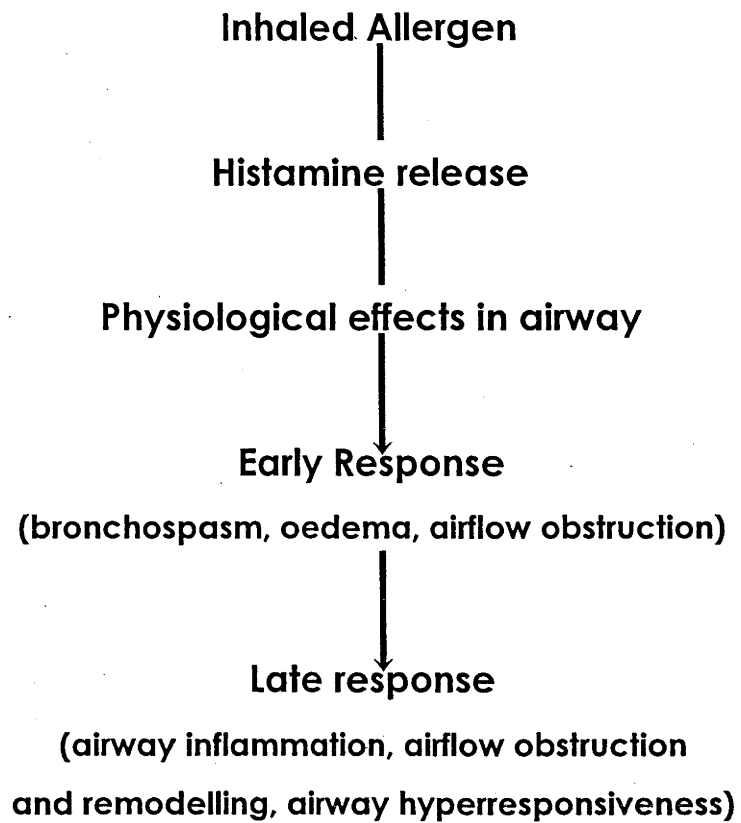
## 1.5 PATHOGENESIS OF ASTHMA

The current concept of asthma pathogenesis (64) is that a characteristic chronic *inflammatory process* involving the airway wall causes the development of airflow limitation and *increased responsiveness*, thereby predisposing the *airways to narrow* in response to a variety of stimuli. In addition, characteristic features of the airway inflammation are an increased number of activated eosinophils, mast cells and T lymphocytes in the airway mucosa and lumen, and an increased thickness of the reticular layer of the basement membrane (sub-epithelial fibrosis). These changes may be present even when asthma is asymptomatic.

The majority of the data regarding the pathogenesis of asthma concentrates on atopic asthma and the imbalance between the Th1 (cell-mediated immunity) and Th2 (humorally-mediated immunity) phenotypes, and is the pathogenesis presented here. However, asthma may also occur through non-allergic mechanisms of inflammation (65), which as stated in Section 1.4 is similar to the inflammation found in atopic asthma.

The response of the airway to inhaled allergen provides insights into immunological mechanisms that contribute to the pathogenesis of atopic asthma. In patients with asthma, inhaled allergen may precipitate acute obstruction of the airway by initiating the release from mast cells of histamine and leukotrienes, which cause constriction of smooth muscles. This early-phase reaction usually resolves within an hour. Four to six hours later, a prolonged late-phase reaction with obstruction of airflow may develop as a result of cytokines and chemokines generated by resident inflammatory cells (for example, mast cells, macrophages, and epithelial cells) and recruited inflammatory cells (lymphocytes and eosinophils) (66) (see Figure 1.1).

**Figure 1.1 Early and late pathophysiological respiratory airway responses to allergen**

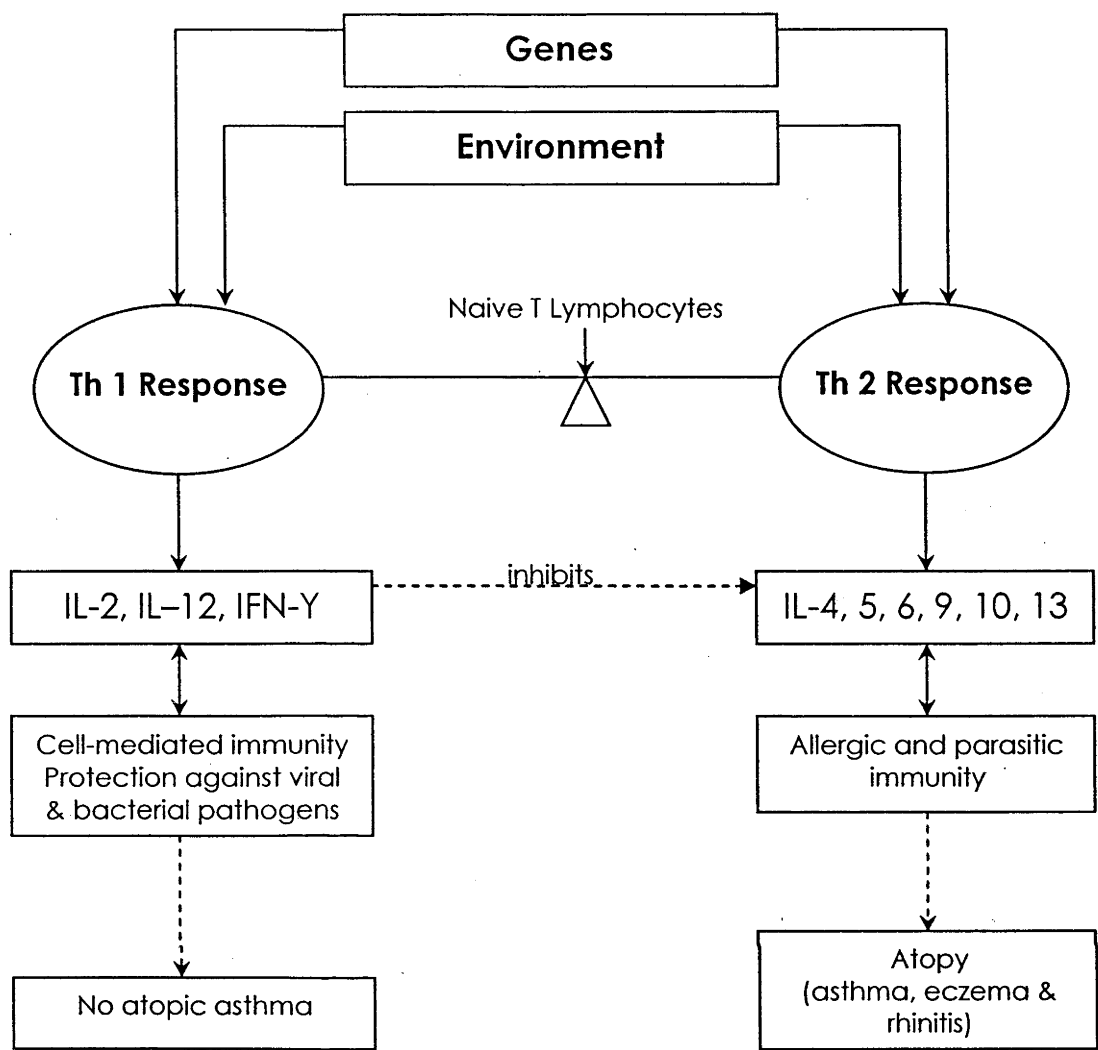


### 1.5.1 Immunopathogenesis of Asthma

Central to an understanding of how susceptible (atopic) individuals develop IgE against certain environmental factors is a knowledge of how the immune system recognizes and responds to the offending agents (67). This involves uptake and processing of allergens, usually at a mucosal surface of the airway by the antigen-presenting dendritic cells, and subsequent presentation of a small peptide to naive T lymphocytes (68) initiating a primary immune response. Terminally differentiated T helper cells 1 and 2 (Th1 and Th2 cells) derive from a common naive T precursor cell depending on the signals received at the time of antigen recognition (69). Th1 responses drive protective, cell-mediated immunity and also inhibit Th2 responses by their release and production of interleukin (IL)-2 (IL-2), tumour necrosis factor (TNF- $\beta$ ), and the cytokine interferon gamma (IFN- $\gamma$ ) (67, 69). In contrast, in those destined to develop an allergic response, the naive T cells differentiate to Th2 cells, Th2 cells produce IL-4, IL-13, IL-5, IL-9, IL-6 (69) and IL-10, and are important in the stimulation of IgE production, mucosal mastocytosis, and eosinophilia (66). A possible immunopathogenic role for Th2 cells in asthma has been postulated on the role that these cytokines play in IgE synthesis and eosinophil regulation (66). The process of polarization of the immune system from a Th2 (allergic) to a Th1 (non-allergic) response (70-72) is called immune deviation (70). This process is presented diagrammatically in Figure 1.2. However, this concept of immune deviation is continuing to be refined (see Section 1.5.4), and, new epidemiologic findings may assist this process of refinement.



Figure 1.2 The development of the immune response \*



\* Based on Holgate, 2000 (67)

## **1.5.2 Timing for the development of the immune response**

The introduction of avoidance measures or other interventions to influence these immune responses requires an understanding of the timing of the immune response. In the first years of life, the immune system of children is relatively immature compared to that of adults (73-76). This creates a “window period” between birth and 5 years of age during which there is an enhanced risk of allergic sensitization and subsequent atopic disease (72), and therefore a period for prevention.

Early exposure to ‘high’ levels of inhalant allergens, particularly during the first 3 months of life, and in some cases possibly in utero, maximizes the risk in genetically susceptible individuals for development of T-cell sensitization and atopic disease (77, 78) (see Section 2.2.1.1). Being born during the pollen season has been associated with a significantly increased risk of developing pollen allergy in later life (77), indicating that early postnatal exposure to ‘high’ levels of allergens during this “window period” for sensitization maximizes the risk for subsequent expression of allergic reactivity to that allergen in adult life. The response of the T-cells to initial encounters with an individual allergen may determine sensitivity to that allergen later in life. As initial exposure to ubiquitous inhalant allergens such as HDM and pollens invariably occurs during the first year of life, the capacity of the infant immune system to deal with such environmental challenges assumes major importance in relation to the aetiology of respiratory allergy (77). Permanent immune responses to common environmental allergens are usually established during these first few years of life (79). The type of immune response to a specific allergen is influenced not only by individual atopic propensity but also by environmental factors during the initial encounters with the allergen (78). Sensitization to aeroallergens occurring at an early age is more strongly associated with asthma risk than late allergic sensitization (43).

## **1.5.3 Immunologic mechanisms for the influence of microbial agents on the prevention of allergic disease**

Initial priming of T-cells to environmental allergens occurs in utero or soon after birth. Initial T-cell priming commonly occurs across the placenta (80, 81), particularly to allergens encountered by the mother in the last trimester of pregnancy (82). The cytokine phenotype of these T-cells is typically Th2-polarised (83, 84). Thus, after birth, priming occurs in an immunological

environment polarized to a Th2 phenotype. T-cell memory is driven by the environmental selection of Th1 or Th2 T-cells. For example, bacterial and viral infections stimulate Th1 cells and parasitic infections induce a Th2 response (see Figure 1.2). Compartmentalisation of allergen-specific T-cell immunity into adult-equivalent Th1 patterns rather than Th2 patterns has been shown to occur in most children before the age of 5 years (72), and it has been reported to be as early as before 2 years (85). Thus, in normal individuals, initial low-level Th2 immunity is converted to Th1 by 5 years of age, whereas the process fails in atopics, leading instead to the consolidation of Th2-polarized inhalant allergen-specific immunological memory involving the production of IL-4, 5, 9, 10 and 13 (72, 86). In children with "established" atopic disease, a disturbed balance in Th-cell subsets (Th1 versus Th2) toward a polarized Th2 phenotype is generally accepted (87-90). The failure of atopic children to develop a long-term, Th1-dependent memory has been proposed to be due to a reduced IFN- $\gamma$  production (83, 91, 92).

The capacity to produce IFN- $\gamma$  is much lower in foetal T cells than in adults, and production of IFN- $\gamma$  increases progressively from birth to age 5 years (93). There is evidence that at-birth IFN- $\gamma$ -producing capacity is lowest in children with a genetic background of atopy, and remains so throughout infancy (92, 94-97), suggesting that slow postnatal development of Th1-associated functions is a primary risk factor for atopy (97). The transient reduction in Th1 function is much greater in individuals genetically at risk of atopy (97). This IFN- $\gamma$  production deficiency is reflected in the slower postnatal up-regulation of allergen-specific Th1 responses, particularly during early infancy. Low capacity to produce IFN- $\gamma$  during initial extrauterine exposure to environmental allergens may compromise the immune-deviation process, given that the underlying process involves IFN- $\gamma$ -mediated inhibition of Th2 cell growth.

Recent studies (98) have shown that a number of allergens, in addition to acting as immunogens, have enzymatic activity that may subvert the immune response toward the Th2 phenotype. In response to the Group I allergen from the HDM *Dermatophagoides pteronyssinus* (Der p 1), peripheral blood T cells show markedly diminished proliferation and IFN- $\gamma$  secretion. These findings indicate that Der p 1 could upset the balance of Th1/Th2 subset distribution by decreasing growth and expansion of the Th1 subset, and, as a consequence, augmenting expansion of the Th2 subset that favours a pro-allergic response. Der p 1 may also contribute to the allergic phenotype by cleaving CD23 on B-cells that would normally serve to inhibit IgE synthesis and thereby disrupt the IgE regulatory mechanism, resulting in an up-regulation of IgE synthesis (98). And, through its ability to disrupt epithelial architecture, Der p 1 may also facilitate its own passage across the epithelium, thus enhancing its (own) access to immune cells (98).

Although allergens such as Der p 1 can potentially create a microenvironment conducive to Th2 cell expansion, normal individuals do not mount Th2 responses to these allergens, which suggests that despite the nature of these antigens, other factors also contribute to the allergic outcome following inhalation of aeroallergens in susceptible individuals. Subsequent allergen exposure in a sensitized individual would cause mediator release, bronchoconstriction and cellular infiltration resulting in histological changes: allergen stimulation being the driving force behind the inflammatory changes (99)

The shift toward a polarized Th2 phenotype during the process of allergic sensitization in children that develop atopy is not completely understood. However, allergen challenge in an atopic patient results in the selective activation, recruitment, and accumulation of specific Th2 cells in the target organs, such as skin and lungs. A prospective study by Prescott et al., 1999 (100), showed an age-dependent decline in Th2 responses to inhalant allergens in non-atopic children, and a reciprocal pattern in those who developed atopy by the age of 2 years. These results support the conclusions of earlier cross-sectional studies (72, 84, 101) that the atopic phenotype is defined by the postnatal boosting of foetal allergen-specific Th2 immunity to inhalants, as opposed to a re-direction (immune deviation) of these responses towards the Th1-cytokine phenotype (100). Thus, the development of atopy appears to be associated with postnatal consolidation of the weakly foetally primed allergen-specific Th2 responses.

#### **1.5.4 Immune deviation or immune modulation**

Although the Th1/Th2 paradigm suggests that Th1 and Th2 cells counterbalance each other and that Th1 cells protect or prevent Th2-mediated allergic disease and asthma, and, in addition, provides a framework within which to understand the immune event that promote airway inflammation and bronchial hyperreactivity, this construct may be oversimplified (65). Th1 responses alone have been shown in murine models to fail to counterbalance Th2 cell-induced airway hyperreactivity but induce reversible airway inflammation (102). Furthermore, the evidence that allergen-induced Th1 cytokine production is down-regulated is now less clear with recent studies finding decreased, no difference or increased IFN- $\gamma$  responses to allergens in atopic subjects (103), suggesting that multiple mechanisms, which have yet to be defined, may be involved in defining the nature of T-cells which mediate allergic and tolerant responses (104). The findings from a recent study (105) that investigated atopic allergy in Estonian children, led the authors to conclude that instead of immune deviation with decreased Th1 and increased Th2

responses leading to atopic disease, there is a mechanism of immune modulation throughout life whereby Th1 and Th2 responses are increased in atopic subjects. Thus, the influence of microbial exposure on the immune system may not yet be completely defined. Critical to any effect will be (i) the timing in relation to the dose and route of allergen exposure, and (ii) the interaction between microbial exposure and other non-infective environmental and lifestyle factors (106).

## **1.6 CONCLUSION**

Asthma is a multifactorial disease, with a polygenic profile, and characterized by different phenotypic groups influenced by a range of environmental factors. Primary prevention strategies directed at adjusting the environment of those at risk of developing asthma are more feasible than altering genetic components, perhaps presenting the best potential for significant decrease in disease prevalence in the future. The age and length of time that an at-risk infant is particularly vulnerable is important. There is a “window of opportunity” in early life where a variety of environmental factors, for example microbial agents, may be important in initiating the development of asthma and atopy. Environmental modification will be important beginning at (or very possibly even before) birth in an effort to control the immune system's balanced response to those environmental risk factors involved in the development of atopic disease.

## **1.7 POST-SCRIPT**

Chapter 2 will discuss the epidemiological evidence for potential environmental risk factors and their role in the development of child asthma with an emphasis on the postnatal environment.

## Chapter 2

# Epidemiological review of child asthma

---

## 2.0 PREFACE

This Chapter discusses the epidemiological evidence relating to the prevalence of asthma in children and the potential environmental factors that may play a role in the aetiology of child asthma. The evidence presented considers primarily the strongest epidemiological studies addressing child asthma that are available, recognizing the limitations arising from a particular study type. Longitudinal studies (cohort studies or intervention studies) may provide a high level of evidence of primary causation. Randomized controlled trials (RCTs) provide the highest quality of evidence and are traditionally considered the gold standard however, observational studies have several advantages over RCTs including lower cost, greater timeliness and a broader range of participants (107). Observational studies are primarily used to identify risk factors and in situations where RCTs are not feasible or unethical (107): the association between exposure early in life to differing environmental factors with the subsequent development of asthma can be considered in these study types. Moreover, prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in the development of a specific disease such as asthma, with confirmation of a possible cause-effect relationship through RCTs. These studies are not always available thus making it necessary to consider other population-based studies of asthma. Retrospective case-control studies, however, due to recall bias and selection bias, reduce their strength regarding the evaluation of predictive/risk factors for the development of allergic diseases. Moreover, cross-sectional studies are not suitable for assessment of cause-effect relationships between exposure to factors and development of allergic diseases.

## 2.1 PREVALENCE OF ASTHMA

At the end of the 20<sup>th</sup> century, the prevalence of asthma in children and young adults was reported to be increasing worldwide by 5%-6% each year (2); although there is recent evidence that this has leveled off or declined (see Section 2.1.3 and Section 8.2.3). Until recently, however, methods for assessing changes in the prevalence of asthma over time were not standardized, making comparisons both within countries and between countries difficult,

prompting concerns that the increases in reported prevalence are largely due to increased awareness (information bias), labeling and differential diagnosis of symptoms (108). Questionnaires are the main methodological tool used in prevalence studies but if supplemented with biological markers, such as lung function tests, they are less prone to diagnosis misclassification. The cross-sectional design of these studies gives no direct information about the incidence of asthma and, prevalence can also be influenced by a variety of factors such as remission, exacerbation and treatment. A difficulty encountered in the interpretation of such studies is that asthma prevalence in a population reflects both asthma incidence and the average duration of the condition. A factor that prolongs or exacerbates asthma symptoms may thereby increase asthma prevalence even if it has no effect at all on the incidence of asthma (109). However, the difficulties in studying true incidence or variations in incidence, such as competing risks which may cause an underestimation of the incidence proportion, support the use of measurement of prevalence changes.

Repeated cross-sectional studies which have determined the prevalence of asthma symptoms using the same methodology, in the same population, and at different time periods, consistently reported an increase in asthma prevalence in recent decades until 1999. These studies are presented in Table 2.1 and have included prevalence studies undertaken in Australia.

**Table 2.1 Worldwide changes in asthma prevalence in children and young adults until 1999\***

Country	Period	Asthma prevalence %		Reference
		1 <sup>st</sup> study	2 <sup>nd</sup> study	
Australia	1964-90	19.1	46.0	Robertson et al. (110)
	1982-92	12.9	19.3	Peat et al. (111)
	1987-92	5.6	9.3	Campbell et al. (112)
Canada	1992-95	9.3	11.4	Adams et al. (113)
	1980-89	3.8	6.5	Infante-Rivarde et al. (114)
	1980-90	1.4	2.6 <sup>a</sup>	Manfreda et al. (115)
		1.3	2.5 <sup>b</sup>	
England	1956-75	1.8	6.3	Morrison Smith (116)
	1966-90	18.3	21.8	Whincup et al. (117)
	1973-86	2.4	3.6	Burney et al. (118)
	1978-91	11.1	12.8	Anderson (119)
England + Wales	1970-81	11.6	20.5 <sup>a</sup>	Fleming and Crombie (120)
		8.8	15.9 <sup>b</sup>	
Finland	1961-86	0.1	1.8	Hahtela et al. (121)
France	1968-82	3.3	5.4	Perdrizet et al. (122)
Germany	1991/2-95/6	3.7	4.1	Von Mutius et al. (123)
Israel	1986-90	7.9	9.6	Auerbach et al. (124)
Italy	1983-93/5	2.9	4.4	Ciprandi et al. (125)
Japan	1982-92	3.3	4.6	Nishima (126)
New Zealand	1969-82	7.1	13.5	Mitchell (127)
	1975-89	26.2	34.0	Shaw et al. (128)
Papua New Guinea	1973-84	0.0	0.6	Dowse et al. (129)
Scotland	1964-89	10.4	19.8	Ninan and Russell (130)
	1989-94	19.8	25.4	Omran and Russell (131)
Sweden	1971-81	1.9	2.8	Aberg (132)
	1979-99	2.5	5.7	Aberg et al. (133)
Tahiti	1979-84	11.5	14.3	Liard et al. (134)
Taiwan	1974-85	1.3	5.1	Hsieh and Shen (135)
U.K.	1978-91	11.1	12.9	Butland et al. (136)
USA	1964-83 <sup>c</sup>	1.8	2.8	Yunginger et al. (137)
	1971-76	4.8	7.6	Gergen et al. (138)
	1981-88	3.1	4.3	Weitzman et al. (139)
	1983-92	9.2	15.9	Farber et al. (140)
Wales	1973-88	4.0	9.0	Burr et al. (141)

<sup>a</sup>Men. <sup>b</sup>Women. <sup>c</sup>Incidence rates per 1000 person-years.

\*Data adapted from Pearce et al 2000 (142).



### **2.1.1 Asthma prevalence studies in Australia in the 20<sup>th</sup> century**

Peat et al., 1994 (111), in serial cross-sectional studies of 8-10 year old children in Wagga Wagga and Belmont, New South Wales, in 1982 and in 1992, found that the prevalence of wheeze in the previous 12 months increased in Belmont from 10.4% to 27.6% ( $p < 0.001$ ) in 1992 and in Wagga Wagga from 15.5% to 23.1% ( $p < 0.001$ ). In Wagga Wagga, parent-reported wheeze in the past 12 months increased by 6.6% and asthma diagnosis by 17.6%. Objective measures of atopy (SPTs to common allergens) and of BHR (histamine inhalation challenge and forced expiratory volume in one second ( $FEV_{1}$ )) were collected in the years 1982 and 1992. The prevalence of airway hyperresponsiveness in atopic children increased by 10.7% (95% CI 7.3, 14.1) (2-fold) to 19.8% in Belmont, and by 6.4% (95% CI 2.9, 9.9) (1.5-fold) to 18.1% in Wagga Wagga. The prevalence of airway hyperresponsiveness increased mainly in atopic children only (with a non-significant increase in non-atopics), but the prevalence of atopy was unchanged (about 28.5% in Belmont and 32.5% in Wagga Wagga).

A further cross-sectional survey (143), with a similar design, was undertaken in Wagga Wagga to compare asthma prevalence from 1992 to 1997 with the previous study. Between 1992 and 1997, the prevalence of wheeze in the past 12 months increased by 5.1% (95% CI 1.2, 9.0), from 22.1% in 1992 to 27.2% in 1997 and asthma diagnosis increased by 8.1% (95% CI 3.8, 12.4). Objective measures of atopy by SPTs to common allergens were also undertaken. There was significant increase in prevalence of atopy by 6.7% (95% CI 2.2, 11.2), between 1992 and 1997, although the increase between 1982 and 1992 was not significant.

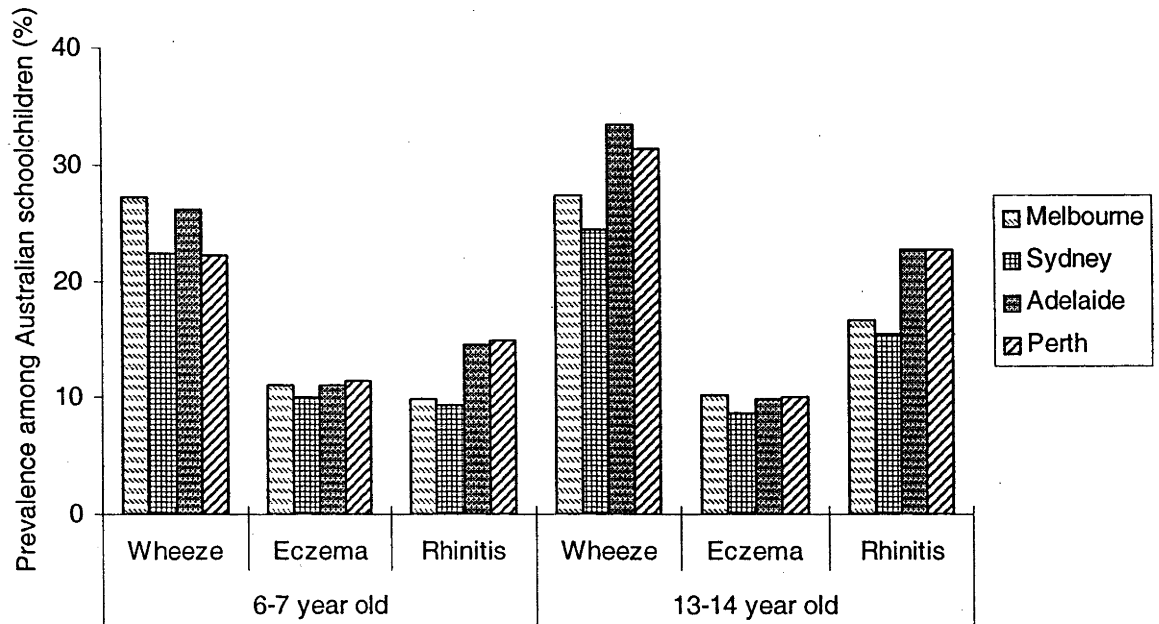
### **2.1.2 International comparisons of asthma prevalence in the 20<sup>th</sup> century**

The International Study of Asthma and Allergies in Childhood Study (ISAAC) (144) has enabled international comparisons of asthma prevalence. Phase 1 of the ISAAC used standardized, and validated, written questionnaires and a video asthma questionnaire to measure the prevalence of self-reported, or parentally reported, symptoms and clinical signs of allergic disease (6, 145, 146). The ISAAC compared the prevalence rates of asthma, allergic rhinoconjunctivitis and atopic eczema over a period of one year in 155 centres in 56 countries with a study population of 257,800 schoolchildren 6-7 years of age and 463,801 schoolchildren 13-14 years of age (6). The ISAAC, the first truly global study of asthma prevalence in children, found that asthma symptom

prevalence varied from 1.6% to 27.2% in the 6-7 year old age group, and 1.9% to 35.3% in the 13-14 year old children. Highest prevalences (>17% prevalence) were reported from the United Kingdom (UK), New Zealand, Australia, Republic of Ireland, North America, Canada and Peru. And, the lowest prevalences (<3% prevalence) in Indonesia, Greece, China, Taiwan, Uzbekistan, India and Ethiopia (6).

In 1993-94, Australia ranked second-highest in prevalence of current wheeze for 6-7 year olds and third-highest for 13-14 year olds (6). As part of the ISAAC, the prevalence of "wheeze in the past 12 months" in children was measured in four Australian cities from 1993-94 by Robertson et al., 1998 (147). The prevalence in 10,914 children aged 6-7 years and 12,280 children aged 13-14 years in Melbourne, Sydney, Adelaide and Perth was 24.6% (95% CI 23.8, 25.5) and 29.4% (95% CI 28.6, 30.2) respectively. These results are similar to the prevalence of wheeze of 27.2% found in Wagga Wagga in 1997 by Downs et al., 2001 (143). In the ISAAC, prevalences of current eczema and allergic rhinitis were 10.9% and 12.0% respectively for the 6-7 year olds, and 9.7% and 19.6% respectively for the 13-14 year olds. The prevalence of asthma, eczema and rhinitis in the four Australian cities (1993-94) are shown in Figure 2.1. Asthma, eczema and rhinitis co-existed in 1.8% of 6-7 year olds and 2.8% of 13-14 year olds. The interrelation between wheeze, eczema and rhinitis in the previous 12 months in Australian schoolchildren (1993-94) is shown in Figure 2.2, with a lower than anticipated correlation found between the three atopic diseases (147). Any association between atopy and asthma appeared to differ in differing locations, suggesting that the relative balance of atopic versus non-atopic asthma may differ by location (148).

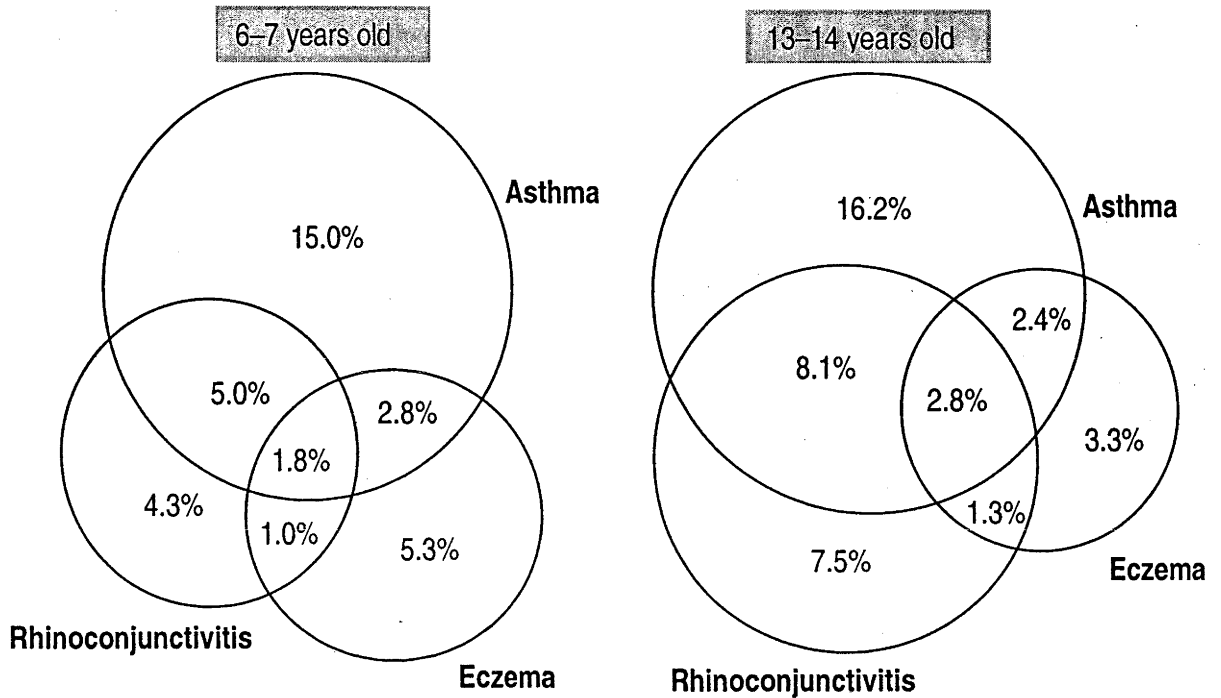
**Figure 2.1 Prevalence of wheeze, eczema and rhinitis in the previous 12 months\* among Australian schoolchildren (1993-94)\*\***



\*12 months preceding winter-spring, 1993, in Melbourne, Sydney, Adelaide and winter-spring, 1994 in Perth.

\*\*Data sourced from Robertson CF, Dalton MF, Peat JK, Haby MM, Bauman A, Kennedy JD, Landau LI. Asthma and other atopic diseases in Australian children. MJA, 1998; 168:434-8.

Figure 2.2 Venn diagrams showing the interrelation between wheeze, eczema and rhinitis in the previous 12 months\* in Australian schoolchildren (1993-94)\*\*



\*12 months preceding winter-spring, 1993, in Melbourne, Sydney, Adelaide and winter-spring, 1994 in Perth.

\*\*Data sourced from Robertson CF, Dalton MF, Peat JK, Haby MM, Bauman A, Kennedy JD, Landau LI. Asthma and other atopic diseases in Australian children. MJA, 1998; 168:434-8.

Based on the ISAAC Phase I findings and other studies of asthma prevalence, Beasley et al., 2000 (8), concluded that the international patterns of asthma prevalence demonstrated five key features: (i) asthma prevalence is increasing worldwide; (ii) asthma is generally more common in western countries and less common in developing countries; (iii) asthma is more common in English-speaking countries; (iv) asthma prevalence is increasing in developing countries as they become more westernized or communities become more urbanized; and (v) the prevalence of other allergic disorders, allergic rhinitis and atopic eczema, may also be increasing worldwide. This final feature has been supported by results from the three UK national birth cohorts of 1946, 1958 and 1970, which have shown a marked increase (5.1%, 7.3%, and 12.2% respectively) in the prevalence of eczema in children aged under 5 years (149).

### **2.1.3 Asthma prevalence studies in the 21st century**

The results of recent studies question the continuing increase in asthma prevalence. Several published papers report either a decline (3, 4, 150-153) or a plateauing (5, 154-156) of child asthma prevalence in the British Isles, Singapore, Hong Kong, Australia, Switzerland and Italy. Two Australian studies have recently reported a decrease in prevalence of child asthma (3, 4). Robertson et al., 2003 (3), using the ISAAC protocol, surveyed 6-7 year old school children in Melbourne between 1993 and 2002 and found the prevalence of reported current wheeze fell by 26% over 9 years, from 27.2% in 1993 to 20.0% in 2002. In that study, however, the prevalence of eczema and allergic rhinitis continued to increase. The 12-month period prevalence of reported eczema increased from 11.1% in 1993 to 17.2% in 2002, and rhinitis increased from 9.7% to 12.7%. The authors were unable to explain the decrease in the prevalence of current wheeze, suggesting that it may have been influenced by the level of symptom complex awareness in the community or the increase in attendance at child care facilities (148) (see Section 2.3.2). Whereas, Toelle et al., 2004 (4), using the same questionnaire as in 1992 (111), found the prevalence of recent wheeze decreased significantly (-4.9%; 95% CI -9.1%, -0.7%) between 1992 and 2002 in schoolchildren from Belmont, New South Wales.

The reported changes in the prevalence of asthma, discussed above, have occurred too rapidly to be in response to changes in genetic variants. Modifications in the pattern of exposure, and changes in susceptibility, to various environmental factors in large portions of the population may be important (6). Epidemiological studies have explored the putative role of environmental risk factors (for example, allergens, tobacco smoke, and air pollution) as well as the loss of possible

protective factors over time, such as early infections and diet. These current putative risk factors, however, cannot fully account for either the worldwide increase in prevalence or the international variations in asthma prevalence that have been observed (8). The major environmental and lifestyle factors that are considered to contribute to the aetiology of child asthma are discussed in the following sections of this Chapter.

## 2.2 PUTATIVE RISK FACTORS FOR ASTHMA

### 2.2.1 HDM Allergens

Indoor allergens, notably from HDM, have received considerable attention as a possible major cause of asthma and of the global increase in prevalence (99, 157). In westernized countries, lifestyle changes have resulted in more time spent indoors, potentially increasing exposure to indoor allergens. In addition, alterations to the domestic environment such as fitted carpets, increased temperatures, tighter insulation, and cold water washing, have increased the opportunity for HDM to grow by making a more conducive environment (158). Peat et al., 1994 (111), showed a 5.5-fold increase in the number of HDM in domestic dwellings in Belmont and a 4.5 increase in Wagga Wagga over a period of 10 years from 1982 to 1992. Dust mite faecal particle allergen becomes airborne, and exposure of the immune system to these foreign proteins in household dust will be directly influenced by the number of particles, their size (and aerodynamic properties) and the solubility of the proteins (159).

The term "house dust mites" applies to all mites of the family Pyroglyphidae, of which the genus *Dermatophagoides* predominates. Four species currently dominate all others: *Dermatophagoides (D.) pteronyssinus*, *D. farinae*, *D. microceras*, and *Euroglyphus maynei* (160). The main determinants for survival are high humidity, moderate temperatures and an adequate food source (human skin scales are a primary source). Two main groups of allergens appear important: Group I allergens (Der p 1, Der f 1 and Der m 1) found in mite faecal pellets; and, Group II allergens (Der p II, Der f II) found in both faecal pellets and mite bodies (99). Many studies discussed in this thesis have not differentiated the specific Group allergen of *D. pteronyssinus*, reporting the allergen as Der p. The possible mechanism of action within the human body of the allergens from these HDMs has been discussed in Section 1.5.3.

### **2.2.1.1 HDM allergen and sensitization**

For an allergen to have a major clinical effect, prior sensitization must have occurred. An individual's degree of susceptibility to allergens, the immunogenic properties of the allergen, and the degree of exposure (99) are all determinants of an allergen-specific immune response. In any population there is a gradient in the ability to respond to allergens: from individuals who do not become sensitized regardless of exposure to others who show extensive sensitization to many different allergens (99). And, even among individuals with a tendency to respond, the development of sensitization to an allergen is dependent on exposure, as other environmental factors operating in early life may modify the incidence of sensitization (161). The ability to respond to an allergen is partially genetically determined.

Provisional standards for both sensitization to mites and also mite-allergen exposure have been recommended by a World Health Organization (WHO) workshop in 1987 (162). It was proposed that a level of 2 µg of Der p 1 per gram of dust (equivalent to 100 mites per gram or 0.6 mg of guanine per gram of dust) should be regarded as a risk factor for sensitization and the development of asthma. The higher level of 10 µg of Der p 1 per gram of dust (or 500 mites per gram of dust) was proposed as a major risk factor for the development of acute asthma in mite-allergic individuals. However, Strachan, 2000 (10), recently stated that a threshold level below which sensitization does not occur, as had been suggested, is now considered unlikely. The HDM allergen is especially immunogenic such that in areas with high mite exposure, such as Australia, New Zealand, UK and the United States of America (USA), the level of mite exposure appears sufficient to sensitize 'all' potentially atopic children (99).

Both skin testing and measurements of IgE antibodies are used to determine sensitization to HDM allergen. Sensitization to an allergen can occur at any age however the predisposed infant is more susceptible to allergen sensitization (see Section 1.5.1). Sensitization to mite allergens commonly starts to be measurable by serum antibodies or by SPT early in childhood. Birth cohort studies (159, 163) and longitudinal studies (164) have shown that positive SPTs to inhalant allergens are unusual before 2 years of age. A prospective study (163) of children born to at least one allergic parent showed that IgG and IgE antibody responses to mite allergen developed in the second and third years of life. Household exposure above threshold levels of Der p 1 (>5,000 ng/g fine dust) in infancy was positively associated with the prevalence of skin test positivity and increased levels of specific IgE to mites (163).

### **2.2.1.2 Mite Allergen Exposure as a risk factor for sensitization**

A clear dose-response relationship between dust mite allergen exposure and sensitization is supported by studies of different communities and climates. Both prospective (161, 165, 166) and cross-sectional studies (167-169) have now shown a dose-response relationship between the level of exposure to HDM allergens and allergic sensitization. The incidence of sensitization to *D. pteronyssinus* in 1,812 children in Germany with a mean initial age of 7.3 years over a two-year period was examined (166). The study identified an increased risk for initial sensitization (odds ratio (OR) 2.2; 95% CI 1.2, 4.1) for increasing levels of Der p 1 in the child's mattress dust (>10 µg/g). The German Multicenter Atopy Study (165) with a prospective cohort of 1,314 newborns followed for three years, using mixed floor dust from the child's bedroom, parent's bedroom and living room, found that in homes with low ( $\leq 25^{\text{th}}$  percentile) dust concentrations, the risk of sensitization to HDM for these children was substantially lower, 1.6% compared to 6.5%, with domestic exposure to the HDM allergen than if dust concentrations were above the 75<sup>th</sup> percentile. Children sensitized to HDM were exposed to significantly higher HDM (median 868 ng/gm versus 210 ng/gm;  $p=0.001$ ) allergen concentrations in carpet dust compared to the group without sensitization. Children with a positive family history of atopy were especially susceptible to even very low levels of exposure. In children with a positive family history of asthma, a mite allergen exposure below 750 ng/gm is sufficient to result in a sensitization rate of 3% whereas, an exposure up to 25,000 ng/gm is necessary to achieve the same sensitization rate in children with a negative family history (165).

Allergen exposure in early infancy appears critical for primary sensitization. Exposure to mite allergen has been measured in the homes of infants studied prospectively (170). When skin prick tested at age 10 years, none of the children exposed to <2 µg Der p 1/g fine dust in infancy developed sensitization to mites or asthma. Conversely, in those exposed to >10 µg/g in infancy, 50% were sensitized to mites. Repeated challenge with an allergen can cause a secondary response with an increase in allergen specific IgE levels.

### **2.2.1.3 Mite allergen sensitization as a risk factor for asthma**

Clinical studies have shown that the proportion of sensitized asthma patients, as reflected by either positive SPTs or presence of specific IgE antibodies to HDM, is significantly higher than for those without asthma (129, 171), with up to 85% of patients with asthma reported as being skin



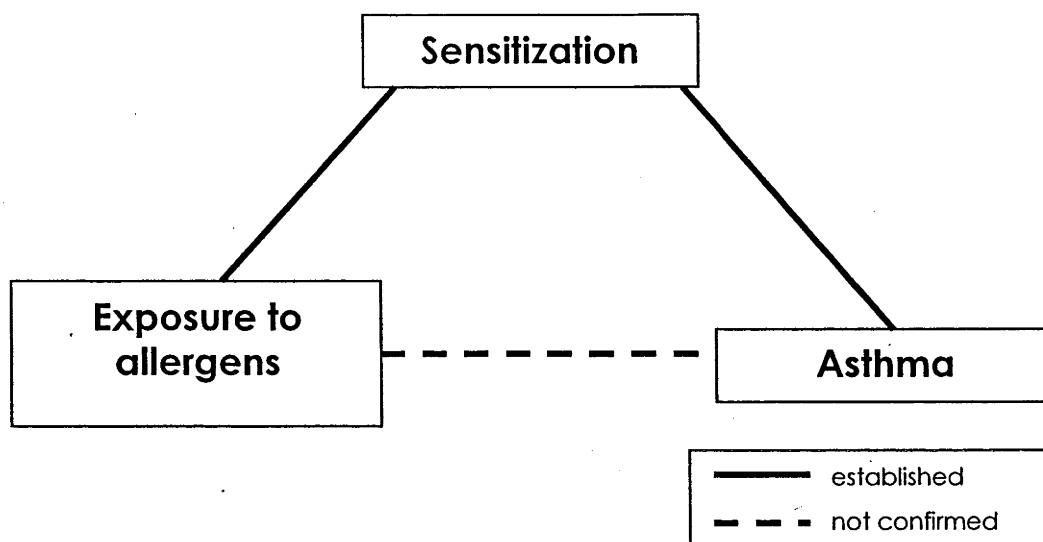
prick sensitive to HDM, as compared with only 5-30% of the general population. HDM sensitization is a significant risk factor for asthma in areas with high levels of HDM allergens in homes (157). The development of early sensitization, that is before the age of six to eight years, was found to be a stronger predictor for asthma than sensitization being only detectable at a later age (172, 173). Furthermore, sensitized individuals are likely to have more severe asthma if exposed to high allergen levels than if their level of exposure is low (158).

Epidemiological studies assessing atopy with SPT responses or IgE can reduce measurement bias attributable to awareness of asthma and differences in diagnostic labeling. Several studies using these objective measures have demonstrated that mite sensitization is a strong independent risk factor for asthma (174-180) and that the risk of asthma increased with the extent of allergic sensitization (174, 179, 181). A large random population sample (176) of children in 7 climatic regions of New South Wales found HDM sensitization to be the most important risk factor for asthma in coastal regions. A longitudinal birth cohort (175) in New Zealand children up to age 13 years, found a strong independent risk of HDM sensitization on the development of asthma (adjusted relative risk (aRR) 6.71; 95% CI 1.21, 13.38). The association was found in only 2% of non-atopic children compared with 33% of HDM sensitive children. A recent study, a birth cohort (174) of 1,456 children from the Isle of Wight, reported that at age 4 years, atopy was closely associated with asthma with a direct and linear relationship, and that HDM sensitization was the most important risk factor for asthma (OR 8.07; 95% CI 4.60, 14.14). However, it should be remembered that a substantial proportion of child asthma is non-atopic. The proportion of cases with allergic disease attributable to atopy is less than 50% (109) (see Section 2.2.3).

#### ***2.2.1.4 HDM allergen exposure as a cause for asthma***

Evidence for a direct association between indoor allergen exposure and asthma is less clear (see Figure 2.3). In most studies the prevalence of sensitization is higher than the prevalence of asthma, suggesting that a higher level of exposure is required for the development of symptoms. In experimental studies, the inhalation of HDM allergen has repeatedly been shown to cause bronchoconstriction and wheeze in sensitized children and adults in a dose dependent manner, inducing both immediate and late responses (99).

**Figure 2.3 Relation between sensitization, exposure to allergens, and development of asthma\***



\*Adapted from Grad R, Lancet 2000; 356:1396-70.

A key finding linking allergen exposure in infancy to the subsequent development of asthma came from the Poole birth cohort (170) in England. In 67 children, selected at being at risk because of family history of asthma, 35 were atopic (positive SPT) and 32 were non-atopic. Of the 17 children with active asthma, 16 were atopic ( $p < 0.005$ ), all of whom were sensitized to the HDM (measured by SPT and IgE levels). The relative risk (RR) of active asthma in any child was 4.8 times greater if he or she had been exposed to more than 10  $\mu\text{g/g}$  of Der p 1 per gram in infancy ( $p = 0.05$ ). The study reported that the age at which the first episode of wheezing occurred was inversely related to the level of exposure to HDM allergen at the age of 1 for all children ( $p = 0.015$ ) but especially for the atopic children ( $r = 0.66$ ,  $p = 0.001$ ) (170).

The German Multicentre Allergy Study (178) also reported a strong association of HDM allergen sensitization with respiratory symptoms and BHR during the first 7 years of life. However, a consistent relationship between HDM allergen exposure and respiratory allergic manifestation was not found. Reports of no association between allergen exposure and asthma could partially reflect the high level of misclassification of exposure (for example, bedroom floor mite allergen level as a proxy measure of inhalational allergen dose) and outcome (through disease misclassification of the asthma sub-types, for example, asthma ever rather than severe wheeze as an indicator of allergen-induced airway disease) (see Section 2.2.1.6). Further studies that use severe symptom as the outcome measure should reduce the level of disease misclassification as this will identify the sub-group that is more likely to reflect allergen-induced

airway disease rather than airway disturbance due to viral infection or other non-atopic factors. Intervention studies will have the greatest weight to show causal effects.

### ***2.2.1.5 Allergen exposure and the clinical severity of asthma***

Precise dose-response relationships between exposure to indoor allergen and asthma severity are difficult to estimate. The level of exposure to indoor allergens necessary to induce and maintain airway inflammation, BHR, and symptoms varies over a wide range (182). The relationship between exposure to indoor allergens and symptoms of asthma is complex. Many studies have observed that approximately 50% of allergic children who are exposed to relevant allergens in their homes do not wheeze (167, 183, 184). Platts-Mills et al., 1997 (183), reported that factors influencing the relationship between exposure and symptoms include: (i) interaction between the effects of exposure to several different allergens; (ii) the influence of multiple factors that can enhance the inflammatory response to allergens; (iii) the lack of a simple objective test that characterizes asthma or inflammation of the lungs; and (iv) the triggers and enhancers that can influence narrowing of the airways or the perceived severity of symptoms, for example exercise, cold air, histamine, viruses and air pollution. Moreover, studies have shown in both children and adults that the severity of asthma symptoms will vary with the level of exposure in persons sensitive to indoor allergens (185, 186).

Several cross-sectional (167, 187, 188) and longitudinal (189-191) studies provide evidence to support a direct relationship between the level of exposure to mite allergens in the home and asthma symptom severity. These studies reported that associations between HDM allergen exposure and clinical severity of asthma were either greater or only detected in HDM sensitized children. The importance of the bed and bedroom as a source of mites is suggested by several of these studies.

A cross-sectional study (167), revealed a dose-response relationship between exposure to Der p 1 and increased risk of current asthma in mite-sensitized children. In mite-sensitized children from six regions of New South Wales, Australia, each with different levels of humidity and concentrations of HDM, current asthma prevalence increased progressively with the level of mite exposure ( $r^2=0.82$ ,  $p=0.013$ ). Going from the lowest to highest HDM-infested areas was associated with an increased prevalence of HDM-positive SPT, ranging from 13% at the low end

to 29% at the high end. In children with positive SPT for HDM, the risk of current asthma doubled with every doubling of Der p 1 level, after adjusting for sensitization to other allergens.

These results have been extended with a small longitudinal study (190) in Sydney, Australia, which showed a significant association between minimum morning peak flow rate and bed Der p 1 (a composite sample from mattress and upper bedding), in mite-sensitized children (aged 8 to 12 years). An association was not found in children without HDM atopy. Results suggested that an increase of one natural log concentration of Der p 1 would lead to an approximately 15 litres (L)/min decrease in peak expiratory flow rate (PEFR), equivalent to about a 6% fall from baseline.

Furthermore, these results show some similarity to a longitudinal study (187) over 12 months in Canada with 52 asthmatic children and 68 adults with asthma. It was reported that the level of HDM allergens was an important determinant of asthma severity in children with HDM allergy/sensitization. Moreover, the study identified mite allergen levels in the mattress to be a more important determinant of asthma severity in children with HDM allergy, than levels in floor samples. After controlling for seasonality, a significant negative relationship between mean PEFR (percent predicted) and HDM allergen concentration (sum of Der p 1 and Der f 1 for mattress and floor) for children allergic to mites only was found. In HDM allergic children, there was about a 5% decrease in mean PEFR (percent predicted) for every 1 log (microgram per gram of dust) increase in HDM allergen concentration (187).

An Australian study (192), using the data from a RCT of mite allergen avoidance to measure the association between changes in Der p 1 exposure and changes in the severity of asthma, showed that in mite-sensitive subjects (from 13-54 years of age) with asthma, changes in mite allergen levels were significantly positively correlated with changes in the severity of airway reactivity. Changes in allergen concentration in the bed were significantly correlated with changes in BHR ( $p=0.003$ ) and symptom score ( $p=0.04$ ). Changes in allergen concentration in the living room floor were only significantly correlated with changes in symptom scores ( $p=0.01$ ).

Thus, these studies have shown that in mite sensitive patients, the level of exposure to mite allergens has a major influence on severity and clinical activity of asthma, using measures of disease severity such as PEFR variability, BHR and pulmonary function.

### **2.2.1.6 Disease misclassification and the role of HDM allergen in asthma severity**

Disease misclassification and the relatively small number of prospective studies available still remain a considerable issue for asthma epidemiology. Asthma is a clinical syndrome reflecting airway inflammation and obstruction (193) (see Section 1.2). The heterogeneity of clinical sub-groups within asthma patients (193) is likely to partially reflect mixed aetiological components. The relative contribution of allergen-induced, irritant-induced and infection-induced wheeze within the broad spectrum of asthma has not yet been clearly identified. The dominant theoretical paradigm for childhood asthma is that of a largely allergic aetiology; however this assumption has been challenged (194) (see Section 2.2.3).

A small number of studies have looked at a sub-group of those children with asthma in an effort to address disease misclassification within the asthma spectrum. Atopic individuals are over-represented at the severe end of the asthma spectrum (181, 195-197). The findings in these studies suggest that symptoms such as frequent wheeze may be better markers of HDM-allergen-related airway disease than a history of asthma or milder symptoms, and, is also consistent with past work that found increasing Der p exposure is associated with increasing wheeze frequency (167).

A population based case-control study (197) in Sheffield, UK, found the most powerful risk factors for severe asthma (defined as 12 or more wheezy episodes or speech limiting wheeze over the previous 12 months) were pet ownership (which indicates high exposure to pet allergens (198)) and the use of non-feather bedding (which may be a marker for high exposure to mite allergens (198)), with little or no effect of parental smoking, gas cooking and mould growth.

In the Australian Capital Territory, Australia, a cross-sectional asthma survey (195) of a population sample of 758, 8-10 year old children and a hospital-based sample of 78 children attending the hospital for asthma, found the clinical features of frequent wheeze or hospital asthma attendance are largely attributable to atopy, but infrequent wheeze or a history of asthma ever are not. Atopic children are over-represented in the severe range of the asthma spectrum. The association between atopy and wheeze by wheeze frequency episodes over the past year was as follows: no episodes (OR 1.00 (reference)); 1-3 episodes (OR 3.27; 95% CI 2.15, 4.97); 4-12 episodes (OR 3.44; 95% CI 1.75, 6.75); and >12 episodes (OR 8.70; 95% CI 3.07, 24.55),

with a higher population attributable fraction (PAF) for > 12 episodes (75%) than 1 to 3 episodes (49%). Atopy was moderately related to asthma ever (OR 2.09; 95% CI 1.52, 2.85; PAF 33%) but was strongly related to 1999 hospital attendance for asthma (OR 16.5; 95% CI 6.76, 42.48; PAF 89%).

In the Tasmanian birth cohort, (TIHS) (196), HDM sensitization was associated with increased wheeze frequency in the past year compared with no wheeze (1-3 episodes: RR 1.49; 95% CI 1.05, 2.13; 4-12 episodes: RR 6.48; 95% CI 3.23, 12.63; >12 episodes: RR 12.75; 95% CI 4.25, 38.24; Test for linear trend,  $p < 0.001$ ). HDM sensitization was only moderately associated with childhood asthma (asthma ever) (unadjusted RR 1.65; 95% CI 1.32, 2.06), suggesting that this outcome measure was less likely to reflect HDM-related airway disease than frequent wheeze. The authors thus concluded that a focus on severe symptoms such as frequent wheeze should reduce disease misclassification in population-based studies examining HDM-induced airway disease (196).

There are multiple other factors such as virus infection, endotoxin exposure, and air pollution that can contribute to the severity of symptoms in allergic individuals (199). These would all tend to interfere with the quantitative correlation between current allergen exposure and symptoms. However the choice of frequent wheeze (>12 episodes) as the outcome measure should reduce the level of disease misclassification by identifying a sub-group that is more likely to reflect allergen-induced airway disease rather than airway disturbance due to viral infection or other non-atopic factors (195).

### ***2.2.1.7 Improvement in asthma with reduction of allergen exposure***

Further evidence for the role of HDM allergen as a putative risk factor in asthma has been provided by studies that examine the effect of reducing allergen exposure on improving asthma symptoms. Several studies in children and young adults have shown short-term improvement in asthma symptoms and BHR with prolonged HDM allergen avoidance away from their residence, and a recurrence of symptoms when the children return to areas with higher HDM levels (200-202). A small number of controlled trials of allergen avoidance have also reported a prolonged decrease in mite allergen exposure with significant improvements in BHR (203-207). However, a recent Cochrane review (208) found that the current chemical and physical methods to reduce

exposure to HDM allergens seem to be ineffective, recommending that other methods of mite control be evaluated.

### ***2.2.1.8 Primary prevention of allergen exposure***

There are few studies of primary prevention. In a prenatally RCT of infants genetically at high-risk of atopy followed until age 4 years in the UK (209), a significant reduction in atopy and allergic symptoms was found in the prophylactic group at ages 1 year, 2 years and was maintained at age 4 years. The prophylactic group (n=58) was either breastfed with their mothers excluding foods regarded as highly antigenic from their diets, or given an extensively hydrolysed formula and, in addition, HDM exposure was reduced through the use of an acaricide to upholstered furniture, bedroom and living room carpets. All the children have now been reviewed at the age of 4 years, and SPTs to a wide range of dietary allergens and aeroallergens have been performed. The control group (n=62), fed on breastmilk or on formula, with no specific environmental measures taken, continues to show more total allergy (OR 2.73; 95% CI 1.21, 6.13), definite allergy (allergic symptoms plus positive SPT) (OR 5.6; 95% CI 1.8, 17.9), and eczema (OR 3.4; 95% CI 1.2, 10.1). More control children have positive SPTs (OR 3.7; 95% CI 1.3, 10.0). The authors concluded that a dual approach to the prevention of allergic disease, avoiding as far as possible sensitization to food and aeroallergens, significantly reduces the risk of atopic disease.

Other prospective studies of primary prevention of asthma and allergies are currently being undertaken (210-212) with early results available. A prospective prenatally randomized cohort study (211) in the UK, The Manchester Asthma and Allergy Study, has reported that environmental manipulation (reduction of exposure to allergens) reduces some respiratory symptoms in the first year of life in high-risk infants (RR 0.44; 95% CI 0.20, 1.00). A second prospective prenatally randomized controlled study (210) in Canada with follow-up through the age of 1 year, found that the multifaceted intervention program (including avoidance of HDM and pet allergens and tobacco smoke) resulted in a reduction (aRR 0.66; 95% CI 0.44, 0.98) in the risk of possible or probable asthma. While encouraging, the authors did conclude that there is no validated definition of asthma at 12 months of age and further follow-up is needed to determine the effectiveness of the intervention program in the primary prevention of asthma when the participants can have their allergic and asthmatic status measured more reliably. The Childhood Asthma Prevention Study (212, 213) is a RCT in Sydney, Australia, where 616 pregnant women

were randomized to an HDM avoidance intervention, comprising the use of impermeable mattress covers and an acaricide or control, and the use of an oil supplement, margarines, and cooking oils containing high levels of omega-3 fatty acids or control. In the children at 18 months of age, the maternal diet resulted in a 9.8% absolute reduction (95% CI 1.5, 18.1) in the prevalence of wheeze ever and a 7.8% absolute reduction (95% CI 0.5, 15.1) in the prevalence of wheeze for >1 week, but there was no effect on serum IgE, atopy or doctors' diagnosis of asthma. Over the 18-month study period, bedding HDM allergen levels in the active HDM intervention group were more than 3-fold lower than levels in the bedding of the control HDM group. However, the HDM avoidance intervention did not influence the development of sensitization and wheeze symptoms (213).

### **2.2.2 Other allergens**

There is clear evidence of communities in which a high prevalence of asthma is associated with indoor allergens other than HDM (183), most commonly cat, dog, alternaria (176, 214) and cockroach (215) allergens, supporting the view that it is specific sensitization to indoor allergens rather than generalized IgE hyperresponsiveness that is associated with perennial asthma. Thus, individuals susceptible to developing atopic disease will become sensitized to the allergens prevalent in the environment.

A systematic review (216) of the literature up to the end of 1999, concluded that exposure to pets appeared to slightly increase the risk of asthma and wheezing in older children over the age of 6 years (OR 1.19; 95% CI 1.02, 1.40). Selection bias may be a major source of error in examining the association between exposure to pets and the risk of asthma as parents of asthmatic children are more likely to selectively avoid or remove pets from the home, biasing the results of prevalence studies (217). However, more recent longitudinal studies (218-222), including large birth cohorts, have observed an inverse relationship between pet keeping in early life and the development of atopic sensitization, hay fever and asthma. Using the Oslo birth cohort (219) of 2,531 children, it was reported that exposure to cats in early life was associated with a reduced risk of developing asthma (aOR 0.7; 95% CI 0.5, 1.1) and allergic rhinitis (aOR 0.6; 95% CI 0.4, 1.0) at age 4 years. Whereas in the Tucson Children's Respiratory Study (221), a birth cohort of 1,246 children, it was found that children living in households with one or more indoor dogs at birth were less likely to develop frequent wheeze than those not having indoor dogs ( $p=0.004$ ). This inverse association was confined to children without parental asthma (adjusted hazard ratio



0.53; 95% CI 0.34, 0.81) and was not evident for children with parental asthma (adjusted hazard ratio 1.19; 95% CI 0.76, 1.88). A prospective birth cohort (220) in Michigan, recently reported exposure to two or more dogs or cats in the first year of life was associated with a significantly lower risk of atopy (measured by SPT) (aOR, 0.23; 95% CI, 0.09, 0.60) and seroatopy (measured by serum IgE) (aOR, 0.33; 95% CI, 0.13-0.83) at age 6-7 years to HDM, cat, dog and grass allergens. The protective effect of exposure to dogs and cats may not be entirely related to allergen exposure, but possibly confounding lifestyle factors or increased exposure to bacterial endotoxin associated with household pets (223, 224) may also be responsible. The role of endotoxin and atopic disease is discussed in Section 2.3.6.

In addition, other inhalant aeroallergens may play a significant role in the aetiology of asthma. For example, exposure to soybean dust (225-227) can result in a steep increase in acute exacerbation of asthma symptoms, but, overall not causing an increase in prevalence, whereas, allergens such as pollen allergens (grasses, weeds and trees) are associated with hay fever or seasonal and episodic asthma (228, 229) rather than persistent asthma (175, 230).

### **2.2.3 Atopy**

Atopy is a clearly established risk factor for asthma. There has been a long held misconception that the majority, if not all, child asthma is allergic however, Pearce et al., 1999 (194), examined population-based studies, each with at least 600 child subjects, and determined the overall proportion of population-based childhood asthma attributable to atopy is only approximately 38%. The same group assessed the available evidence on the association between allergen exposure and the subsequent risk of asthma at the population level. They concluded that aeroallergen exposure is not a major risk factor for the primary causation of asthma in children (109).

Moreover, atopy cannot be regarded as an environmental exposure (142) as, for example indoor allergen exposure, smoking, and air pollution, which could by itself explain the increases in asthma prevalence. Atopy is a biological response to various exposures (for example, the production of specific IgE antibodies to environmental allergen exposure) which is modified by susceptibility factors (genetic or environmental) and as such should not be considered as a primary causal exposure (109), that is, it is an intermediate on the pathway by which an environmental exposure causes asthma. In addition, standardized comparisons across populations or time periods show only weak and inconsistent associations between the

prevalence of asthma and the prevalence of atopy (194), thereby indicating that the changes in prevalence of asthma are unlikely to be directly linked to changes in atopy. The work of Pearce et al., 1999 (194), is highly important and, if only 38% of child asthma is due to atopy, then the long held misconception that the majority, if not all, child asthma is allergic has probably hampered asthma research. Thus future studies will need to investigate both (i) other mechanisms that may lead to the development of asthma, and (ii) the factors that are responsible for atopic individuals becoming asthmatic.

## **2.2.4 Air Pollution**

### ***2.2.4.1 Outdoor air pollution***

The increase in allergic respiratory diseases, which is observed more in urban than in rural areas, is paralleled by increasing atmospheric concentration of traffic-related air pollutants such as gases, for example sulphur dioxide and ozone, and respirable particulate matter, in particular diesel exhaust emissions (231). A correlation has also been found between increased atmospheric levels of air pollution and increased frequency of mortality for respiratory and cardiovascular diseases (232). These pollutants, besides acting as irritants, increasing airways hyperreactivity and exacerbating symptoms in already allergic subjects (233-236), are thought to be possible causal factors which act to modulate the immune response, with an adjuvant activity on IgE synthesis (231, 237, 238).

The effects of air pollutants on lung function will depend largely on the type and environmental concentration of pollutant, the duration and timing of pollutant exposure and the exposed subjects' predisposition to develop airway hyperresponsiveness. A cross-sectional study in Germany reported that high rates of road traffic diminish forced expiratory flow and increase respiratory symptoms in children (239). Other cross-sectional studies have, however, not reported an increase in the prevalence of asthma in relation to air pollution (176, 240). A case-control study (241) of patients aged 2-64 years, from two general practices in London, UK, showed no increase in risk of asthma needing treatment with living close to busy roads. In children under 16 years of age, the adjusted OR for being treated for asthma when living 150 metres or less from busy roads compared with more than 150 metres from them was 0.96 (95% CI 0.78, 1.22). This study may have failed to demonstrate a causal relationship between exposure to air pollutants and the development of asthma as it reviewed only the place of current residence, and did not consider lifetime residence, particularly during birth and the early infancy

postnatal period. Prospective birth cohorts are still required to fully examine the effect of air pollution.

#### **2.2.4.2 Indoor air pollution**

The effect of different types of indoor air pollutants remains to be fully determined. An association between exposure to household nitrogen dioxide (NO<sub>2</sub>), from heating and/or cooking appliances, and increased respiratory symptoms has been reported in several studies (242-244). In the Tasmanian birth cohort, living room gas heater use in infancy was associated with subsequent child asthma (aRR 1.92; 95% CI 1.33, 2.76) and indoor pollutants from gas combustion were found to increase the risk for HDM sensitization (aRR 1.98; 95% CI 1.04, 3.79) at age 7 years (245). In an earlier prospective study of 6-11 year old Australian schoolchildren, Pilotto et al., 1997 (244), reported significant dose-response relationships between exposure to NO<sub>2</sub> and mean rates for respiratory symptoms such as cough with phlegm (p=0.04).

#### **2.2.5 Environmental Tobacco Smoke**

The extent to which parental cigarette smoking, either before or after birth, influences the development of atopy has been extensively discussed and it appears to have little, if any, impact (246). A review of observational studies (247) up to 1999, that reported IgE, skin prick positivity, hay fever or eczema (considered separately from asthma), failed to find a positive association of exposure to environmental tobacco smoke (ETS) on allergic sensitization. A subsequent study (248), in the Isle of Wight supported the review's conclusions: in a birth cohort of 1,218 children neither maternal smoking during pregnancy or after birth increased aeroallergen sensitization or the development of respiratory allergic disease at age 4 years (248).

However, there is now substantial evidence from studies in both human infants and animal models, to suggest that foetal exposure to active maternal smoking during pregnancy adversely affects infant lung function (249). Maternal smoking during pregnancy results in structural and hence functional changes to the developing lung, such that exposed infants have small airways at birth (249). A number of studies have documented that exposing the foetus to tobacco smoke during gestation leads to reduced lung and airway function (250-252), airway obstruction (250, 252), and airways hyperresponsiveness (253) in the newborn period. Together these alterations

in lung and airway function, and their persistence throughout infancy, suggest that exposure to products of tobacco smoke during foetal life and early postnatal life, a time of extremely rapid lung development, may have long lasting consequences for airway and lung structure and function (249), with suggestion that forced expiratory flows are reduced on average by approximately 20% in infants whose mothers smoke (249).

A systematic quantitative review (254) up to April 1997, of the evidence relating parental smoking to the prevalence of respiratory symptoms in school-age children concluded that there was a causal relationship between parental smoking and asthma (pooled OR 1.21; 95% CI 1.10, 1.34, for either parent smoking). Moreover, several more recent cross-sectional studies (136, 255-258) have consistently reported an association between parental smoking and increased prevalence of asthma and wheezing in childhood. Studies using objective measures of lung function have also showed, in children exposed to ETS, an association with decrease in airway calibre and an increase in airway responsiveness (259). A meta-analysis (260), up to April 1997, of the relationship between BHR as assessed by challenge test, and exposure to ETS (largely maternal smoking) in 10 population samples suggests a small but real increase in BHR amongst the children of smoking mothers (OR 1.29; 95% CI 1.10, 1.50).

There are accepted difficulties using epidemiological studies (247) in separating the effects of pre and postnatal smoke exposure as most parents who smoke during pregnancy continue to do so thereafter (249). It has been estimated that 90% of mothers who smoke during pregnancy still do so 5 years later (261). However, several cross-sectional (262, 263), longitudinal (264) and prospective birth cohort (56, 245, 265) studies have reported a positive association between maternal smoking during pregnancy or very early infancy and child asthma. The Southern California Children's Health Study (263) investigated the exposure of maternal smoking during pregnancy on asthma in 5,762 school-age children. In utero exposure to maternal smoking without subsequent postnatal ETS exposure was associated with increased prevalence of physician-diagnosed asthma (OR 1.8; 95% CI 1.1, 2.9). Current ETS exposure was associated with wheezing, but not physician-diagnosed asthma. It was concluded that ETS operates as a co-factor with other environmental factors, such as intercurrent infections, as a trigger of wheezing attacks, rather than as a factor that induces asthma; whereas in utero exposure acts to increase physician-diagnosed asthma (263).

In 15,712 children who were part of a British birth cohort (56), maternal smoking during pregnancy was an independent determinant of wheeze (OR 1.39; 95% CI 1.22, 1.58) at age 5

years. The effects of either exposure to smoking during pregnancy or at 5 years of age were similar, both exhibiting a dose-related association with cumulative wheeze, but in mothers for whom both of these smoking measures were known, smoking during pregnancy was slightly more strongly related (56). In the Tasmanian birth cohort, early infant exposure to ETS at one month of age was shown to be positively associated with child asthma (245). In smoking households, infant exposure to smoking in the same room was associated with increased asthma at age 7 years (aRR 1.52; 95% CI 1.01, 2.29). However, for infants living in non-smoking households, exposure to any smoking in the same room did not predict asthma (56).

Thus, observational studies have provided considerable evidence for the adverse role of parental smoking and child asthma. RCTs will be able to address the effects of reducing exposure to ETS. In addition, future studies distinguishing the role of prenatal versus postnatal exposure in the aetiology of asthma are required to inform public health prevention programs.

### **2.2.6 Heredity**

A history of asthma in the immediate family is the best recognized risk factor for asthma and has been reported in a large number of epidemiological studies (266, 267). A recent study (266) in 306 children (median age 3.5 years) from 217 Boston families with at least one parent with physician-diagnosed "asthma, hay fever or allergies", found that the multivariable OR for childhood asthma when the mother had asthma was 4.1 (95% CI 1.7, 10.1); for paternal asthma, 2.7 (95% CI 1.0, 7.2). However, as discussed in Section 1.3, there is strong evidence suggesting that asthma is a polygenic trait, where maternal phenotype may have a greater influence than paternal phenotype on child atopic disease, and recognition of the different phenotypes will assist the gene hunt.

## **2.3 THE HYGIENE HYPOTHESIS**

It is evident that the putative risk factors, discussed in Section 2.2, for the development of asthma probably cannot fully account for either the worldwide increase in prevalence or the international variations in prevalence that have been observed. Epidemiological studies have identified additional environmental and lifestyle factors that may be either a risk or protective factor for the development of asthma. In an endeavour to explain the rise in the inverse association between

family size and hay fever, the “Hygiene hypothesis” was proposed by Strachan in 1989 (268). The Hygiene hypothesis postulates that infection, bacterial and viral, protects against atopy. In summary, this stated:

*“These observations ...could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally ...Over the past century declining family size, improved household amenities and higher standards of personal cleanliness have reduced opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic disease.” (268)*

Bacterial and viral infections are known to influence cytokine levels, potentially suppressing the Th2 immune responses involved in IgE mediated allergy and probably determining the phenotype of the subsequent specific Th1 response (269) (see Section 1.5.1). Early life environmental exposure to such infections is hypothesized to cause an infant’s immune system to shift away from its Th2 profile thereby diminishing the likelihood of the development of a clinical allergic diathesis. As a corollary, it was hypothesized that changes to infant diets, early use of antibiotics, and reduced exposure to bacterial products predispose to the persistence of Th2 responses in childhood (270). The decline in cross-infections within young families caused by decrease in family size and improvement in hygienic standards is, among the set of characteristics of the western lifestyle, possibly responsible for the increase of atopy prevalence (271). Many epidemiological studies have consistently demonstrated that factors that are surrogates or indirectly related to early childhood infections are associated with the prevalence of atopy and asthma. These factors are discussed in the following sections and include family size, use of day care centres, use of antibiotics, immunizations, endotoxins, and a rural lifestyle.

### **2.3.1. Large family size; sibship; and birth order**

Strachan, 1989 (268), hypothesized that the sibling effect could be explained as a protective effect of childhood infections on the development of atopy. The Hygiene hypothesis interprets the variation in allergy risk with family size as a reflection of differential exposure to infection acquired in childhood from contact with siblings. The negative association between the number of siblings (older siblings being more influential (272)) and the development of atopic disorders was first demonstrated by Strachan: children who come from large families are at a decreased risk of having hay fever (268). The British National Child Development Study, a birth cohort, found that at age 11 and 23 years, hay fever was inversely related to the number of children in the

household at age 11 years. The number of older siblings had a more powerful independent effect on the prevalence of atopy than did the number of younger siblings. Strachan reported that the negative association of the number of older siblings (birth order) with atopic disease was more important than the negative association of the number of younger siblings with atopic disease, and postulated that high rates of infection in those exposed to other children, particularly those exposed to older children, may confer some protection against hay fever and eczema (268).

Many studies have shown an inverse association of family size with objective measures of allergic sensitization such as SPTs or circulating levels of aeroallergen-specific IgE (273). Children of large families have an increased risk of early respiratory infection (274). Firstborn children are often exposed to common infections after their enrollment in kindergarten or school, whereas children born subsequently are often exposed much earlier, through their siblings. Thus, having more siblings may be associated with an increased exposure to viral infections early in life (275). The Tasmanian birth cohort (276) reported that a history of upper respiratory tract infection (URTI) in infancy was associated with family size (aOR 1.17; 95% CI 1.05, 1.31).

Many other population studies have also identified a sibling effect on atopy using objective measures such as SPTs (272, 277, 278) and/or specific IgE levels to aeroallergens (279-281). Moreover, studies have identified a sibling effect on asthma and wheeze (57, 276, 282, 283). A cross-sectional survey (278) among school children aged 9-11 years in Germany, found that the prevalence of atopic sensitization (as measured by SPT) decreased linearly with increasing number of siblings (OR 0.96 for one sibling, OR 0.67 for five or more siblings;  $p=0.005$ ). And, recently, the Detroit Childhood Allergy Study, a birth cohort (280), reported that first-born children were at a higher risk of allergen-specific IgE (OR 1.92; 95% CI 1.16, 3.18) and positive SPT at 6 years of age (OR 1.68; 95% CI 1.02, 2.75). A population-based study (279) in the Netherlands, also reported that in families with a parent with asthma, children with more siblings (both older and younger) were less likely to have positive specific IgE to common aeroallergens (aOR 0.73; 95% CI 0.56, 0.97).

Two cross-sectional studies, one in the UK and one in Australia, have reported an association between siblings and asthma. A large UK study (282) of 11,924 family sets, found in children aged 5-11 years that three or more siblings compared with no siblings was highly inversely associated with a child's asthma or wheezing (OR 0.5; 95% CI 0.4, 0.6). And, in children aged 3-5 years from Wagga Wagga and Lismore, New South Wales, having three or more older siblings

decreased the risk of recent asthma (aOR 0.16; 95% CI 0.04, 0.71), but no effect was found for having less than 3 older siblings (283).

Birth cohorts have reported similar findings. The Tasmanian birth cohort (276) found family size at birth showed a per sibling association (aOR 0.86; 95% CI 0.74, 0.99) with hay fever but not with asthma. However, in contrast, family size at age 7 years was inversely associated with asthma (aOR 0.82; 95% CI 0.72, 0.92) and hay fever (aOR 0.82; 95% CI 0.71, 0.96). Increased household density was also associated with a higher risk of early URTIs (aOR 1.77; 95% CI 1.07, 2.94) but not for lower respiratory tract infections (LRTIs). The apparent protective effect of large household size and asthma could not be explained by an increase in reported early respiratory illness. A history of early respiratory illness, although prospective, was based on parental interviewing and the possibility of selection bias must be considered. The first year of life may not be the most critical time for the protective effect of large household size to be mediated in relation to asthma, but this effect had occurred by the 7<sup>th</sup> year of life (276). A dose-response trend for asthma was reported for children aged 6-13 years followed since birth in the Tucson Children's Respiratory Study (57). The presence of one or more older siblings at home protected against the development of asthma (aRR for each additional older sibling 0.8; 95% CI 0.7, 1.0).

These studies have demonstrated that family size plays an important role in the development of atopic disease. However, the importance of the number of older siblings versus overall family size, the critical period for effect of family size on atopy and the biological basis for the effect remain unclear. A recent review (273) in 2002, of 53 studies from 1965, strongly supported the "protective" effects of having a higher number of siblings for the risk of atopic eczema, asthma, hay fever and allergic sensitization. For eczema, 10 of 11 studies reported an inverse association with number of siblings (weighted OR = 0.66), 22 of 31 studies on asthma (weighted OR = 0.93), all 17 studies on hay fever (weighted OR = 0.56), and 14 of 16 studies on allergic sensitization (weighted OR = 0.62). The authors concluded however, that despite epidemiological support, there was no comprehensive biological explanation for this "protective" effect of a higher number of siblings and that the causal nature of the effect was not adequately explained by the "Hygiene hypothesis"; other alternative explanations may include in utero programming or endocrine effects (273).



### 2.3.2 Day Care Centres

A similar effect to sibship may be expected from exposure to children outside the home. Family and sibship size have decreased in many westernized countries (57, 284) where the percentage of older children may be far greater than for infants (57). Increased child-to-child contact occurs in day care centres and in western countries, the number of working mothers has increased and more children are attending day care outside of the home (285) with exposure from early in life. Moreover, there is evidence that attendance at day care centres during the first 3 years of life increases the risk of respiratory infections when compared with those children who remain at home (285-291). In a retrospective cohort study of 1-7 year old children in Finland, attendance at day care centres increased the risk of respiratory infections (common cold aRR 1.69; 95% CI 1.43, 2.01) in children under 2 years of age (290).

Attendance at day care before age 2 years has been shown in cross-sectional (292, 293) and longitudinal studies (280) to be inversely associated with atopy, as defined by a positive SPT. In addition, in children from large families (more than 3 members), age of entry to day care had no effect on atopy (292). In a cross-sectional study (292), 2,471 children were examined in three age-groups (5-7, 8-10, and 11-14 years) from 3 towns in eastern Germany. In children from small families (up to three people), the prevalence of atopy (measured by SPTs and IgE) was higher among children who started to attend day nursery at an older age than in those who started to attend at a younger age ( $p < 0.05$ ). Compared with children who first attended day nursery at age 6-11 months, the adjusted ORs for a positive SPT were 1.99 (95% CI 1.08, 3.66) for children who attended at age 12-23 months and 2.72 (95% CI 1.37, 5.40) for those who attended at age 24 months and older. In children from large families (more than three people), age of entry to day nursery had no effect on atopy. These findings accord with the hypothesis that early infection may protect against allergies in later life (292). The Detroit Childhood Allergy Study (280) similarly found that early day care use (before 1 year of age) was associated with a decreased risk of seroatopy (OR 0.57; 95% CI 0.34, 0.96).

In a prospective birth cohort (285) of 1,268 Minnesotan children followed up to 2 years of age, day care centre attendance was found to be an important risk factor for LRTI in young children (rate ratio 2.0; 95% CI 1.7, 2.2) and was associated with a 3-fold risk of having recurrent wheezing illnesses. The results in this study may have identified early transient wheeze in this

young age group. Other studies have found an inverse relationship between attendance at day care centres and child asthma (57).

The Tucson Children's Respiratory Study (57), distinguished between prevalence of wheezing disorders, which may be the sub-group of children born with smaller airways in whom wheezing does not persist, or those whose wheezing illnesses appear to represent the early onset of asthma (52, 294) (see Section 1.3.2.1) and incident diagnoses. The attendance at day care during the first six months of life protected against the development of asthma (aRR 0.4; 95% CI 0.2, 1.0). Children with more exposure to other children at home or at day care were more likely to have frequent wheezing at the age of 2 years than children with little or no exposure (aRR 1.4; 95% CI 1.1, 1.8) but were less likely to have frequent wheezing from the age of 6 years (aRR 0.8; 95% CI 0.6, 1.0) through the age of 13 years (aRR 0.3; 95% CI 0.2, 0.5).

Thus, attendance at day care centres during infancy is a risk factor for wheezing associated with LRTI early in life, but it appears to protect against wheezing associated with atopy later in childhood. These findings show the importance again of considering asthma phenotype with increased precision in that the association with wheeze differed by age of onset.

### **2.3.3 Early respiratory infections and subsequent atopic disease**

The early epidemiologic studies in Papua New Guinea (295) reported that respiratory infections were more common among young children in the Highlands, where asthma prevalence was exceedingly low, than in the coastal regions of the country, where asthma occurred more frequently. However, such ecologic findings do not provide strong evidence. Since that time, several cross-sectional and prospective studies have reported that early respiratory infections may be associated with atopic disease, including asthma (276, 296-298). The Oslo Birth Cohort Study (299) found a positive association between children with LRTIs during infancy and asthma at 4 years of age (aOR 3.4; 95% CI 2.3, 7.0). The risk of current asthma was, however, inversely related to older siblings after controlling for early respiratory infections. LRTIs in the first year of life were associated with an increased risk of current asthma (aOR 3.84; 95% CI 2.82, 5.24 for two or more illnesses) but not atopy in the Western Australia Pregnancy Cohort Study. This association was evident for both non-atopic and atopic asthmatics (300).

Episodes of rhinitis early in life may also protect against the development of asthma. In the German Multicenter Allergy Study (301), compared with children with one or less episode of runny nose before the age of 1 year, those with 2 or more episodes were less likely to have a doctor's diagnosis of asthma at age 7 years (OR 0.52; 95% CI 0.29, 0.92) or to have wheeze at age 7 years (OR 0.60; 95% CI 0.38, 0.94), and were less likely to be atopic, determined by IgE concentrations to various allergens, before the age of 5 years. Similarly, having one or more viral infection of the herpes type in the first 3 years of life was inversely associated with asthma at age 7 years (OR 0.48; 95% CI 0.26, 0.89). However, repeated LRTIs in the first 3 years of life showed a positive association with wheeze up to the age of 7 years (OR 3.37; 95% CI 1.92, 5.92 for 4 or more infections vs 3 or less infections) (301). The authors concluded that repeated viral infections other than LRTIs early in life may reduce the risk of developing asthma up to school age (301). A random sample of more than 15,000 school children in Germany, using the ISAAC protocol, found asthmatic children with recurrent early childhood infections as assessed retrospectively by parental questionnaires, were at a lower risk of being symptomatic at school age (302). When considering atopic and non-atopic asthmatic children separately, the highest risk of asthma with repeated early childhood infections was found for non-atopic asthma (OR 24.29; 95% CI 11.86, 49.76). The authors concluded that a sub-group of children with a triggering or inducing of asthmatic symptoms through repeated early childhood infections may exist within the "asthma syndrome" which has a better prognosis and is less related to the atopic phenotype (302).

In summary, these studies have provided conflicting results on the relationship between early infections and asthma. However, the relationship between early respiratory infections and atopy depends on a number of factors including timing, anatomical site, dose, protractedness, exposure to other infections, and host characteristics (303), including genetic predisposition (302), as well as the stage of immunological development and type of infection.

### **2.3.4 Intestinal flora and antibiotics**

Recent retrospective and cross-sectional studies have reported an increased risk of asthma and atopic disease associated with the use of antibiotics in infancy (302, 304-308). There is, however, the possibility of disease misclassification in the determined prevalence of current asthma and also misclassification with parent recall of their child's wheeze and antibiotic use. Both the frequency and age at the time of antibiotic use may be important in the subsequent

development of asthma. A retrospective study (305) in Oxfordshire, UK, found that oral antibiotic treatment for any clinical indication in the first two years of life was the strongest predictor of subsequent atopic disorders (asthma, hay fever or eczema), (aOR 2.07; 95% CI 1.64, 2.60). In some studies (305, 308), this association was dose-dependent with atopic disorders increasing with the number of antibiotic courses received in the first two years of life. A cross-sectional study (306) in 5-10 year old children at Rudolf Steiner <sup>1</sup> schools in New Zealand, found a strong association for asthma (OR 4.05; 95% CI 1.55, 10.59) if antibiotics were used in the first year of life and a lesser association (OR 1.64; 95% CI 0.60, 4.46) if antibiotics had been used only after the first year of life when compared with children who had never used antibiotics.

The bacterial flora of the gastro-intestinal tract (GIT) plays an important role in maintaining the integrity of the enterocyte, modulating metabolic and immunologic processes, and protecting against colonization by invasive pathogens (309, 310). Confrontation with microbial pathogens through stimulation via indigenous microflora colonizing the infant GIT drives the postnatal maturation of the mammalian immune system (310-312). It is hypothesized that exposure to commensal microflora of the gut, that promote normal immunity in early life, is disrupted or diminished by antibiotic use (313), which alter the stable gut flora by promoting the colonization of pathogenic bacteria (309). Oyama et al., 2001 (314), using a mouse model, showed that neonatal antibiotic use induced a Th2-skewed response with increased serum levels of total IgG1 and IgE, enhanced in-vitro IL-4 secretion and reduced in vitro IFN- $\gamma$  secretion. These results suggested that antibiotic use during infancy may disturb the intestinal microflora and thereby prevent postnatal Th1 cell maturation, thus resulting in a Th2-polarized immune deviation (314). This same group of researchers subsequently showed, again using murine models, that adequate probiotic intervention after antibiotic treatment may improve the intestinal ecosystem and thereby prevent the Th2-shifted immunity induced by neonatal antibiotic use (315).

In retrospective studies, these findings of an association between antibiotic use in early life and asthma may be due to recall bias and/or reverse causation, that is, the use of antibiotics may be the consequence of an increased occurrence of respiratory infections in children having asthma. To explore this, a cross-sectional study (304) in Belgium, reported that children who received antibiotics in their first year of life are at risk of subsequently developing asthma (aOR 1.7; 95% CI 1.0, 3.1) and allergic diseases at age 7 and 8 years, but this increased risk was only found in children who are genetically predisposed to atopic immune responses. These results suggested

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<sup>1</sup> Steiner schools follow an anthroposophic lifestyle: use antibiotics restrictively, have few vaccinations, and their diet usually contains live lactobacilli, which may affect the intestinal microflora.

that the use of antibiotics in early childhood may affect the immune system in the presence of a genetically determined tendency towards atopic (Th2-like) responses. However, the Tasmanian birth cohort (276) and a prospective birth cohort (316) in Boston, USA, have subsequently reported that among children with a familial history of atopy, the use of oral antibiotics in the first year of life was not associated with recurrent wheezing, asthma, allergic rhinitis, or eczema at age 5 years (316), supporting possible reverse causation as an explanation of the previously reported link.

### **2.3.5 Immunizations**

Epidemiologically, several of the common infectious diseases of childhood provide the opportunity to explore the temporality of the exposure-response relationship. The proportion of children contracting pertussis, measles and mumps has reduced substantially in the developed world as a result of the introduction of vaccines. With the exception of mumps, this reduction in these infectious diseases occurred prior to the earliest reports of increases in the prevalence of allergic disease (317). Immunization could possibly have either positive or negative effects on the incidence of allergic disease. Three theoretical reasons for a possible association of asthma with vaccination have been recently proposed by DeStefano et al., 2002 (318) : (i) vaccines or their adjuvants may have direct IgE-potentiating effects; (ii) vaccination may directly stimulate Th<sub>1</sub> immunity; and (iii) vaccination may reduce the burden of infection in early childhood.

Positive associations with pertussis vaccination and atopic diseases have been reported in a small number of studies (305, 319-321). In the Christchurch Health and Development Study, a birth cohort, none of the non-immunized children developed asthma by the age of 10 years compared with nearly one quarter of the immunized children (321). There were limitations to the study however, as the number of non-immunized children was small (23 of 1,265 subjects) and the differential use of health services, leading to different rates of asthma detection, could not be excluded (321). A retrospective birth cohort in Oxfordshire (305) reported a statistically significant association between pertussis immunization and asthma (OR 1.44; 95% CI 1.17, 1.85). However, the possibility of confounding effects and reverse causation could not be excluded (305). Two other studies, one in the UK (319) and one using the USA Third National Health and Nutrition Examination Survey (320), also reported an association but these were cross-sectional surveys and may be subject to recall bias.

Methodologically stronger studies have not shown any association between pertussis immunization and atopic disease. In a RCT in Sweden (322), 669 children were evaluated for the development of atopic disease, including asthma, from age 2 months to 2.5 years. The incidence of asthma, and other atopic diseases, was similar in the groups of children who received whole-cell pertussis vaccine, acellular pertussis vaccines and placebo (diphtheria-tetanus only). The Avon Longitudinal Study of Parents and Children cohort in the UK, found no increased risk for wheezing illnesses associated with pertussis immunization in young children from birth to 42 months of age (323). The most recent study (318) evaluated the suggested association between childhood vaccinations and risk of asthma in a birth cohort to 6 years of 167,240 children enrolled in four health maintenance organizations in the USA. In this study 11% (18,407) children developed asthma. The relative risks of asthma were: 0.92 (95% CI 0.83, 1.02) for diphtheria, tetanus and whole cell pertussis vaccine; 1.09 (95% CI 0.9, 1.23) for oral polio vaccine; 0.97 (95% CI 0.91, 1.04) for measles, mumps and rubella (MMR) vaccine; 1.18 (1.02, 1.36) for *Haemophilis influenzae* type b (Hib); and 1.20 (95% CI 1.13, 1.27) for hepatitis B vaccine. These weak associations observed for Hib and hepatitis B vaccines seemed to be explained by health care utilization or information bias (318).

The immune responses to measles and measles vaccine are complex, involving both Th1 and Th2 responses (318) and studies have provided conflicting results. Shaheen et al., 1996 (324), in a historical cohort study of 262 young adults from Guinea-Bissau found that children with a documented history of measles infection, before 6 years of age, were less atopic, as measured by positive allergen-specific skin test (OR 0.36; 95% CI 0.17, 0.78) than children who did not contract measles (usually because they have been immunized). However, in a very large cross-sectional nationwide study (325) in Finland of 547,910 individuals, a statistically significant association between measles infection and atopy at all ages was found. The age-adjusted prevalence ratio among those who had had measles compared with those who had not was 1.67 (95% CI 1.54, 1.79) for asthma (325). Whereas a retrospective birth cohort in the UK (305) and the birth cohort from the four US health maintenance organizations (318) did not find that children immunized for measles were at an increased risk of developing asthma compared with non-immunized children.

Shirakawa et al., 1997 (303), reported an inverse association between positive tuberculin responses and atopic disorders among Japanese children, suggesting that BCG immunization may influence the Th lymphocyte balance, resulting in decreased atopy. This inverse relation, however, has not been confirmed by three other studies (326-328). Significant inverse correlation

between national tuberculosis notification rates, from the World Health Organization, and the prevalence of asthma symptoms in subjects from the ISAAC have been reported (329). An increase in tuberculosis notification rates of 25 per 100,000 population was associated with an absolute reduction in the prevalence of wheeze ever of 4.7%. However, a major limitation of this ecologic analysis (where the analyses has been based on countries rather than individuals) for making causal inference is ecological bias (330), which is the failure of expected ecologic effect estimates to reflect the biologic effect at the individual level.

### **2.3.6 Endotoxins: a rural versus urban lifestyle**

Endotoxin, a component of the cell wall of gram-negative bacteria, is a potent pro-inflammatory agent and causes reversible airway obstruction in subjects with established asthma (331). However, bacterial endotoxins are also potent inducers of the Th1 cytokines IFN- $\gamma$  and IL-12 which inhibit the proliferation of Th2, thereby having the potential to decrease allergen sensitization in cells (224, 332). It has been postulated that exposure to endotoxin at a critical time might shift the developing immune system to a predominantly Th1-type responsiveness, thus protecting against asthma and allergies (270, 333) (see Section 1.5.1).

Endotoxins are ubiquitous in nature, being found abundantly in stables where pigs, cattle and poultry are kept, and they are also present in normal urban indoor environments as a constituent of house dust with significant positive associations found between house dust endotoxin levels and household pets (cats and dogs) (334-337). In comparison to children from non-farming families, farmer's children are exposed to higher concentrations of endotoxin both in stables and in dust from kitchen floors and mattress (338-342) and several studies have examined the possible protective effects of a farming environment against asthma in children. Children from farm environments, where endotoxin levels are higher (340), are reported to have a significantly decreased risk of developing atopy and asthma (341-348) than children from a non-farming environment. However, this protective effect has also been observed in children from non-farming households where there are high mattress endotoxin levels (342).

Endotoxin has been considered as a potential marker for a lower hygienic level (335) and as such several studies have supported the Hygiene hypothesis by reporting that exposure to high concentrations of endotoxin very early in life is related to an increased prevalence of non-specific respiratory diseases. A German prospective cohort (337) of infants at high risk for developing

asthma found that during the first six months of life, the risk for non-specific respiratory infections was increased (OR 1.69; 95% CI 1.25, 2.28) by exposure to high concentrations of endotoxin in dust from the mother's and child's mattresses.

A study in the USA, measuring allergen sensitization by SPT in 61 infants at risk for asthma (aged 9-24 months) reported that allergen-sensitized infants had significantly lower house dust endotoxin levels than non-sensitized infants (mean 468 vs 1035 EU/ml, respectively;  $p=0.01$ ) (224). A recent cross-sectional study (342), found that endotoxin levels in a child's current mattress were inversely related to the occurrence of hay fever, atopic asthma and atopic sensitization in 6-13 year old children in rural Germany, Austria as well as Switzerland. Non-atopic wheeze and asthma was not significantly associated with the endotoxin level. Atopic asthma was inversely associated (OR 0.42; 95% CI 0.18, 0.96) with exposure to farming during the first year of life and also current endotoxin exposure (OR 0.52; 95% CI 0.30, 0.90) (342). Litonjua et al., 2002 (218), undertook a longitudinal analysis of childhood wheezing in a birth cohort in Boston, USA, in children from allergic or asthmatic parents. In that study, 226 children (<5 years of age) were followed over a 4-year period and an increased risk for wheeze was associated with high levels of house dust endotoxin early in life which rapidly decreased over time (Test for trend,  $p=0.005$ ), suggesting that exposure to endotoxin might protect against further episodes of wheezing as the children get older (218). Wheezing episodes of older children are more often associated with an atopic phenotype and the results of these two studies may be interpreted as a possible protective effect of endotoxin on atopic wheeze.

The epidemiological associations of environmental endotoxin exposure in early life reported in these studies are consistent with the Hygiene hypothesis associations of other microbial exposures or infections with a lower incidence of atopic disease. Endotoxin may be a factor in both atopic and non-atopic asthma. However, the timing of endotoxin exposure may be important. Douwes et al., 2002 (349), recently reviewed studies of endotoxin exposure and atopy; endotoxin and asthma; and, farming and asthma; concluding that exposure to environmental endotoxin might prevent the primary causation of allergic asthma, but it may be both a primary and secondary cause of non-allergic asthma, in particular in the aetiology of occupational asthma caused by organic dust exposure. Moreover, farming per se is not always linked to a reduced risk of allergy, and exposure of farmers to storage mites, pesticides, herbicides and disinfectants have all been implicated either directly or indirectly as potential causes of asthma (350).



## **2.4 RISK AND PROTECTIVE ENVIRONMENTAL FACTORS NOT WITHIN THE HYGIENE HYPOTHESIS**

In addition to factors that are explained solely by the Hygiene hypothesis, there are several other risk and protective factors that have been associated with the development of asthma. These are discussed briefly in the following Sections.

### **2.4.1 Breastfeeding**

The literature regarding the relationship between infant breastfeeding and the development of childhood asthma is conflicting. In 1988, Kramer (351) suggested that previous studies assessing the relation between breastfeeding and the development of atopy and asthma were methodologically flawed. Several more recent birth cohort studies (352-357), with follow-up periods ranging from 2–17 years, have shown protective relationship between breastfeeding and the development of allergy, allergic symptoms, wheezing illness and asthma; though other studies (358, 359) have failed to confirm this, reporting that breastfeeding increases the risk of childhood asthma. The longitudinal Dunedin Multidisciplinary Health and Research Study (359) assessed respiratory history, function and SPTs in 1,037 children every 2-5 years from ages 9 to 26 years; each child's history of breastfeeding had been independently recorded in early childhood. Children who were breastfed were more likely than those who were not breastfed to have current asthma with AHR or current wheeze with AHR at all ages up to 21 years with one exception (at age 15 years). Generalised estimating equations, allowing for repeated measures analysis, showed that children (aged 9-21 years) who were breastfed were more than twice as likely as those who were not breastfed to have wheeze or current asthma (OR 2.09; 95% CI 1.42, 3.08) (359). Whereas, the Western Australian Pregnancy Cohort Study (352) found exclusive breastfeeding for at least 4 months was associated with a significant reduction in the risk of physician-diagnosed childhood asthma at age 6 years (OR 1.31; 95% CI 1.05, 1.64). In Sweden, a birth cohort (357) of children up to 2 years of age reported that exclusive breastfeeding for 4 or more months reduces the risk of asthma (OR 0.66; 95% CI 0.51, 0.87). In that study, the group of children that benefited the most from breastfeeding were those with a parental history of atopic disease independently of maternal asthma.

The issue regarding whether infants of asthmatic mothers should be breastfed has created further controversy. The Tucson Children's Respiratory Study (360) found the relationship between

breastfeeding and asthma or recurrent wheeze varies with the age of the child and the presence or absence of maternal asthma and atopy in the child. Exclusive breastfeeding for  $\geq 4$  months within the first 2 years of life was associated with significantly lower rates of recurrent wheeze (OR 0.45; 95% CI 0.2, 0.9), irrespective of maternal asthma or atopy in the child. Whereas breastfeeding was associated with an increased risk of asthma beginning at the age of 6 years, but only for atopic children with asthmatic mothers (360). But, the Western Australian Pregnancy Cohort Study (361) found a consistent protection conferred by exclusive breastfeeding against current asthma in children aged 6 years with asthmatic mothers. Breastfeeding was associated with lower rates of asthma in children of asthmatic mothers and in both atopic and nonatopic children. Exclusive breastfeeding for less than 4 months, compared to children exclusively breastfed  $\geq 4$  months, was a significant risk factor for current asthma (aOR 1.35; 95% CI 1.00, 1.82), and this risk was not altered by atopy or maternal asthma status.

Unlike a RCT, these observational studies have been hampered by difficulties in classifying breastfeeding, notably between exclusive breastfeeding and being breastfed, confounding and other biases. The first randomized trial (362), conducted in Belarus as part of PROBIT, the Promotion of Breastfeeding Intervention Trial, was able to assess the role of breastfeeding duration and exclusivity on atopic eczema, gastrointestinal and respiratory infections. Infants from the intervention sites were significantly more likely to be breastfed and had a significant reduction of atopic eczema in the first 12 months (aOR 0.54; 95% CI 0.31, 0.95). The study did not report on any associations with asthma or atopy.

Breastfed and formula fed infants differ in the development of the intestinal flora considered of importance for protection against harmful microorganisms and for the maturation of the intestinal immune system. Thus, a possible mechanism related to the Hygiene hypothesis through which the protective effect of breastfeeding may operate is the establishment of normal intestinal flora. Harmsen et al., 2000 (363) found that the components of the faecal samples from breastfed infants were mainly lactobacilli and streptococci while samples from formula-fed infants often contained staphylococci, *Escherichia coli* and clostridia. Any effect of breastmilk to protect from atopic disorders could be the result of a reduced exposure to alimentary allergens in early life. Breastmilk contains immunodulatory and anti-inflammatory factors that protect against allergic sensitization and influence the development and maturation of the infant's immune system after birth (364, 365). These immunological properties of breastmilk neutralize foreign proteins to prevent catching infections, to produce a favourable intestinal flora, and to induce tolerance (366).

## 2.4.2 Diet

Temporal patterns indicate that changes in diet may be associated with the increase in asthma (367). Westernization has resulted in a change in diet for many population groups with an increase in the amount of polyunsaturated fat and a fall in saturated fat, a decrease in fresh vegetables and fruits, containing antioxidants and magnesium, and an increase in vegetable oils and margarine, containing omega-6 polyunsaturated fatty acids. There is also evidence for a decrease in the consumption of oily fish which contains omega-3 polyunsaturated fatty acids (368).

Increased intake of unsaturated fatty acids may increase the risk of the development of atopic diseases. The consumption of polyunsaturated margarine and oils, containing omega-6 fatty acids, may promote the formation of IgE from T-cells (369). A small number of epidemiological studies have demonstrated a positive association between polyunsaturated fat intake on atopic disorders in children (123, 283, 369). In Australia, a cross-sectional study of 535 preschool children, reported high intakes of polyunsaturated fats was associated with an increased risk of recent asthma (OR 2.03; 95% CI 1.15, 3.60) (283). Two observational studies (123, 369) reported that butter intake was inversely associated with the development of atopy, suggesting that the relative quantities of saturated fats in the diet may be of importance. Validation of the questionnaire was reported in only one (283) of these three studies. However, even though this type of measurement error will result in a lack of precision, the effect on the results would bias the reported effects toward the null for the dichotomous exposure (330). An ecological study (370) compared the intake of trans fatty acids in 14 European countries to asthma atopy and prevalence from the ISAAC study. A positive association was found between per capita consumption of trans fatty acids and the prevalence of asthma ( $\beta=20.9$ ), allergic rhinoconjunctivitis ( $\beta=8.2$ ) and atopic dermatitis ( $\beta=12.40$ ) (Test for trend,  $p<0.001$ ) (370). One of the strongest relationships in the ISAAC study was reportedly the "McDonalds Index": the more McDonalds outlets in a country, the higher is the prevalence of symptoms (371).

Fish consumption (in the form of omega-3 fatty acids) has demonstrated a protective effect on atopic disorders in a small number of studies (368, 369, 372). In Australia, a population based study of 7-14 year old children (372) found a significant inverse association between regular fish intake ( $\geq$ once a week) and BHR (defined as  $\geq 20\%$  fall in FEV<sub>1</sub> measured by bronchial challenge), with an aOR=0.35 (95% CI 0.10, 0.90) (372). This same research group subsequently reported in a stratified case control study using this same population, that only oily fish ( $>2\%$  fat)

consumption was associated with a reduced risk of current asthma (aOR 0.26; 95% CI 0.09, 0.72) (368). No other food groups or nutrients were associated with a positive or negative risk of current asthma. A recent retrospective case control study in Finland reported that children who develop atopic disease had consumed statistically significantly less fish compared to non-atopic controls ( $p < 0.001$ ) (369). Moreover, a recent RCT, the Childhood Asthma Prevention Study (212, 213) (see Section 2.2.1.8), reported that with a diet intervention containing high levels of omega-3 fatty acids by the mother during her pregnancy, there was a 9.8% absolute reduction (95% CI 1.5, 18.1) in the prevalence of wheeze ever and a 7.8% absolute reduction (95% CI 0.5, 15.1) in the prevalence of wheeze for >1 week in the children at 18 months of age whose mothers had the intervention diet compared with children of the control group of mothers (213). Thien et al., 2004 (373) conducted a Cochrane review of dietary marine n-3 fatty acids (fish oil) supplementation and placebo in 9 RCTs undertaken between 1986 and 2001. No consistent effect on FEV<sub>1</sub>, peak flow rate, asthma symptoms, asthma medication use or BHR was found. Two of the studies were conducted in children. In Australia, Hodge et al., 1998 (374), reported that fish oil supplementation and a diet that increases omega-3 and reduces omega-6 fatty acids in 39 asthmatic children aged 8-12 years over a 6-month period, had no effect on the clinical severity of asthma in these children.

A recent review of epidemiological studies (375) considered the effects of dietary nutrients on asthma. The review concluded there is relatively persuasive evidence that reduced magnesium and vitamin C intake, and increased sodium consumption, may be involved in the aetiology of asthma, though these hypotheses remain unproven (375). However, Cochrane reviews, based on currently available evidence, were not able to conclude whether dietary salt reduction (376) or vitamin C (377) have a specific role in the treatment or management of asthma.

### **2.4.3 Socioeconomic variations**

British birth cohort studies have reported an increased prevalence of atopic disease with higher social classes (378, 379). Socioeconomic variations in the prevalence of allergy are evident not only in western countries such as Britain and the USA (271), but also in the German Democratic Republic before German unification (380) and in urban Ghana (381) where the prevalence of atopy and exercise induced bronchospasm in urban rich in Ghana was significantly higher than in the urban poor or rural children aged 9-16 years,  $p < 0.005$  and  $p < 0.01$  respectively. The variation with parental socioeconomic status is independent of, and more powerful than, the effect of the

child's own socioeconomic status as an adult, and is also independent of family size and birth order (271).

These epidemiological findings add support to the hypothesis that a higher prevalence of early infections, being more common in lower social gradients, could protect against the development of allergic diseases (382). However, the Hygiene hypothesis offers only a partial explanation for the socioeconomic gradient, with a higher prevalence of atopic diseases among children from more affluent families. Correlates of educational status, such as positive health-related behaviour with early presentation to medical care and thus detection of the disease, may cause selection bias towards higher asthma diagnosis in the higher social classes. Socioeconomic status should not be considered as directly causal, but it encompasses environmental influences which may also impact on the risk of an atopic disease and which need to be considered.

#### ***2.4.3.1 Australian indigenous population***

A cross-sectional population study of four remote Australian indigenous communities in Queensland, the Northern Territory and South Australia (383) in 1990/91 found recent wheeze to be low in rural indigenous children: 3.5% (95% CI 0.1%, 6.8%) in children aged 5-7 years and, 1.9% (95% CI 0.1%, 3.7%) among 8-12 year olds. More recent studies, however, have reported a higher prevalence of recent wheeze in indigenous communities. In 1993, a cross-sectional study (384) in an isolated community in northern Western Australia reported a higher prevalence of current wheeze in indigenous female children (<18 years) than in non-indigenous children (24.4% versus 20.4% respectively). Though, the prevalence of recent wheeze in indigenous male children (<18 years) was lower than in non-indigenous males (13.5% versus 30.9% respectively) (384).

Two reported studies which retrospectively reviewed hospitalization for asthma among indigenous and non-indigenous children also provide conflicting results. Williams et al., 1997 (385), comparing Aboriginal and non-Aboriginal hospitalization patterns from 1988 to 1993 in Western Australia, found consistently higher rates of admission for asthma for indigenous than non-indigenous children (1-4 years: RR 2.1 (95% CI 2.0, 2.2); 5-14 years: RR 1.4 (95% CI 1.3, 1.5)). Also, the rates were higher in non-metropolitan than metropolitan areas. Whereas, Whybourne et al., 1999 (386), reviewed the separation data from the Royal Darwin Hospital, Northern Territory, between 1991 and 1997 for children aged 1-9 years, and found that the

hospitalization rate for asthma for indigenous children was significantly lower than for non-indigenous children (rate ratio 0.72; 95% CI 0.59, 0.86). The hospitalization rates were not significantly different between rural and urban indigenous children or between urban indigenous and non-indigenous children. However, hospitalization rates are not a good proxy for prevalence and, as many indigenous communities are remote, a factor that restricts their access to metropolitan facilities, the true accuracy may not be reflected in these results (387).

Moreover, several other studies have reported asthma prevalence rates similar or higher for indigenous populations in non-remote communities. The 1995 National Health Survey (388) collected information from more than 54,000 people of whom almost 1,800 were Aboriginal or Torres Strait Islander (indigenous) descent. Indigenous Australians who live in non-remote areas showed a trend for higher prevalence rates of asthma compared to non-indigenous Australians also living in non-remote regions. Both ethnic groups had a similar age distribution pattern of illness, with a higher prevalence in childhood (388). A cross-sectional study in two non-remote towns in rural New South Wales in 1997, Downs et al., 2001 (389), found that recent wheeze and asthma compared to 27.3% for non-indigenous children (difference 3.7%; 95% CI -4.0%, 11.3%). For asthma, the prevalence was 39.4% versus 39.3% (difference 0.1%; 95% CI -8.0%, 8.2%) for indigenous versus non-indigenous respectively.

Some of the observed differences between these studies may be explained by a lack of standardized methods, such as different questionnaires and different age groups, across these studies. Valery et al., 2001 (387), used the standardized and validated ISAAC questions to address some of these methodological differences in a more recent study of five randomly selected remote communities in the Torres Strait and Cape York Peninsula. This cross-sectional study of 1,650 children aged 0-15 years concluded that the prevalence of asthma in these remote indigenous communities is much higher than previously reported and is comparable to non-indigenous urban centers. Overall, the prevalence of self-reported ever wheezing was 20.6% (95% CI 18.6, 22.6); recent wheeze in the past 12 months 12.4% (95% CI 10.8, 14.0); and ever having asthma 15.8% (95% CI 14.0, 17.6). The authors also reported significant intercommunity differences in prevalence of asthma symptoms even in neighbouring communities; some of these being partially explained by socioeconomic factors such as education and employment status.

A two-stage questionnaire survey conducted in 1999 through 2001 in the Australian Capital Territory, Australia, is the first to examine the prevalence of respiratory symptoms among indigenous children living in major metropolitan environments. Glasgow et al., 2003 (390), using

ISAAC questions, found that urban indigenous primary school children (4-6 years old) had more recent wheeze (21%, OR 1.4; 95% CI 1.0, 2.0) and parent-reported asthma (24%, OR 1.8; 95% CI 1.3, 2.5) than non-indigenous children (both 15%). This higher respiratory morbidity in indigenous children did not appear to be due to factors closely related to the atopic diseases of hayfever or eczema. In addition, rates of ETS exposure were much higher for indigenous children compared to non-indigenous children among the sub-group of children with respiratory symptoms (OR 3.5; 95% CI 2.1, 5.9) (390).

Thus, the majority of these reported studies have demonstrated a high prevalence of recent wheeze in indigenous communities. Peat & Veale, 2001 (391), recently reviewed the burden of respiratory illness in remote and non-remote Australian indigenous communities. They reported that the aetiology of asthma in indigenous communities is not clear, however indigenous communities continue to be exposed to the environmental factors of low immunization rates, low rates of breastfeeding and high rates of cigarette smoking; all factors that may increase the prevalence of asthma (see Sections 2.3.5, 2.4.1 and 2.2.5).

#### ***2.4.3.2 USA urban minority population***

Among African-American children, asthma is more prevalent and more severe than among non-African-American children (392, 393). Yet, Kay, 2001 (394), considered that the Hygiene hypothesis is not easily reconciled with the increased prevalence of atopic asthma among poor black children reported in the Second National Health and Nutrition Examination Survey (395) in the USA, as the living conditions of this population may be expected to be more comparable to those of other economically disadvantaged populations, and which, under the Hygiene hypothesis, would predict a lower burden of atopic disease. However, using the 1988 Child Health Supplement to the USA National Health Interview Survey (393), it was found that the higher prevalence of asthma among black children is not due to race or to low income per se, and that all children living in an urban setting are at increased risk for asthma. Compared with non-urban white children, urban children, both black and white, were at significantly increased risk of asthma: urban and black (aOR 1.45; 95% CI 1.14, 1.86), urban and white (aOR 1.22; 95% CI 1.01, 1.48), whereas non-urban black children were not. African-American children are, however, more likely to live in cities. In the Childhood Allergy Study in Detroit (396), the prevalence of physician-diagnosed asthma was 10% for both African-American and European-American groups, but non-urban middle class African-American children were found to be more reactive to

methacholine ( $p=0.001$ ) and had significantly higher total IgE ( $p=0.001$ ) than European-American children, supporting the hypothesis that African-American children may be predisposed to more severe asthma. The Yale cohort (397) found that African-American children are more likely to receive an asthma diagnosis, after adjustment for symptom frequency and medication use in the first two years of life, than non African-American children.

Thus, the difference in the observed and expected asthma prevalence among African-American children may be related to a number of factors that these children are exposed: premature birth, passive smoking, substandard housing, increased time indoors, decline in physical activity, air pollution, increase in obesity, poor diet, decreased access to health care, exposure to some allergens, less pet keeping, diagnostic bias, and genetic or biologic characteristics (392, 393, 396). Many of these factors may influence asthma severity, possibly resulting in an increased prevalence in this particular group, despite a similar incidence of disease (398).

#### **2.4.4 International variations and westernization**

The unification of Germany provided a unique opportunity to study the impact of East and West European living conditions on the prevalence of respiratory and allergic disorders in two ethnically similar populations over time. In 1991-92, von Mutius et al., 1994 (399), found that atopic sensitization to common aeroallergens, assessed by SPT, was considerably more frequent in West German 9-11 year old children than in their peers in East Germany (36.7% vs 18.2%, OR 2.6; 95% CI 2.3, 2.9). In 1995-96, 5-6 years after the unification, von Mutius et al., 1998 (123), undertook a second similar study in Leipzig, (East Germany) in 9-11 year olds. These children spent their first 3 years of life under eastern German living conditions and were then subsequently exposed to a western lifestyle. The prevalence of hay fever (2.3% vs 5.1%, OR 2.2; 95% CI 1.5, 3.3) and atopic sensitization (19.3% vs 26.7%, OR 1.5; 95% CI 1.3, 1.8) increased significantly between 1992-92 and 1995-96. There was no significant change in the prevalence of asthma, asthma-related symptoms, or BHR. Thus, factors operating very early in life may be particularly important for the acquisition of childhood asthma, whereas the development of atopic sensitization and hay fever may also be affected by environmental factors beyond infancy. This rapid increase in the prevalence of hay fever and atopic sensitization points towards the importance of lifestyle factors.



#### **2.4.4.1 Migrants**

Studies in migrants from developing to developed countries support the aetiological environmental changes associated with westernization. The nature of these environmental changes is obscure, but speculation has focused on increased air pollution or other toxins in the environment, inhalant allergens, increased indoor exposure to HDM allergens in less well ventilated modern homes, dietary changes, high residential density and the use of woollen blankets (400). One factor temporally associated with the rise of atopic diseases is the decline of many infectious diseases in developed countries as the result of improved living standards and immunization programs: childhood respiratory infections that might strongly modify the developing immune system, both systemically and within the lung, include measles, whooping cough and tuberculosis (401).

Children of immigrants have been found in some countries to be at greater risk for developing allergic manifestations than the population in general (400, 402). The prevalence of asthma was studied in Tokelauan children aged 0-14 years (402). Migrant Tokelauan children in New Zealand were found to have a significant increase in the prevalence of asthma, eczema and rhinitis compared to their non-migrant peers living in Tokelau (25.3% versus 11.0%, respectively). For those children examined in New Zealand there was no significant difference in the prevalence of asthma between those children who were born in New Zealand and those who were born in Tokelau.

Immigrants arriving from south-east Asian countries with a low prevalence of asthma, and now living in countries with a high asthma prevalence, such as Australia, reportedly demonstrate an increased risk of asthma and allergic disease (403). The prevalence of atopic disease, including asthma, in Asian immigrants, increased significantly with the length of stay in Australia, independent of age at arrival, sex and atopic status (Test for trend,  $p=0.05$  for asthma;  $p<0.001$  for hay fever) (404).

## **2.4.5 Pre and perinatal risk factors**

The association of perinatal factors with the risk of asthma and atopic diseases has been measured through parental or patient reporting, medical record review or study documentation at birth. Several factors have been identified and are discussed in the following Sections.

### ***2.4.5.1 Gestational age, low birth weight and premature birth***

Many studies have suggested that a history of preterm birth is associated with decreased lung function in childhood (78, 405). In addition, a number of studies have shown that low birth weight and premature birth are important risk factors for subsequent asthma. In a cross-sectional study of 9-11 year old German school children, premature girls (<37 weeks gestation) with a birth weight of 2,500 gm or less, had significantly more current asthma (OR 2.6; 95% CI 1.4, 4.7) and recurrent wheezing (OR 1.7; 95% CI 1.1, 2.7) than term girls (405). These differences were not shown in boys. In a population of 4,795 male conscripts born between 1973 and 1975 in Denmark (406), the prevalence of asthma in male conscripts with a birthweight below 2,501 gm was significantly greater compared with conscripts with a birth weight of 3,001-3,500 gm (aOR 1.5; 95% CI 0.7, 3.1) (406). In the largest study to date, data on 149,398 Swedish male military conscripts (age 17-20 years) was record-linked to the Swedish Medical Birth Register (407). This historical cohort study reported the prevalence rates of allergic rhinitis among those with term birth (>36 weeks), moderately preterm birth (33-36 weeks) and very preterm birth (<33 weeks) as 15.2%, 13.1% and 11.6%, respectively. For those born at less than 33 weeks gestation versus those born between 37 and 41 weeks gestation, the aOR was 0.82 (95% CI 0.68, 0.98) for hay fever. Lower birth weight, less than 2,500 gm (aOR 1.26; (95% CI 1.09, 1.46); and 2,500-3,000 gm ( aOR 1.19; 95% CI 1.10, 1.30), and younger maternal age were both independent risk determinants of asthma, which remained even in the sub-set of asthmatics with hay fever (407).

The prevalence of atopy, however, was not increased in children of preterm birth (405, 408). Therefore, these finding suggest that factors other than atopic sensitization, such as functional airway abnormalities, may increase the risk that wheezing and asthma will develop in prematurely born children. In premature and very low birthweight babies, the aetiology for reversible airway obstruction may be more a function of smooth muscle hypertrophy than atopy (405) (see Section 1.3.2).

Increased gestational age has been reportedly associated with the later development of atopy, but the relationship with subsequent asthma is not well defined. A record linkage study (409) of birth records of 7,862 infants born in a Danish municipality found that children born at 41 weeks gestation had an increased risk of atopic dermatitis compared with children born at 39-40 weeks (aOR 1.32; 95% CI 1.06, 1.63). In a prospective birth cohort of 31 years in Finland (410), an apparent linear association was found between longer gestation and atopy. Children born at 41 weeks or more gestational age were at the highest risk (aOR 1.65; 1.16-2.34). Values were for 39-40 weeks: aOR 1.42 (95% CI 1.02, 1.98); 36-38 weeks: aOR 1.22 (95% CI 0.87, 1.70); and  $\leq 35$  weeks: 1.00 (referent). No associations with gestational age were observed for doctor-diagnosed asthma (410).

The linkage of data from nationwide and population-based registries, as used in some of these studies above, avoids a disease-dependent bias resulting from recall bias in retrospective interviews. However, the analysis is restricted to variables included in the registers and many potential confounding variables, which may perhaps explain the observed effects in the statistical analysis, are often not included.

#### ***2.4.5.2 Head circumference at birth***

A large head circumference at birth may be a marker for enhanced risk of atopic sensitization (411) but currently there is limited epidemiological evidence regarding head circumference and asthma risk. Several studies have reported a significant positive association between large head circumference at birth and atopy (412-414). A New Zealand longitudinal birth cohort (414), the Dunedin Multidisciplinary Child Development Study, found that infants with a head circumference of 37 cm or more at birth had a greatly increased risk of increased total IgE at 11 years of age (aOR 3.4; 95% CI 1.4, 7.9). The relationship was non-linear with a step-up in prevalence in those with a head circumference of more than 37 cm. Recent asthma symptoms were not associated with head circumference (414). However, only one study to date has reported an association between a large head circumference at birth and asthma in childhood. A longitudinal study of a birth cohort (415) in New Zealand, found that children with head circumference at birth of 37 cm or greater had odds of asthma that were 1.8 ( $p < 0.01$ ) to 3.0 ( $p < 0.0001$ ) times higher than the odds for children of lesser head circumference.

### **2.4.5.3 Sex differences**

Epidemiological data on asthma prevalence support a sex difference that varies with age in the risk of having asthma (416). Asthma and wheezing is more prevalent in boys than in girls prior to puberty; during puberty the male disadvantage disappears and women older than 20 years appear to have higher prevalence and morbidity rates of asthma than do males (416).

### **2.4.5.4 Parental ages at birth**

Young mothers have been reported to have an increased risk of having a child with asthma compared with mothers over 30 years of age (417). In over 1,200 infants born in Arizona, USA, infants of mothers less than 21 years of age, when compared with infants of mothers aged over 30 years, were at a significantly greater risk of wheezing lower respiratory tract illnesses during the first year of life (aOR 2.4; 95% CI 1.8, 3.1) (275). A retrospective cohort study (407) of Swedish conscripts similarly found that lower maternal age (less than 20 years) was significantly associated with an increased risk for asthma in infants (aOR 1.28; 95% CI 1.16, 1.42). Both biological and environmental factors, such as socioeconomic status, may be a possible explanation for these findings.

### **2.4.6 Obesity and physical activity**

The potential contribution of obesity and physical inactivity to the observed worldwide asthma epidemic has been recently debated (418). There is evidence of a positive association between asthma and obesity in children (419-424). A case-control study of urban minority children aged 4-16 years (419) in the USA, reported a significant difference in asthma status between those children with a body mass index (BMI) at or above 85<sup>th</sup> percentile ( $p < 0.04$ ). Children with asthma were also significantly more overweight than controls (mean $\pm$ SD, 22.5% $\pm$ 28.3% vs 12.0% $\pm$ 19.6% overweight,  $p = 0.004$ ). The difference in obesity between children with asthma and controls was significant for both sexes and across the 4.5 to 10.9 years and 11 to 16 years age groups. Asthma severity was not related to obesity. Similar results were reported from the British National Study of Health and Growth (422), in a cross-sectional analysis of 18,218 children 4-11 years old, where BMI and asthma were associated (OR for the comparison of the 10<sup>th</sup> and 90<sup>th</sup> centiles of BMI 1.28; 95% CI 1.11, 1.48). Furthermore, a recently reported cross-sectional study

(424) of 12,388 children aged 2 months to 16 years from the Third National Health and Nutrition Examination Survey in the USA found that children with a BMI  $\geq 85^{\text{th}}$  percentile had significantly greater doctor-diagnosed asthma (OR 1.94; 95% CI 1.09, 3.46). In a prospective study (425), the Odense schoolchild study in Denmark, of asymptomatic children followed from 9.7 to 10.5 years of age, physical fitness was inversely related to the new development of physician-diagnosed asthma (OR 0.93; 95% CI 0.87, 0.99). However, it should be remembered that early undiagnosed asthma may prevent physical activity and asthma may lead to obesity, thus disease-related changes in behaviour may have contributed to these associations.

## **2.5 ENVIRONMENTAL FACTORS INCONSISTENT WITH THE HYGIENE HYPOTHESIS**

### **2.5.1 Respiratory syncytial virus**

There is evidence to suggest that respiratory tract infections, particularly respiratory syncytial virus (RSV) infections, increase the risk of asthma in later life (see Section 2.3.3). The Tucson Children's Respiratory Study (426) found RSV LRTIs before the age of 3 years are associated with a significant increase in the risk of subsequent frequent wheeze OR 4.3 (95% CI 2.2, 8.7) compared with children who had no LRTIs. A recent review (298), of retrospective and prospective studies from 1978 until 2000, confirmed an association between RSV bronchiolitis in infancy and subsequent development of reactive airway disease or allergic sensitization in childhood. This association was strongest for children who experience severe RSV illness that required hospitalization. A family history of atopy or asthma did not explain the association. One possible explanation is that severe respiratory tract infections either damage lung tissue or impair the development of the lung in such a way as to promote asthma. The timing of the infection may also be relevant and have specific effects on immune system ontogeny, lung development or both (298).

### **2.5.2 Parasites**

Helminth infections are highly prevalent in large parts of the developing world, where allergy is uncommon. Ecological data support an inverse relationship between countries with a high prevalence of parasitic infection having very low asthma rates and countries with high asthma rates having very low rates of parasitic infection (427). Infestation of children with helminth

parasites, which are potent stimuli for allergen-associated Th2 immunity (high levels of total and parasite specific IgE), is paradoxically associated with reduced susceptibility to atopy (428). This challenges the Th1/Th2 paradigm and the Hygiene hypothesis for atopy. Moreover, the notion that a reduction in the overall microbial burden will result in weak Th1 imprinting and unrestrained Th2 responses that allow an increase in allergy, is contradicted by observations that the prevalence of Th1 autoimmune disease, such as Type I diabetes, is also increasing and that Th2-skewed parasitic worm (helminth) infections are not associated with allergy (429). Worldwide helminth infections and allergic diseases do not overlap despite both conditions being accompanied by strong Th2 immune response, suggesting an alternate immunological framework for the Hygiene hypothesis than simple Th1/Th2 imbalance. While helminths may stimulate Th2-mediated immune responses, they additionally trigger anti-inflammatory mechanisms which limit the magnitude of ensuing in vivo responses to allergen (430)

As stated above, there has also been an increase of the autoimmune diseases (in which the immune response is dominated by Th1 cells) such as Type 1 diabetes, Crohn's disease, and multiple sclerosis (431). In addition, the geographic distribution of both these allergic and autoimmune diseases follows a north-south gradient (431), and genetic-environmental factors are believed to influence susceptibility to these diseases. There is also a trend toward an association between allergic and autoimmune diseases in individual patients: the frequency of atopic disease is increased in patients with Type 1 diabetes and rheumatoid arthritis (431, 432). A strong positive association has been reported between a history of Th2-mediated allergic disorders and Th1-mediated autoimmune disorders, such as asthma and diabetes, coeliac disease and rheumatoid arthritis, using cross-sectional survey and register data in children (433) and adults (432). At a population level a strong positive association has been shown between the occurrence of Type 1 diabetes and symptoms of asthma (434), further supporting the co-existence of Th1/Th2 diseases.

These studies demonstrate that the existence of Th1 type disease does not reduce the risk of asthma. Co-existence of Th1 and Th2 diseases may suggest a common environmental factor or factors underlying these conditions (433). These findings have led some authors to consider additional processes for the development of atopic disease. Sheik et al., 2003 (432), suggest that reduced exposure to infectious agents in early childhood might adversely affect the developing immune system, leading to the generation of inappropriate immunologic responses to autoantigens (manifesting as autoimmune disease), allergens (manifesting as atopic disease) or both. Whereas Kemp & Bjorksten, 2003 (106), report that early life immune deviation may not be

a critical factor in preventing the development of atopic disease but a mechanism of immune modulation throughout life whereby both Th1 and Th2 responses are enhanced or suppressed in concert, and any effect will depend critically on the timing in relation to the dose and route of allergen exposure, and that the interaction between microbial exposure and other non-infective environmental and lifestyle factors are of critical importance (see Section 1.5.4).

## 2.6 CONCLUSION

There is compelling evidence that the prevalence of child asthma has increased in recent decades, though, this increase may have now plateaued in some countries (see Section 2.1.3). This Chapter has discussed both putative and protective factors that may contribute to the risk of development of asthma, but their relative importance in terms of the attributable fraction of atopic disease is difficult to determine. The identification of environmental risk factors for child asthma will provide the basis from which to develop strategies for prevention. And, it is therefore important to consider all possible changes in the environment and lifestyle that correlate with the time course of the increase in asthma prevalence. The role of bedding and possible effect modifiers in the development of child asthma has not been overviewed in this Chapter, but is discussed in detail in the introduction and discussion sections of each subsequent relevant Chapter enabling the findings in these Chapters to be interpreted and discussed with reference to the previously reported findings.

Several authors have suggested that changes in exposures within the indoor environment have been responsible for the trends in the prevalence of asthma (170, 435). Yet, very few studies have compared the increase in asthma prevalence over time with changes in the identified potential risk factors for asthma and atopy development. An overall increase in atopic diseases has accompanied the decline in infectious diseases. However, despite the strong inverse associations that have been reported between family size (number of siblings) and atopy and/or asthma, the role that family size plays in explaining increases in asthma prevalence is relatively minor. The progressive reduction in family size between 1961 and 1991 (2- to 3-fold reduction in the proportion of families with 4 or more children) may have led to only a 1% to 5% relative increase in the prevalence of asthma in childhood in the UK and New Zealand (284).

Two population based case-control studies in the UK also investigated the association between childhood wheeze and characteristics of the home environment to assess whether changes in

these characteristics between 1978 and 1991 may have contributed to an increase in the population prevalence of wheeze of 20% (Prevalence OR 1.20; 95% CI 1.04, 1.39) among school children (136). Over that time period, compared with the controls, cases were found to have experienced: (i) increases in the proportion of children living in accommodation with central heating in the bedroom (50% to 79%) and in the living room (57% to 81%); (ii) increases in the proportion of children using non-feather pillows (44% to 67%); and (iii) little change in proportion using gas for cooking (75% versus 77%) or the proportion owning furry pets (58% versus 52%). Interestingly, the rise in the use of non-feather pillows was large enough to explain 57% (95% CI 18%, 96%) of the 20% increase in wheeze prevalence; whereas the rise in the use of gas for cooking was only large enough to explain 4% of the 20% increase. When all the risk factors, including non-feather pillows, were investigated in the multifactorial analysis they appeared to explain 52% of the increase in the population prevalence odds of wheeze. The type of pillow was one factor for which changes in exposure over time were conducive to an increase in prevalence. Further studies are required to assess the relative importance of other risk factors (for example, women smoking, dietary factors, and antibiotic use) that may have changed over time and may contribute to an increasing prevalence of atopic disease.

Objective evidence suggests that the primary immune response to inhalant allergens is a Th2 response, which occurs during the first 5 years of life and is unusual before the age of 2 years. Although wheezing is common before the age of 2 years, the majority of cases are transient and do not go on to develop into persistent asthma. In regards to HDM, there is a proven association between allergen exposure and allergen sensitization. There is also a strong association between indoor allergen sensitization and asthma. However, despite very strong evidence for a role for HDM allergens in asthma, there is ongoing controversy as to whether allergens play a causal role in the development of the disease. The effects of sensitization, prolonged time course, and difficulty measuring allergen inhaled may all obscure the dose-response relationship (159).

Increased exposure to indoor allergens over time because of changes in houses and increased time spent indoors may be a contributing factor to the increase in asthma prevalence. In Australia, from 1982 to 1992, in the towns of Belmont and Wagga Wagga, the prevalence of recent wheeze in children aged 8-10 years, increased 1.5-fold to about 25% and the prevalence of BHR increased 2-fold to almost 20%. The populations of HDM increased 5-fold during the study period, but similar evidence has not been reported from other places (367). HDM allergens have been shown to play a major role in child asthma but this role may be underestimated due to



measurement error. Moreover, this Chapter has outlined several of the possible factors which may be linked to a modern lifestyle and that may decrease the threshold for wheezing among allergic individuals (159).

## **2.7 POST-SCRIPT**

This thesis will explore further the association of environmental factors and HDM sensitization and child asthma. My study will consider the role infant and child bedding, and in addition possible pollutants that may potentiate the role of HDM allergens, play in the development of HDM sensitization and child asthma. Chapter 3 will describe the design and the methodological approach undertaken for each study that has been analysed in this thesis.

## Chapter 3

### Thesis study design and methodology

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#### 3.0 PREFACE

This thesis explores the associations between the home bedding environment and HDM sensitization and child asthma. My analyses have been carried out on pre-existing data obtained from three studies previously undertaken by the Menzies Centre for Population Health Research in Tasmania, Australia: (i) The 1988-1995 Tasmanian Infant Health Survey (TIHS) was a prospective birth cohort conducted to investigate the aetiology of SIDS; (ii) The 1997 Childhood Allergy and Respiratory Health Survey (CARHS) was a follow-up of children who as infants participated in the TIHS; and (iii) The cross-sectional 1995 Childhood Asthma Survey included all children turning 7 years of age in Tasmania. This Chapter presents the aim and hypotheses of my thesis. The design features of each of the three Tasmanian studies are also described. In addition, this Chapter discusses the strengths and limitations of the two main study types used, prospective cohort and cross-sectional studies, and their applicability in asthma studies.

#### 3.1 THESIS AIM AND HYPOTHESES

The aim of this thesis is to identify home environmental risk factors for HDM sensitization and child asthma, focusing on infant and child bedding and the bedding environment. The study includes detailed analyses of infant and child bedding, and also other environmental factors, and their associations with HDM sensitization and childhood asthma. The specific hypotheses of this thesis are:

- (i) the type of underbedding or mattress an infant at one month of age, or a child, at 7 years of age, sleeps on is related to child HDM sensitization and/ or the respiratory symptoms of wheeze (Chapter 4);
- (ii) the use of, predominantly synthetic, cocoon/baby nests or sleeping bags in infancy is associated with the respiratory symptoms of wheeze in childhood and/or HDM sensitization (Chapter 5);

- (iii) the association between synthetic quilt use and frequent wheeze is significantly stronger among children who slept supine compared with children who slept non-supine (Chapter 6);
- (iv) the association between bedding items and child wheeze is of a greater magnitude for composite bedding than for individual bedding items (Chapter 7); and
- (v) other home environmental factors interact with bedding items to influence the bedding-wheeze association (Chapter 7).

## **3.2 THE STUDY DATASETS**

### **3.2.1 The Tasmanian Infant Health Survey**

The Tasmanian Infant Health Survey (TIHS) was an 8-year birth cohort study of children born during the period from 1988 to 1995 in Tasmania (436). This study operated from six obstetric hospitals where approximately 93% of births in Tasmania occurred, and it consisted of infants born at higher risk of SIDS. Infants born within these hospitals were scored to assess the risk of SIDS using a local perinatal score model (437). The composite score (437) was based on maternal age (years), birth weight (gm), infant sex, breastfeeding, season of birth and duration of second stage of labour (minutes). Infants that exceeded a scoring cutoff ( $\geq 532$ ) were eligible for inclusion and the sample of eligible infants represented approximately one-fifth of livebirths in the State from 1988 through 1995 (437). The scoring system is outlined in Table 3.1.

**Table 3.1 Component scores for model predicting infants at high risk of SIDS in Tasmania**

<b>Risk factor</b>	<b>Category</b>	<b>Component score*</b>
Age	Age in years	(-10.3 x age)
Sex	Females	200
	Males	261
Birthweight	Under 2,000gm	200
	2,000-2,499gm	82
	2,500-2,749gm	49
	2,750-3,499gm	-68
	3,500+gm	-28
Month of birth	March, April	200
	May to July	146
	Other months	114
Breastfeeding	Breastfed	200
	Not breastfed	280
Duration 2 <sup>nd</sup> stage of labour	<5 mins	200
	5-14 mins	235
	>14 mins	185
Caesarian		207
Born before arrival at hospital		235

\*Included in study if score  $\geq$  532.

Compared with all live births, there was a relative overrepresentation of low-birth weight infants (<2,500 g), 21.9% (2,155/9,826); male infants, 69.0% (6,781/9,826); infants born in March/April, 32.9% (3,230/9,826), or May through July, 26.5% (2,601/9,826); and infants born to younger mothers; and, there was an under-representation of infants whose mothers intended, at hospital interview, to fully breastfeed (245). Singletons with a score over the cut-off were eligible to join the survey; multiple births were automatically eligible. Infants with severe neonatal disease or a major congenital anomaly, infants for adoption and infants who would not be resident in Tasmania at one month of age were excluded from the study (n=15 of 1988 cohort data) (436). From 1 January 1988 until 31 December 1995, 11,070 live-born infants in Tasmania were eligible for inclusion in the survey, of these eligible infants 9,826 (89%) participated in both the hospital and home interviews. Of 13,592 live born infants in Tasmania in 1988 and 1989, 2,791 were eligible for the TIHS. The eligibility criteria and study methods are reported in more detail elsewhere [26]. Standard study measurements were collected by trained research nurses in three stages.

### **3.2.1.1 Study measurements (438)**

*The hospital interview.* The first interview was conducted with the mother in hospital on the fourth day of the infant's life. Sociodemographic, obstetric and perinatal data were included in the data collected. It involved four major areas:

- (i) The early postnatal questionnaire: including sociodemographic characteristics, education, family history, prenatal medical history and clinical contact, smoking, alcohol and drug history, and expected feeding practice. At this time, information was collected on whether the infant had any siblings, parents, or grandparents with asthma;
- (ii) The Maternal Nutrition Survey: the CSIRO Division of Human Nutrition food frequency questionnaire "Frequpan" 1987, Adelaide, Australia was used to assess dietary intake during the third trimester of pregnancy;
- (iii) The obstetric and perinatal data sheet: detailing type and progress of delivery, Apgar score, gestation, neonatal disease, placental weight and state, maternal blood group and rhesus status; and
- (iv) The physical infant measurements: including weight, length, head circumference, tricep and subscapular skinfold measurements and mid-upper arm circumference.

*The home interview.* A home visit and interview was conducted during the fifth postnatal week. For premature infants ( $\leq 36$  week's gestation) this visit was done at 40 weeks post conceptional age. For babies kept in hospital because of complications, the home visit was delayed until the infant had been at home for at least two weeks. In 1988, 1,111 of 1,307 eligible infants (85% of eligible) participated in a TIHS home interview at 1 month of age. The median postnatal age at home interview was 33 days (inter-quartile range 30-40 days). At this interview, a comprehensive structured verbal questionnaire was administered on a large number of parental, infant, environmental and child-care factors.

Data from the home interview included infant illness, health service attendance and family health history over the preceding month, pattern and type of infant feeding, parental smoking practice, child care patterns, home heating, ventilation and housing details, pets (dogs and/or cats) and other characteristics of the infant and of parental care. The room where the baby usually slept at night was defined as the infant bedroom. The infant's usual sleep position, infant 24-hour sleeping patterns and features of the infant's sleeping environment, including type of pillow, mattress liner, mattress and bed, type of overnight clothing and bedding used during the previous night and also the number and types of upper bedding items that would be used in cold weather were recorded.

Anthropometric and temperature measurements were made on the one-month old infant. A developmental assessment was conducted and included:

- weight, length, head circumference, tricep and subscapular skinfold measurements and mid-upper arm circumference;
- temperature measurements – skin temperature, per axilla temperature, core temperature; and
- a clinical assessment of infant development.

Physical features of the infant's home and bedroom were also documented by the interviewer and included:

- 24-hour maximum-minimum temperature on day of home visit for infant's room, external southern aspect of house, geographical area;
- humidity in infant's room, external southern aspect of house, geographical area; and
- physical features of the house, in particular, the infant's room.

*The telephone interview.* A third interview was conducted by telephone usually with the same parent respondent as for the home visit, when the infant was approximately 10 weeks postnatal age to review infant progress, medical attention, illness history, feeding and immunization. It included a review of infant progress, infant illness history, immunization status, reaction to needle prick of immunization, medical care, child health clinic attendance, infant weight at last weighing and infant feeding pattern. The median postnatal age at interview was 80 days (inter-quartile range 73-93 days).

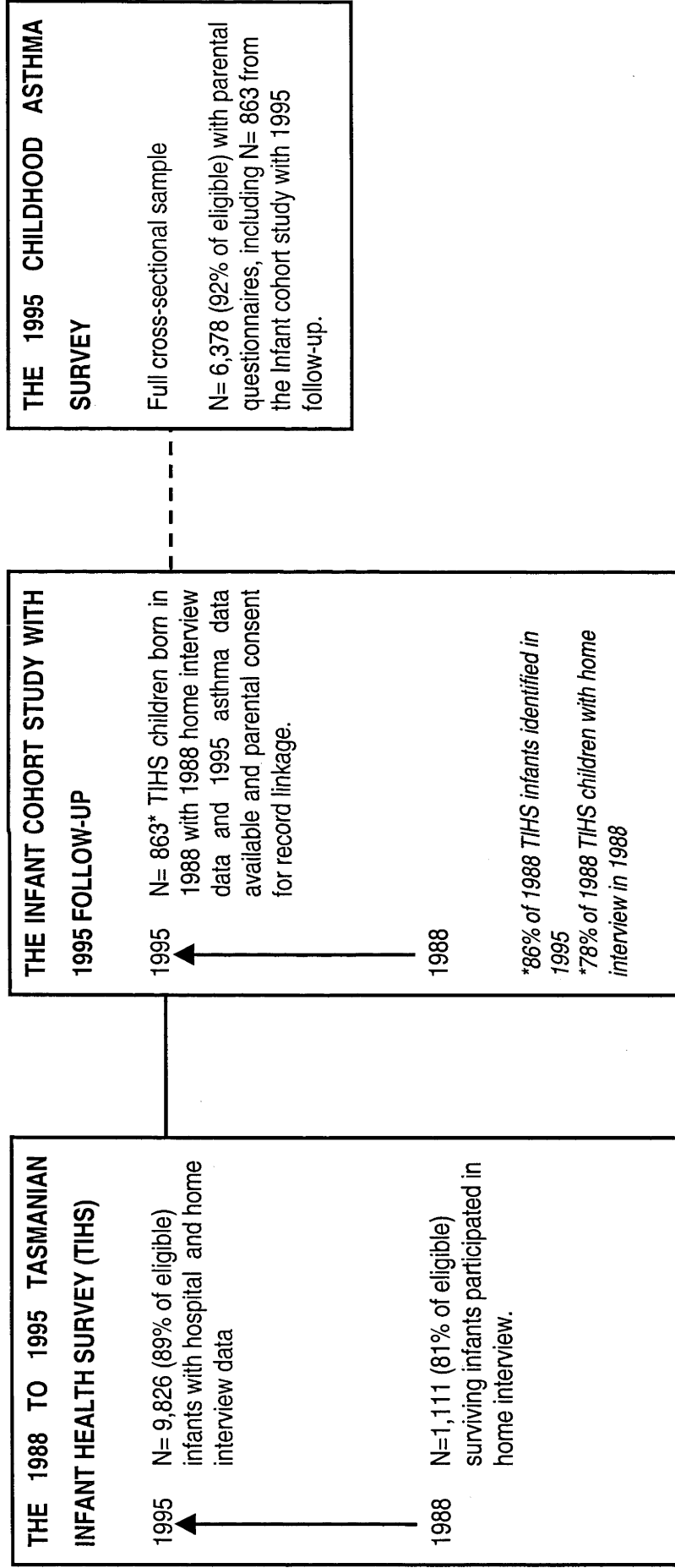
### **3.2.2 The 1995 Childhood Asthma Survey**

In 1995, a cross-sectional survey was conducted on all children who turned seven years of age in Tasmania. In March 1995, parental questionnaires were distributed through all primary schools, home learning, and distance education organizations in the State to the parents of children reaching the age of 7 years in 1995. The questionnaire included questions from the 1968 Tasmanian Asthma Survey (439) and the ISAAC (6). A total of 6,911 children born in 1988 were identified as being resident in Tasmania in 1995. By December 31, 1995, questionnaires had been completed for 92% (6,378/6,911) of eligible children. The 71-item questionnaire (see Appendix 1) included questions from the ISAAC (6). The questionnaire contained, in sequence: identification; questions from the 1968 Tasmanian Asthma Survey (439); the eight core questions on asthma and wheeze from the ISAAC protocol (6, 144) (see Section 3.2.2.1); asthma medication use; hospitalization for respiratory illness; attendance at regular child care; history of respiratory illness (bronchitis, pneumonia); family history (siblings, parents and grandparents) of atopic and other disease; maternal/paternal history of asthma, wheezy breathing, or hay fever; maternal and paternal education, occupation, and employment; parental and other smoking; whether mother or others smoke in same room as child; duration of breastfeeding; age of introduction to solids; some aspects of current diet; history of a cat as family pet; and details of the current home environment. Regular child care was defined as the child attending a child care arrangement with more than two other children at least once a week for three hours or more. The term "asthma" refers to any history of asthma (ISAAC question 6), and "current asthma" is defined as a positive history of asthma (ISAAC question 6). The child's age (in completed years) at onset of wheezy breathing or asthma was obtained. In addition, exercise challenge lung function testing was additionally conducted on 414 children (92% of eligible children) at 23 randomly selected schools in southern Tasmania.

In 1996, the data from this study were record linked to the pre-existing database from the TIHS. Of the 1,111 children who participated in the 1988 TIHS home interview, 863 (78%) also participated in the 1995 Childhood Asthma Survey, provided data on asthma status, and agreed to record linkage. The relation between the TIHS, the 1995 Childhood Asthma Survey and the Infant cohort study (TIHS) with 1995 follow-up is shown in Figure 3.1.



Figure 3.1 The relationship between the Tasmanian Infant Health Survey and the 1995 Childhood Asthma Survey



### 3.2.2.1 Study measurements

(i) *The Questionnaire.* As there is no gold standard for the definition of asthma, the risk of misclassification of outcome is significant. The use of the term *current wheeze* (usually defined as wheeze in the past 12 months) has the advantage of freedom from any bias arising from the diagnostic label of asthma (48). The validity of the ISAAC questions has been previously examined. A positive history of wheeze or whistling in the chest over the past 12 months had a sensitivity, the probability that the question correctly classifies those with asthma as having the disease, of 0.85, and a specificity, the probability the question correctly classifies those without asthma as non-diseased of 0.81, for respiratory physician-diagnosis of asthma (440).

The 8 core questions from the ISAAC on asthma and wheeze included in the 1995 Childhood Asthma Survey were:

Has your child ever had wheezing or whistling in the chest at any time in the past?

Has your child had wheezing or whistling in the chest in the last 12 months?

How many attacks of wheezing has your child had in the last 12 months?

In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?

In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?

Has your child ever had asthma?

In the last 12 months, has your child's chest sounded wheezy during or after exercise?

In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

(ii) *Exercise challenge lung function testing.* The exercise protocol used in the 1995 Childhood Asthma Survey was based on the work of Haby et al., 1994, (441) who reported that exercise challenge is a practical epidemiological tool for objective measurements of bronchial responsiveness in children. In this study, the children were instructed to take a maximal breath in and then blow out as hard and fast as they could in the standing position without a nose clip. After instruction and two practice attempts, each child performed sets of three forced expiratory manoeuvres (FEV<sub>1</sub> measurements) until two readings within 100 ml of one another were obtained in a set. The highest FEV<sub>1</sub>, overall, excluding the two practice attempts, was taken as the

baseline measurement of FEV<sub>1</sub>. The child then ran for six minutes on a 100 metres track with a nose clip and heart rate monitor (442). Following exercise, FEV<sub>1</sub> measurements were made at three, five and 10 minutes. At each point, three expiratory manoeuvres were performed. The minimum of the maximal values recorded at three, five, and 10 minutes was defined as the postexercise FEV<sub>1</sub>.

A population-based sample of 199 seven year old children in Tasmania reported that the probability a child will demonstrate BHR after exercise is related to the responses to the ISAAC questions, "Has your child ever had asthma?" and "Has your child had wheeze or whistling in the chest in the past 12 months?" (442). In addition, it was found that the respiratory response to exercise was consistent with parental responses to the ISAAC questionnaire. The median percentage fall in FEV<sub>1</sub> was significantly higher in children whose parents responded positively to ISAAC questions on a history of wheeze ( $p=0.003$ ) or asthma ( $p=0.0005$ ), recent wheeze ( $p=0.0005$ ) or sleep disturbance due to wheeze ( $p=0.0005$ ) (442).

### **3.2.3 The 1997 Childhood Allergy and Respiratory Health Survey**

In 1997, a follow-up study of the TIHS study participants born in 1988 to 1989 was conducted in Northern Tasmania through school records. This follow-up study was called the 1997 Childhood Allergy and Respiratory Health Survey (CARHS). Eligible children and their parents were invited to attend the Launceston General Hospital for a parental interview and child assessment. The 74-item parental questionnaire (see Appendix 2) included the eight childhood questions on asthma and wheeze from the ISAAC (6) (see Section 3.2.2.1) and also questions on the home environment such as child bedding and other factors. In Northern Tasmania in 1997, 499 (84%) of the 596 children identified as participants in the 1988-89 TIHS at birth agreed to participate in the CARHS study. SPT data were not obtained on one autistic child. For 456 of these children, TIHS home visit data as well as the initial TIHS hospital interview data were also available. Satisfactory lung function recordings were achieved for 495 children.

### 3.2.3.1 Study measurements

(i) *Skin prick testing.* In epidemiologic studies, both skin testing and measurements of IgE antibodies are used to determine sensitization to HDM allergen. The relationship between serum IgE antibodies and specific skin responses to the same protein produced by HDMs of the genus *Dermatophagoides*, is close ( $r$  values 0.7-0.8) (443). In the CARHS, SPT was used to assess the cutaneous reaction to exposure to the HDMs *D. pteronyssinus* and *D. farinae*, cat, dog, alternaria, ryegrass, cow's milk, egg, and peanut (Hollister-Stier purified allergen extracts supplied by Bayer, Sydney, Australia) and positive (histamine 10mg/ml and 1mg/ml) and negative (glycerine) controls. Wheal size was determined at 15 minutes. Der p and Der f extracts were both used because both mites have been found in Tasmanian homes (444). Skin wheal allergen reactions of 2 mm or greater at 15 minutes were classified as positive, but analyses in this thesis were also conducted with regard to the wheal size of mite allergens using both a 3 mm cut-off and wheal size as a continuous variable. Children with a positive SPT to any of the allergens tested for were classified as atopic. Children with a positive SPT to either *D. pteronyssinus* or *D. farinae* were classified as sensitized to HDM (445).

2. *Lung function tests.* Baseline lung function measures were obtained for each child. Trained research nurses performed the testing. The children were asked to perform forced expiratory manoeuvres standing without a nose clip following a standard protocol (446) using a Fleisch type electronic spirometer (Model AL 0642; Vitalograph, Buckingham, UK), which was calibrated to within 1% of calibration volume at the beginning of every session and checked hourly thereafter. FEV<sub>1</sub> (in litres) and forced vital capacity (FVC), the total volume of air that can be expelled from the lungs in litres, were measured for each subject. A ratio of FEV<sub>1</sub>/FVC, the percentage of lung volume that could be expelled in one second, was used as a measure of airway obstruction (447).

3. *Statistical hypothesis testing.* For this thesis, the level of statistical significance is a  $p$  value of 0.05. That is, results are considered "significant" when the  $p$  value is less than 0.05; and "not significant" when the  $p$  value is greater than 0.05 (448).

## 3.2.4 Type I and Type II errors

### 3.2.4.1 Type I error

A Type I error (or *alpha* error) refers to the rejection of the null hypothesis when it is in fact true. In this thesis, the alpha ( $\alpha$ ) level of 5% is selected as the criterion to judge the p value. Thus, an hypothesis testing procedure is valid if, whenever the null hypothesis is true, the probability of rejection (that is, the probability that  $p \leq \alpha$ ) does not exceed the *alpha* level (provided there is no bias and all test assumptions are satisfied) (330). An alpha level of 0.5% would indicate that the likelihood of erroneously rejecting the null hypothesis is 5% and  $p=0.05$  (449). When multiple comparisons are evaluated for any associations, chance guarantees a certain proportion of such associations. And, many false positives are possible when many associations are studied (448). The analyses of the hypothesised associations in this thesis however, were on a relatively small and finite number of exposures – underbedding, mattress and bed type, and composite bedding – and I have reported positive and negative associations. These exposures pertain to the specific a priori hypotheses outlined in Section 3.1. There was also a considerably larger number of confounders. In addition, I have assessed the consistency of findings between the three studies. More weight has been placed on findings replicable in each of the three data sets. And, in accordance with Rothman, 1986 (448) all associations assessed have been reported as if each one alone was the sole focus of the study. For those findings, consistent across the studies, the likelihood of Type 1 error is reduced.

### 3.2.4.2 Type II error

A Type II error (or *beta* error) occurs when the null hypothesis is false, but it is not rejected and there is a real difference between the study groups. The probability of a Type II error is related to the power of a study by the equation (330): Probability (Type II error) =  $1 - \text{Power}$ . The power of a study is defined as the probability of rejecting the null hypothesis and concluding that there is a statistically significant difference between the study groups if one truly exists (449). Type II errors result when the magnitude of an effect, biases, and random variability combine to give results insufficiently inconsistent with the null hypothesis to reject it (330). This failure to reject the null hypothesis can occur either because the effect is small, the observations are too few, or both, as well as from biases (330). Although the cross-sectional 1995 Child Asthma Survey is large, the two cohorts are of smaller sample size. For rare exposures, the statistical power of the study to

detect an effect may be inadequate. I have considered the issue of Type II error within the Chapters of this thesis where this issue is pertinent to interpretation, particularly in Chapter 5 (see Section 5.7).

### **3.2.5 Ethics**

These studies were approved by the Ethics Committee (Human Experimentation) of the University of Tasmania and parents provided informed written consent, including consent for data linkage between the TIHS and the 1995 Tasmanian Asthma Survey, and for the TIHS and 1997 CARHS.

## **3.3 THEORETICAL STUDY DESIGN ISSUES**

The Tasmanian studies comprised two main study types: a prospective cohort and a cross-sectional study. The strengths and limitations of these two study designs are discussed in the following sections, and further methodological issues are discussed throughout the thesis. As it is not feasible here to sample on disease status, a nested case-control analysis within the already collected cross-sectional data was also used in Chapter 6 (see Section 6.3.2) in order to match on confounder status to increase efficiency. RCTs do provide the highest level of evidence regarding causation (28) and the potential for selection bias is reduced in comparison to both cohort and cross-sectional studies. However, for child asthma studies, RCTs may raise ethical concerns when the study would require the infant to be exposed to a potential cause of disease such as some of the bedding items discussed in this thesis. Moreover, the paediatric phenotypes of asthma are distinguished by their age of onset (see Section 1.3.2.1) thus requiring studies to be undertaken over several years (80% of atopic asthma will begin by age 6 years). An RCT over this same period of time would realistically experience issues of lack of compliance by the study participants. In addition, there would be ethical issues pertaining to the administration of potentially harmful forms of bedding (for example, sheepskin) which require evaluation. In regard to an "hierarchy of evidence" (28), a prospective cohort study is considered to provide the next level below a RCT. Host & Halken, 2002 (28), identify several study criteria for the evaluation of possible risk factors in allergic disease: truly prospective; well-defined inclusion criteria; sufficient duration of follow-up; and, a proper sample size for adequate statistical evaluation. This Tasmanian birth cohort, which has been followed for 7 years, meets these study criteria and does

provide an appropriate study to explore infant exposures that may be associated with child asthma.

### **3.3.1 Design aspects of a prospective cohort study**

A cohort is a particular “closed” set of individuals, an enumerable set of persons, all experiencing an admissibility-defining event in a domain that is restrictive in both place and time (450).

By recording disease occurrence in a defined group, absolute and relative risks measures can be obtained from a cohort study, providing measures of disease incidence, or mortality rates, and it is these rates that provide the basic measures of disease risk. Cohort studies have an extended period of observation relating to disease experience, and sometimes to exposure experience as well, and, the individual is the unit of observation. These two features contrast with those of cross-sectional studies in which populations are compared on both exposure and disease occurrence at the same time (450) and incidence rates cannot be calculated.

In a prospective cohort study, exposure measurement occurs before disease status is known. The study samples on a population group or by exposure status and then follows up study subjects over time with regard to disease occurrence. As participants are free from the disease at the time their exposure status is defined, the temporal sequence between exposure and disease can be more clearly established (449). Therefore, the cohort design is advantageous for studying the temporal relationship between exposure (such as bedding items) and outcome (child sensitization or asthma-wheezing). Cohort studies also allow examination of several effects or outcomes after a single exposure as well as the development of wheezing or asthma subsequent to exposure (or no exposure) to bedding. One difficulty in using a childhood cohort to examine the occurrence of asthma or sensitization is that neither outcome occurs uniformly over time, asthma symptoms may be intermittent and the development of either might be protracted (451).

In prospective cohort studies, recall bias can usually be eliminated (452) and selection bias reduced. Recall bias is a form of measurement bias (see Section 5.7.2 and Section 6.5.1) where bias in evaluating an effect arises from errors in obtaining the needed information, and can occur whenever there are differential errors in the classification of subjects either on exposure or outcome (448). Recall bias where recalled exposure information is misclassified differentially for those with and without the disease (37), should not occur. Selection bias (see Section 5.7.1) in

cohort studies can occur when the selection of exposed and non-exposed subjects is related to the disease outcome (449). For cohort studies with a high participation rate and then good follow-up, problems of selection bias should also not arise (452), provided that the follow-up does not favour particular exposure groups. This can be checked by examining the data, then comparison of the disease experience among different sub-groups of the study cohort should be unbiased. Losses to follow up, both in exposed and non-exposed subjects, represents the greatest potential bias of a cohort study (451). Failure to collect outcome data on the greater proportion of subjects can render a study “uninterpretable” (449). Thus, in all cohort studies, the level of selection bias and how it may influence results should be assessed.

As cohort studies require a commitment over many years, another disadvantage is expense. The follow-up period will be influenced by natural history of the disease as well as sample size considerations. Repeated measures of current exposure can be obtained allowing a better understanding of diseases with different time effects, however, this more frequent monitoring may also prove expensive.

Three principal multiplicative measures of effect are used in cohort studies (453): (i) the rate ratio (incidence rate ratio); (ii) the risk ratio (cumulative incidence ratio), and, (iii) the (incidence) odds ratio. The first two measures are sometimes referred under the generic term of relative risk, and the odds ratio is often interpreted as an estimate of relative risk. They are all approximately equal when the disease is rare during the follow-up period (for example, cumulative incidence of less than 10%) (453). However, when the incidence of an outcome of interest is common in the study population (>10%), the OR can no longer approximate the risk ratio (454). The more frequent the outcome, the more the OR overestimates the risk ratio when it is more than 1 or underestimates it when the OR is less than 1 (454, 455). Measures of effect are discussed below in Section 3.4.3. Relative risk guides inferences of cause and effect when an association is observed between an exposure and disease occurrence in epidemiological studies (456). Relative effect measures are based on the ratio of an absolute effect measure to a baseline measure of occurrence (330). Where possible, both relative and absolute measures of risk should be considered. Cohort studies allow the determination of absolute risk. The risk difference quantifies the potential importance of this association in absolute terms, that is the absolute risk.

The full picture of the long-term health effects of a given exposure can be provided only by the cohort approach. In this regard, cohort studies have several distinct advantages over cross-sectional observations (457). The most important of these are that the predictive power of early



factors can be assessed and age effects clarified (457). Studies operating over a sufficient time-period to be able to provide data relevant to children's asthma are now able to examine the association between long-term outcomes, through childhood and factors measured both during pregnancy and in early life. These studies have provided unique and important contributions to the understanding of respiratory disease in childhood (457). However, where ethical and feasible, RCTs provide more rigorous evidence on the role of bedding in asthma.

### **3.3.2 Design aspects of a cross-sectional study**

In a cross-sectional study all information collected refers to the same point in time, providing information of the population status with respect to disease or exposure variables, or both (37). As both exposure and health outcome are determined simultaneously, the risk measure is that of disease prevalence rather than incidence. Cross-sectional studies are commonly used to learn about risk factors for diseases of long duration. Diseases of short duration are not suitable for this type of study as too few people would have the disease at any given point in time (458). A major advantage over cohort studies is reduced costs, as they can be undertaken over a relatively short time frame. A cross-sectional study may also be used rather than longitudinal data when current exposure is likely to be a reliable proxy for past exposure, and where reliable recall of past exposure is difficult to ascertain (37).

However, although an association can be shown between exposure and outcome, cross-sectional studies are limited in their ability to establish causality (459). A further limitation is that cross-sectional studies are biased toward sampling diseases of long duration; a series of prevalent cases will have a higher proportion of cases with disease of long duration than a series of incident cases. There is a potential for selection bias when there is a difference in exposure status between subjects in whom the disease is short or fatal, and those who live with the disease for a long time (330). People who either recover or die from a disease quickly have less chance of being included in the disease group (458). In cross-sectional studies, where intermittent diseases with remissions periods, such as asthma, are being studied, it is critical that disease measurement involve questions about past symptoms in order to avoid disease misclassification.

There are two effect measures that can be ascertained from cross-sectional data with a dichotomous variable, the prevalence rate ratio (PRR) and prevalence odds ratio (POR) (460). The relationship between a variable and the disease can be examined (i) in terms of the

prevalence of disease in different population sub-groups defined according to the presence or absence or level of the exposure variables, and (ii) in terms of the presence or absence (or level) of the variables in the diseased versus the non-diseased (461).

### 3.3.3 Measures of effect or association

In epidemiology, summary parameters are used to estimate the association between an exposure and an outcome, in a defined population. These measures of association are frequently based on incidence rates and on risks of developing disease.

#### 3.3.3.1 Cohort studies

Assuming that the exposed and non-exposed groups are otherwise comparable with regard to risk for disease, measures of disease occurrence can be compared to assess the effect of exposure.

In cohort studies, the measure of primary interest is often the rate ratio (incidence density ratio) where the measure of association is based directly on incidence rates over a defined time period. The incidence rate ratio is defined as the ratio of rates for two groups differing in their exposure to a possible risk factor for the disease under study and is shown by the equation:

$$\text{Incidence rate ratio (incidence density ratio)} = \frac{\text{incidence rate of disease for exposed}}{\text{incidence rate of disease for unexposed}} \quad (458)$$

A second effect measure is the risk ratio (cumulative incidence ratio) which is the ratio of the cumulative incidence in the exposed group to that in the non-exposed group. The cumulative incidence (incidence proportion) is the proportion of study subjects who experience the outcome of interest at any time during the following period (450). When the outcome is rare over the follow-up period the risk ratio is approximately equal to the rate ratio (453). The risk ratio is based on a comparison of probabilities of developing the disease. It is defined as

$$\text{Risk ratio} = \frac{R_1 \text{ (risk among exposed)}}{R_0 \text{ (risk in unexposed)}}$$

These relative measures of effect, the risk ratio and incidence rate ratio, range from zero to infinity.

A third possible measure is the (incidence) odds ratio which is the ratio of the incidence odds in the exposed group ( $a/c$ ) to that in the non-exposed group ( $b/d$ ) (see below). Again, when the outcome is rare over the study period (454) the incidence odds ratio is approximately equal to the incidence rate ratio (453).

The risk difference is the difference in cumulative incidence between the exposed and non-exposed groups and is represented by  $R_1 - R_0$ . Risk difference (values from  $-1$  to  $+1$ ) and incidence rate difference (values from  $-$  infinity to  $+$  infinity) are measures of absolute effect. Relative risk is used to refer to either an incidence rate ratio or a risk ratio. Relative risk is non-linear and takes on values between zero and infinity. Although relative measures of effect are useful, they do not incorporate the issue that risks of similar magnitudes will be more important for common rather than uncommon exposures at the population level. The population attributable fraction is discussed in Section 4.3.3.4.

Each of these relative effect measures involves the ratio of a measure of disease occurrence in the exposed group to that in the non-exposed group. These three measures of disease occurrence all involve the same numerator (for example, HDM sensitization or asthma) but differ in whether their denominators are based on person-time at risk, persons at risk, or survivors. They are all approximately equal when the disease is rare during the follow-up period (see Section 3.3.1). The odds ratio is readily biologically interpretable only in so far as it estimates the incidence proportion or incidence density ratio (462).

The odds ratio relates to the odds of having the disease and is defined by (449)

$$\frac{a/c}{b/d} = \frac{ad}{bc}$$

Where

$a$  = the number of individuals who are exposed and have the disease

$b$  = the number who are exposed and do not have the disease

$c$  = the number who are not exposed and have the disease

$d$  = the number who are both non-exposed and non-diseased

### 3.3.3.2 Cross-sectional studies

In cross-sectional studies, since the time dimension is not available, the measures of association are: (i) the prevalence rate ratio (PRR), the proportion of the population with the disease, and (ii) the prevalence odds ratio (POR), the ratio of affected to non-affected individuals (463).

Based on the measures above (449),

$$(i) \quad PRR = \frac{a/(c+b)}{c/(c+d)}$$

$$(ii) \quad POR = \frac{a/c}{b/d}$$

The POR and the PRR estimate true parameters using different scales. PRR is a probability measured on a linear scale from zero to one, whereas (prevalence) OR is non-linear and takes on values between zero and infinity.

Only under certain conditions does the odds ratio approximate the risk ratio: when the incidence of an outcome of interest in the study population is low (<10%) the OR is close to the risk ratio (see Section 3.3.1). However, the more frequent the outcome becomes, the more the OR will overestimate the risk ratio when it is more than 1 or underestimate the risk ratio when it is less than 1 (454). As an estimate of relative risk, the OR is biased away from one. This issue should be particularly kept in mind for studies on child asthma, a disease of high prevalence. When the duration of disease is similar among the exposed and non-exposed subjects and when the risk of disease is sufficiently small, the rate ratio, risk ratio and the OR give nearly identical values (458), that is  $POR = \text{incidence rate ratio}$ .

### 3.3.4 Confounding

Confounding is a systematic error that is key to control in epidemiological studies (see Section 5.7.3). It is defined as the distortion of a disease-exposure association brought about by the association of other factors with both disease and exposure, the latter associations with disease being causal (464). Thus, a confounding factor is a factor that, in addition to being causally

related to the disease or outcome of interest (for example, asthma) is also correlated with, but is not a consequence of, the exposure being investigated. During analysis of a study, confounding can be seen to have occurred if the estimate of exposure effect (risk ratio, odds ratio, or rate difference) is altered after adjustments for another factor, which has been referred to as the change-in-estimate criterion (465) in which variables are selected based on relative or absolute changes in the estimated exposure effects (466). Confounders may cause an overestimate, underestimate, or may even change the direction of a true association between exposure and disease (449). Factors that might potentially confound, either positively (strengthening the magnitude of effect) or negatively (reducing the magnitude of effect), any association between bedding and wheeze, may include, for example, the family history of asthma.

For observational studies, potential confounders can be controlled for in the study design through matching cases and controls on confounder status, and restriction. However, controlling for confounding in the analysis is a more common approach. Control of confounding is achieved either by stratification, which reduces or eliminates confounding by evaluating the effect of an exposure across strata of the confounding variable, or by multivariate analysis (330) which adjusts for confounding through mathematic modeling.

### **3.3.5 Multivariate analysis**

Multivariate analysis is able to describe simultaneously the effect of exposure on outcome and the effect of other factors that may be confounding or modifying the effect of exposure. Multivariate models can also be used for other factors operating in other ways, for example intermediates. The types of multivariate models most frequently used in child asthma are multiple logistic regression and multiple linear regression.

#### ***3.3.5.1 Multiple logistic regression***

The appropriate multiple logistic regression predicts the proportion of subjects with the feature of interest (or, equivalently, the probability of an individual having that characteristic) for any combination of the explanatory variables in the model (467). A logistic regression model enables us to predict the probability of a particular outcome in relation to several prognostic variables by providing an odds ratio. When the outcome of interest is a binary factor, such as disease or no

disease, logistic regression can be used to estimate odds ratios of disease adjusted for relevant confounding factors.

The logistic regression model is based on the equation (467)

$$\ln \left( \frac{p}{1-p} \right) = \alpha + \beta x_i$$

Where  $p$  is the probability of the outcome being present with a range from 0 to 1, and  $(1-p)$  is the probability of the outcome not being present. The ratio  $p/1-p$  is referred to as odds  $p$  and has a range of zero to infinity. The logarithm of the odds ( $\ln [p/1-p]$ ) will have a range from  $-\infty$  to  $+\infty$ . The ratio of  $\ln (p/1-p)$  estimates the log odds ratio of the outcome being present and is referred to as the logit,  $\alpha$  represents the intercept term and  $\beta$  is the regression coefficient. The regression coefficient  $\beta$  is a basic measure of the strength of relationship between the exposure and the outcome.

If the data have been collected for several exposures (which could also be potential confounders) then this model (468) becomes:

$$\ln \left( \frac{p}{1-p} \right) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k$$

where  $x_2 \dots x_k$  are the additional exposures or confounders (covariates) and  $\beta_2 \dots \beta_k$  are their corresponding regression coefficients (468). The  $\beta$  parameter provides a log-form estimate of the odds ratio associated with that particular term, adjusted for all the other terms in the model. The antilogarithm of the  $\beta$  parameter will provide the point estimate of the odds ratio for that term and the standard error of the term can be used to calculate the confidence interval for that point estimate (469).

### **3.3.5.2 Multiple linear regression**

Multiple linear regression analysis yields a regression model in which the dependent (or outcome) variable is expressed as a combination of the explanatory variables (predictor variables or covariates) (467). Multiple linear regression is used when the outcome of interest is a

continuously distributed variable, such as lung volume. If  $Y$  denotes the dependent variable, then its relationship to the predictor variables is described by (458):

$$Y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k$$

As for logistic regression,  $\alpha$ ,  $\beta_1$ , ...,  $\beta_k$  are coefficients estimated from the data, and  $x_1$ , ...,  $x_k$  are the set of values for the regressor variables. The coefficients indicate the magnitude of the increase (or, if negative, the decrease) in the value of the dependent variable resulting from an increase of one unit for the relevant predictor variable, while holding constant all other predictor variables in the model (458).

### **3.3.5.3 Generalized linear models**

Logistic regression is used for the analysis of cross-sectional studies to obtain prevalence odds and odds ratios, and is suitable when the dependent variable in the logistic regression equation is the log odds of having the disease at the time the study is conducted, rather than of developing new disease (458). Logistic regression yields an OR rather than a risk ratio even in a cohort study (37). In cohort studies, logistic regression does not account for possible different durations of follow up for cohort members or for change in values of variables over time (459). Cox proportional hazard models (see Section 4.3.3.1) and generalized linear models (463, 470) can be used to estimate the risk ratio and risk difference multivariately for prospective binomial data. By choosing different link functions or transformations of prospective binomial or binary data, risk ratio and risk differences can be estimated in the generalized linear model framework. Risk ratio and risk difference parameters can be related to regression coefficients for fitting binomial data by assuming a functional relationship between disease probabilities and a linear combination of the covariates. In generalized linear models, the linear predictor (%LP) when there are  $k$  covariates is defined as the sum of the products of unknown regression coefficients and the values of the covariate  $\beta_k$  for the  $i$ th proportion (470):

$$\%LP = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k$$

A monotonic link function relates the covariates for each proportion to its respective probability through the linear predictor. The regression coefficient  $\beta_k$  represents the difference in the probability, transformed by the appropriate link function, associated with a unit change in the

value of the covariate  $x_k$  when the other  $k - 1$  covariates remain constant (470). The “log” link function and binomial error structure can be used to obtain relative risk ratio estimates (470). However, due to the complex nature of the generalized linear model framework, computing is intensive and the model may not always converge (455).

### **3.4 POSTSCRIPT**

The TIHS was undertaken to explore the possible risk factors for SIDS. It has provided detailed information regarding an extremely large number of factors such as infant characteristics and the home environment, including infant bedding and sleeping practices, parental history and care, and sociodemographic variables. Thus, this prospective birth cohort has provided a wealth of infant information that has been followed up through the 1995 Child Asthma Survey and the 1997 CARHS. Both these latter two studies have specifically addressed the respiratory health of children aged 7 and 9 years respectively in Tasmania. These three data sets have been analysed to determine associations between the home bedding environment and HDM sensitization and child asthma. Chapter 4 will discuss the relationship between underbedding, mattress and bed type and HDM sensitization and respiratory health.



## Chapter 4

# The association between underbedding, mattress and bed, and allergic sensitization and respiratory health

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## 4.0 PREFACE

This Chapter explores the associations between underbedding, mattress and bed type with child HDM sensitization and asthma. The two prospective studies, the 1997 CARHS and the Infant cohort study with 1995 follow-up, and the cross-sectional 1995 Childhood Asthma Survey have been analysed and the findings are described in this Chapter. The findings from the 1997 CARHS, reported in this Chapter, have been recently published (see Appendix 3):

Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. An association between plastic mattress covers and sheepskin underbedding use in infancy and house dust mite sensitization in childhood: a prospective study. *Clin Exp Allergy* 2003; 33(4):483-9.

## 4.1 INTRODUCTION

Early infancy has been identified as a critical period for primary sensitization (165, 471) to indoor inhalant allergens such as HDM (see Section 1.5.2). The bedding environment during infancy may play an important role in increasing an infant's likelihood of HDM sensitization (14, 170). Infants spend prolonged periods in bed with close proximity to bedding items, enhanced further by their sleep position, and there is increasing evidence that the bedroom is the major site of mite exposure (472). Air sampling has identified the bedroom as the major site of exposure to HDM allergens (473), with airborne mite allergen levels during sleep about 10-fold higher than during usual domestic life in the living rooms of the same houses. The use of new upper bedding appears to be an effective measure for reducing airborne mite allergen exposure (474). After changing to new bedding, the geometric mean level of exposure to airborne Der p 1 was reduced from 102 pg/m<sup>3</sup> to 19.9 pg/m<sup>3</sup>. Encasing pillows, quilts and mattresses in allergen occlusive covers also reduced airborne Der p 1 levels by approximately 6-fold (102.1; 95% CI 54.6, 228.6 to 17.5; 95% CI 7.2, 42.7) pre and post intervention respectively (475).

Several cross-sectional studies have shown that later sensitization to mites is strongly associated with HDM mattress level in childhood (168, 169, 476, 477). Lau et al., 1989 (168), in a cross-sectional study determined the concentrations of HDM in 183 dust samples of mattresses of 133 atopic and 50 non-atopic children, (mean age 9.3 years), in Germany. The authors reported a strong correlation between HDM allergen exposure (Der p 1 or Der f 1) and specific IgE sensitization. Atopic children with significant (>+2,000-10,000 ng/gm) or high (>=10,000 ng/g) amounts of HDM in their mattresses were found to have significantly higher serum IgE antibodies to *D. pteronyssinus* or *D. farinae* than patients with very low (<400 ng/g) concentrations of *D. pteronyssinus* or *D. farinae*. The relative risk for sensitization in the highly exposed group versus the group with very low exposure was 7-fold to 32-fold increased. Furthermore, the use of foam mattress was found to be associated with sensitization to *D. pteronyssinus* at age 5 years or older in a cross-sectional study in Ethiopia (OR 1.97; 95% CI 1.16, 3.33) (478).

Prospective data on infant underbedding and subsequent HDM sensitization and respiratory symptoms has not been previously examined. This is likely to be an important area because different bedding items differ with regard to HDM allergen levels. The concentrations of HDM have been found in previous studies to vary between the underbedding items as a result of their different material composition (9) as well as the capacity of the individual item to provide a microclimate conducive to the proliferation of HDM. Infant sheepskins because of their frequent use, dampness and warmth can contain very high populations of mites (14, 479). In addition, mattress type has been the determinant for differing Der p 1 levels of beds in some studies. Innerspring mattresses were found to have a greater mite allergen concentration than foam in Australian and New Zealand studies (9, 480) yet other studies have shown either no difference between the two mattress types (477) or even foam mattress harbouring higher levels of HDM than innerspring mattresses (14, 481, 482). Both sheepskins and mattresses have been shown to accumulate allergen rapidly (483, 484), whereas, mattress covers have been shown to be effective in reducing the amount of HDM allergen (485, 486) but data on their role in asthma is less clear. However, the use of mattress covers which provide a barrier effect to HDM, may alter the concentration of HDM found in beds (485-487).

A Swedish study (486) using the bedding of 7 atopic children sensitive to HDM, reported that following a six-month period of mattress and pillow encasement in semi-permeable polyurethane covers, there was an average difference of 98% ( $p < 0.001$ ) between the vacuumed amount of mite allergen on top of the covers. Furthermore, the Melbourne House Dust Mite study (485) assessed the long-term effectiveness of mite avoidance measures in the homes of 85 asthmatic

children in Melbourne, Australia, on 10 home visits over a 16-month period. The use of semi-permeable polyethylene mattress encasements substantially lowered the concentration of Der p 1 recovered: 4.2 ug/gm (95% CI 2.5, 6.5 ug/gm) at the fourth visit compared with 28.4 ug/gm (95% CI 22.0, 36.6 ug/gm) at the third visit. When the mattress encasements were then removed, the Der p 1 concentration in dust obtained from the mattress itself had fallen relative to the levels 12 months previously: 13.8ug/mg (95% CI 10.5, 18.1) compared with 28.4 (95% CI 22.0, 36.6);  $p < 0.0001$ . However, a recent Cochrane meta-analysis (488) reported that the use of mite control measures, including mattress barrier covers, did not result in a statistically significant improvement of asthma (see Section 4.7.2).

Furthermore, mattress and bedding are two of the main reservoirs of HDM (489, 490) and also a potential source of pulmonary irritants in the form of volatile organic compounds (VOCs) (491, 492) (see Section 4.7.2). Thus, an effect of bedding type on allergen sensitization may not only be due to allergen levels (493). Waterproof infant cot mattress covers release VOCs (494) that may be associated with airway inflammation (either atopic or non-atopic) in humans (491, 495) and animals (492), and the promotion of sensitization to allergens (496). Moreover, inhalant HDM allergen sensitization is an important determinant of childhood asthma (167, 170, 175) (see Section 2.2.1.3).

Previous studies have reported conflicting results regarding associations between mattress type and wheeze. A case-control study in New Zealand of 233 children found no association between asthma and current mattress characteristics: kapok versus foam mattress (OR 0.35; 95% CI 0.09, 1.33); and, innerspring versus foam (OR 0.87; 95% CI 0.57, 1.33) (179). A retrospective analysis of a birth cohort, also in New Zealand, similarly found no significant associations between mattress type used in the first three years of life, or at any time to age 9 years, and asthma or wheeze at age 9, or at any subsequent age up to 15 years (497). Whereas, the large population-based survey in Ethiopia reported a positive association of synthetic foam mattress and current wheeze (OR 1.48; 95% CI 1.14, 1.91) (478). Also, a retrospective case-control study of 7-9 year old children in New Zealand reported an increased risk of asthma with the parental recalled use of sheepskin bedding in their first year of life (aOR 1.91; 95%CI 1.11, 3.33) (179).

This Chapter examines the prospective relationship between an infant's underbedding, mattress or bed and HDM sensitization and asthma in childhood. Personal HDM allergen load could be affected by proximity. Therefore, the infant's usual sleep position and its association with subsequent HDM sensitization is also examined. In addition, the association between current

use of underbedding and respiratory symptoms is described. The aim of this Chapter is to test the hypotheses that the type of underbedding and mattress an infant at one month of age, or a child, at 7 years of age, sleeps on is related to child HDM sensitization and/ or the respiratory symptoms of wheeze.

## 4.2 METHODS

At the home interview conducted as part of the TIHS, data were collected on the type of underbedding, mattress, cot or bassinet used by the infant. Underbedding is defined as any form of bedding lying underneath the infant or child's body. In this study, it refers to undersheets, sheepskins and mattress liners (fitted or not). Mattresses are considered as a separate bedding item. Pillows are not classified as underbedding items, and have been reported elsewhere (13), and are considered in Chapter 7. Sheepskin is a common form of underbedding for infants in Australia and comprises the animal hide with the natural wool fibres attached. Infants are typically placed directly on the sheepskin. The use of a sheepskin as underbedding at the time of interview or intention to use sheepskin in cold weather was recorded in order to avoid the effect of current season when questioned. Responses of plastic to the type of mattress lining used were classified as having plastic mattress covers. A plastic mattress cover is used mostly as a mattress protector from wetting. The material structure of the infant's cot or bassinet was also recorded at the home interview. In addition, the usual sleeping position of the infant was recorded. To examine the influence of bedding on HDM sensitization, SPTs were classified as described in Section 3.2.3.1. The prospective association between the particular type of infant underbedding, mattress or cots and subsequent HDM sensitization (as determined by the child's SPT in 1997) and/or respiratory symptoms in childhood are examined using (i) the 1997 CARHS, and (ii) the children who participated in both the 1995 Childhood Asthma Survey and in the TIHS as infants, that is, the Infant cohort study with 1995 follow-up.

For the 1995 Childhood Asthma Survey, the child's current mattress type and coverings were recorded in addition to the current bed type. Allergy covers are recommended (183, 498, 499) to reduce HDM levels within the bedding and comprise fabric impermeable to HDM antigen. The use of an electric blanket or intention to use an electric blanket in cold weather was recorded. The full cross-sectional data of the 1995 Childhood Asthma Survey is analysed to provide associations between the current childhood underbedding and bed type, and respiratory symptoms.

## 4.3 STATISTICAL METHODS: THE 1997 CARHS

### 4.3.1 Exposure variables

The main bedding exposure variables of interest are the use in infancy of sheepskin underbedding, plastic mattress cover, cotton undersheet, and foam mattress. The majority of other mattresses were ti-tree. Ti-tree is native to Australasia and the bark is used for mattress filling. Cot types were either plasticaine or wood/steel frames. Plasticaine is plastic covered cane. Composite bedding is considered in Chapter 7. Two additional variables were constructed: one variable for the use of both a sheepskin and a plastic mattress cover; and the other variable for the use of neither a sheepskin nor a plastic mattress cover. In this Chapter, all six variables were dichotomous for exposure or no exposure to the bedding variable. The sleep position was recorded as the infant's usual sleep position and the variables were (i) side versus prone and (ii) supine versus prone. Infants with no usual sleep position recorded or missing data were excluded.

### 4.3.2 Outcome variables

HDM sensitization refers to a positive SPT to either *D. pteronyssinus* or *D. farinae*. Sensitization to the other indoor aeroallergens, cat and alternaria, and the outdoor aeroallergen ryegrass, were also outcome variables. (see Section 3.2.3.1). In accordance with the ISAAC terminology, *Recent wheeze*, refers to one or more wheeze episodes over the past 12 months (6). *Night wheeze* is defined as the child's sleep being disturbed one or more nights per week in the past 12 months due to wheezing. *A history of asthma (Asthma ever)* refers to a positive response to the question, "Has your child ever had asthma?" (6). Wheeze frequency over the past year was also examined. Wheeze over the past year was defined as 1-3 episodes; 4-12 episodes; or greater than 12 wheeze episodes (frequent wheeze). Each wheeze outcome was compared to a baseline group of no wheeze.

The continuous outcome variables of lung function were: FEV<sub>1</sub> in litres; FVC in litres; and the lung volume ratio (FEV<sub>1</sub>/FVC) as a percentage (447).

### 4.3.3 Statistical methods to examine HDM sensitization

#### 4.3.3.1 *The Cox proportional hazards model*

The Cox proportional hazards model [29] was applied as the main method of analysis for the risk of subsequent HDM sensitization. The hazard or risk ratio (RR), as a measure of relative risk, was used as the measure of effect to report any risk associations, firstly for exposure to outcome associations without any potential confounders, and secondly, for the multivariate analysis that included potential confounders. "Time to event" was defined as the period in days from birth to the date of assessment. Children not HDM sensitized at the time of follow-up assessment were considered censored.

The regression model proposed by Cox (500) is a multiple regression model for analysis of censored survival data and it may be used to study and utilize the pattern of covariation of many variables with the hazard (501). Cox proportional hazards model uses a mathematical model to adjust for multiple covariables, and not stratification as does the Mantel-Haenzel procedure (502).

The Cox proportional hazards model is based on the instantaneous hazard designated  $h(t)$ , which is the risk that the event will occur for a subject in a small time interval ( $\Delta t$ ) at time  $t$ , given the subject did not have the event before that time (501). The risk function (for instantaneous risk it is called a hazard function) applicable to the general population is labeled  $h_0t$ . The hazard function for a specific individual is  $h_i(t)$ . And the ratio of the hazard functions, comparing that for an individual with that for the general population [ $h_i(t)/h_0t$ ] can be considered constant. The value of this constant depends on the characteristics (that is, explanatory variables) of the individual (502).

Cox (500) suggested that the fixed ratio of the two hazard functions be considered as an exponential function of the explanatory variables:

$$\frac{h_j(t)}{h_0t} = e^{\beta_1 x_{1j} + \beta_2 x_{2j} + \beta_3 x_{3j} + \dots}$$

Where  $x_{1j}$  is the value of explanatory variable 1 for the  $j$ th individual,  $x_{2j}$  and  $x_{ij}$  are the values of the second and  $i$ th variables for the  $j$ th individual (502).

By taking the logarithm of each side and recognizing that the hazard function ratio expresses relative risk, the equation becomes:

$$\ln \text{ relative risk} = \beta_1 x_{1j} + \beta_2 x_{2j} + \beta_3 x_{3j} + \dots$$

From this equation it can be seen that the model assumes that the explanatory variables are linearly related to  $\ln$  RR (503). The equation provides relative risks for each subject, since although  $h_0(t)$  is unknown, it is the same for each subject (502). When interest is in determining the relative risk of morbidity or mortality of two groups, adjusted for potentially confounding variables, one of the variables (say  $x_1$ ) can be an indicator variable so that  $x_{1j} = 1$  if the  $j$ th individual is in the specified group (perhaps being exposed to a bedding item) and  $x_{1j} = 0$  if not in that group. Under these conditions, the  $\ln$  RR of an event comparing exposed to non-exposed, and adjusted for various confounding variables ( $x_2$  and  $x_3, \dots$ ), is  $\beta_1$ . If  $x_2$  were also a dichotomous variable, the  $\ln$  RR comparing exposed persons with  $x_2$  present to those non-exposed with  $x_2$  absent would be  $\beta_1 + \beta_2$  (502). The methods are analogous to those used for multiple regression and the results may be similarly interpreted. Thus  $\beta_j$  represents the estimated change in  $\ln$  RR for each unit change in  $x_j$  after removing from both  $x_j$  and  $\ln$  RR their linear relationship with the other explanatory variables included in the analysis (502).

#### **4.3.3.2 Confounder identification**

To identify potential confounders, the association between a large number of factors and HDM sensitization were examined (Table 4.2). I further examined how these factors related to the bedding exposures of interest. More than 80 potential confounders were examined to see how they each related separately to use of the individual exposure variables and HDM sensitization in terms of magnitude and statistical significance. Several factors, early introduction of solid food, home gas heating and private health insurance at birth, are associated with sensitization to HDM and have been previously reported (504). Moreover, it has been previously shown in this population in a cross-sectional analysis that feather bedding is inversely associated with HDM sensitization (196).

### **4.3.3.3 Proportional hazards model**

A proportional hazards model was then constructed as follows. For each exposure, potential confounders (330) were added to the model as covariates if the variables were associated with HDM sensitization in the exposure to outcome analysis, or were reported to be related to HDM sensitization or asthma in the literature. I examined the confounding effect of these factors on each exposure-disease association using change-in estimate methods (466). Those factors that altered the point estimate for the exposure-HDM association by 10 percent or more were included as potential confounders. To confirm that the final confounder sets used were the most appropriate, I then added in the remaining variables in Table 4.2 as individual factors into the final model. None of these factors altered the adjusted risk ratios reported in Table 4.3. Family history was defined as asthma in any of the infant's siblings, parents or grandparents. A positive family history at birth may result from shared bedding practices within the family (505), thus the possible contribution of family history of asthma to the association between bedding and HDM sensitization was explored and not merely treated as a routine confounder.

### **4.3.3.4 Population attributable fraction**

The aetiologic fraction of HDM sensitization in childhood attributable to either plastic mattress cover or sheepskin use in infancy was calculated as  $p(aRR-1)/aRR$ , where  $p$  = the proportion of children with either plastic mattress cover or sheepskin use in infancy among those with the outcome of HDM sensitization and  $aRR$  = the relative risk estimate for either plastic mattress cover or sheepskin use and HDM sensitization, after adjustment for the confounders listed in Table 4.2 (330). In a population in which there are exposed and unexposed individuals, as in this birth cohort, the incidence due to a given exposure is calculated as  $I_t - I_o$ , where  $I_t$  = total incidence in the population and  $I_o$  = incidence in non-exposed (456). The population attributable fraction (PAF) assumes causality, that is, that the exposure causes the outcome and gives the proportion of the occurrence of the disease in exposed individuals that was due to the exposure.

### **4.3.4 Statistical methods to assess respiratory symptoms**

A generalized linear model (see Section 3.1.5.3) with a log link function and binomial error structure was used to control simultaneously for multiple confounders and to obtain confidence



intervals for RR estimates (452). Confounders were selected using the change-in estimate methods (466). Those factors that altered the point estimate for the exposure-wheeze association by 10 percent or more were included in the final model. It is not appropriate to use Cox proportional hazards model for the analysis of wheeze. Unlike HDM sensitization where a child was determined as having the "event", either a positive or negative SPT by the time of assessment, the date of wheeze occurrences have not been ascertained. Only the first event contributes to the analysis in Cox's regression. Repeated episodes in the same individual are not statistically independent and cannot be considered as separate timed events in proportional hazards regression (506). Further, unlike sensitization, wheeze is intermittent throughout the course of the illness - some non-wheezing children will have had wheeze but not in the last 12 months. Thus, wheeze does not fit a cumulative incidence pattern.

#### **4.3.4.1 Lung function tests**

Multiple linear regression models (see Section 3.1.5.2) were used to examine continuous outcomes, such as FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC. The ratio of FEV<sub>1</sub> to FVC was taken as a measure of airway obstruction (196, 504).

### **4.4 RESULTS: THE 1997 CARHS**

#### **4.4.1 Characteristics of the study population**

In Northern Tasmania in 1997, parents of 499 (84%) of the 596 children identified as participants in the 1988-89 TIHS at birth agreed for their children to participate in the CARHS study. SPT data were available on 498 as one autistic child did not undergo the SPT. Data on the use of underbedding was available on 460, for mattresses on 457, for cots on 459 children. Overall, 23.3% of the children were sensitized to mite allergen, *D. pteronyssinus* or *D. farinae*. Respiratory symptoms were common: 30.8% of the children reporting recent wheeze, 20.7% night wheeze and 37.8% wheeze ever. The characteristics of the study sample are shown in Table 4.1.

Plastic mattress covers (55%, 254/460) were used more commonly than sheepskin underbedding (23%, 106/460) in early infancy. Other types of mattress covers used included cotton, wool or synthetic material. Undersheets were predominantly cotton (91.4%). The use of foam mattresses (52%, 237/457) was also common. Non-foam mattresses were predominantly ti-tree

(40%) or other (8%). Cots were mostly either plasticine (41.0%) or comprised a wood or steel frame (47.1%). The complete time period of use for each particular bedding item was not available. Infants more commonly slept on their side (57.2%) than on their back (7.9%) as reported by their parents.

**Table 4.1 Characteristics of the Study Population in the 1997 CARHS**

<b>Categorical measures</b>	<b>%</b>	<b>n/total N*</b>
Male	71.5	357/499
<i>D. pteronyssinus</i> sensitization**	22.5	112/498
<i>D. farinae</i> sensitization**	11.9	59/498
HDM sensitization**	23.3	116/498
Ryegrass sensitization***	17.1	85/498
Other indoor aeroallergen sensitization****	7.0	35/498
Cat sensitization	2.8	14/498
Alternaria sensitization	4.0	20/498
Dog sensitization	0.2	1/498
<b>Respiratory symptoms</b>		
Recent wheeze	30.8	153/497
Wheeze episodes in past 12 months		
No wheeze	67.0	321/479
1-3	23.0	110/479
4-12	6.7	32/479
>12	3.3	16/479
Night wheeze	20.7	101/487
Asthma ever	37.8	188/497
<b>Underbedding</b>		
Neither sheepskin nor plastic cover use	30.2	139/460
Only sheepskin use in infancy	14.6	67/460
Only plastic mattress cover	46.7	215/460
Both sheepskin and plastic cover	8.5	39/460
Cotton undersheet use	91.4	380/416
Other	8.6	36/416
<b>Mattress type</b>		
Foam mattress	51.9	237/457
Natural fibre mattress*****	40.7	186/457
Other	7.4	34/457

**Table 4.1 continued**

<b>Categorical measures</b>	<b>%</b>	<b>n/total N†</b>
<b>Cot type</b>		
Plasticaine	41.0	188/459
Wood/steel frame	47.1	216/459
Other	12.0	55/459
<b>Sleep position</b>		
Prone	40.6	187/461
Side	54.0	249/461
Back	3.5	16/461
Other	2.0	9/461
<b>Continuous variables</b>	<b>Mean</b>	<b>Standard deviation</b>
Age (in years)	8.7	0.6
Maximum Forced Expiratory Volume (FEV <sub>1</sub> ) (in litres)	1.70	0.28
Maximum Forced Vital Capacity (FVC) (in litres)	1.88	0.36
FEV <sub>1</sub> /FVC ratio (%)	0.91	0.07

\*Small N for some characteristics: bedding items (N=416).

\*\*Any skin prick reaction of greater than or equal to 3 mm to mite allergen, *D. pteronyssinus* or *D. farinae*.

\*\*\*Any skin prick reaction of greater than or equal to 3 mm to ryegrass.

\*\*\*\*Any skin prick reaction of greater than or equal to 3 mm to alternaria, cat or dog.

\*\*\*\*\*Natural fibre comprises ti-tree or kapok mattresses.

#### 4.4.2 Potential predictors of HDM sensitization

Table 4.2 shows the unadjusted risk ratios for the bedding variables and potential confounders and the associations with HDM sensitization. The unadjusted RR showed that sheepskin only use, without a plastic mattress cover, in infancy was significantly associated with sensitization to HDM in childhood (unadjusted RR 2.12; 95% CI 1.12, 4.04). The use of only plastic mattress covers was also associated with a significant increase in the risk ratio of HDM sensitization (unadjusted RR 1.96; 95% CI 1.18, 3.25). The use of both a sheepskin and a plastic mattress cover was significantly associated with HDM sensitization (unadjusted RR 2.97; 95% CI 1.51, 5.86). A cotton undersheet was not associated with HDM sensitization in childhood ( $p=0.948$ ). Foam mattress use in infancy was not significantly more likely to be associated with HDM sensitization in childhood (unadjusted RR 1.01; 95% CI 0.69, 1.48). Plasticine infant cots were not associated with HDM sensitization in childhood ( $p=0.296$ ). Individual adjustment for the factors, listed in Table 4.2, considered as potential predictors of subsequent HDM sensitization did not alter the point estimate for the exposure-HDM association by 10 percent or more.

**Table 4.2 Unadjusted risk ratio for infant underbedding, mattress and potential predictors of HDM sensitization\* in the 1997 CARHS**

	HDM sensitization	
	Unadjusted RR (95% CI)	p value
<b>Infant bedding variables</b>		
Sleep environment (reference group)**		
<b>Underbedding</b>		
Neither sheepskin nor plastic cover	1.00 (reference)	-----
Only sheepskin	2.12 (1.12, 4.04)	0.022
Only plastic mattress cover	1.96 (1.18, 3.25)	0.009
Both sheepskin and plastic cover	2.97 (1.51, 5.86)	0.022
Cotton undersheet (no cotton undersheet)	0.98 (0.51, 1.88)	0.948
<b>Mattress type</b>		
Foam mattress (other mattress)***	1.01 (0.69, 1.48)	0.945
<b>Cot type</b>		
Plasticaine (wood, steel or other)	0.83 (0.59, 1.18)	0.296
<b>Potential confounding infant variables</b>		
<b>Maternal factors</b>		
Mother smoking during pregnancy	0.89 (0.62, 1.30)	0.566
Teenage motherhood	0.75 (0.43, 1.32)	0.323
At-birth family history of asthma	1.30 (0.90, 1.89)	0.168
<b>Infant factors</b>		
Infant only child	0.29 (0.07, 1.19)	0.087
Infant first born	0.78 (0.54, 1.14)	0.203
Low birth weight	1.15 (0.73, 1.82)	0.550
Infant bottle fed at one month	1.03 (0.69, 1.54)	0.883
Solid food introduced by phone interview at 10 weeks	1.26 (0.85, 1.85)	0.247
Infant exclusively breast fed by phone interview at 10 weeks	0.74 (0.48, 1.15)	0.183

**Table 4.2 continued**

	HDM sensitization	
	Unadjusted RR (95% CI)	p value
<b>Infant sleep position</b>		
Usual sleep position in infancy = supine	1.00 (reference)	-----
Usual sleep position in infancy = prone	1.33 (0.47, 3.73)	0.591
Usual sleep position in infancy = side	1.33 (0.48, 3.71)	0.582
<b>Household factors</b>		
Private health insurance at birth	1.86 (1.29, 2.70)	0.001
Home gas appliance use	1.83 (0.89, 3.77)	0.101
No-one smoking in same room as infant	1.18 (0.80, 1.72)	0.402
More than six residents in household at birth	1.23 (0.76, 2.00)	0.404
Cat as pet during infancy	1.42 (0.97, 2.08)	0.069
<b>Bedroom factors</b>		
Use of foam pillow at one month age	0.62 (0.27, 1.41)	0.251
Infant sleeping in bedroom alone	0.75 (0.50, 1.13)	0.176
Carpet in infant's bedroom	1.13 (0.59, 2.17)	0.716
Humidity in infant's bedroom >75%	1.44 (0.70, 2.98)	0.321
Window in infant's bedroom open at night	1.06 (0.70, 1.60)	0.774
Use of feather quilt as child	0.65 (0.45, 0.95)	0.025

\*Skin prick reaction of greater than or equal to 3 mm to either mite allergen, *D. pteronyssinus* or *D. farinae*.

\*\*Reference group properties not listed for brevity.

\*\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.1).

#### **4.4.3 Prospective association between underbedding and HDM sensitization**

Table 4.3 reports the association between underbedding and mattress type and HDM sensitization after adjustment for confounders. The adjusted risk ratios for subsequent HDM sensitization remained significant when the different bedding combinations of sheepskin use and/or plastic mattress cover use were compared against a reference variable of neither sheepskin nor plastic mattress cover use. There was very little additional effect with exposure to both sheepskin and plastic mattress cover in infancy. Both sheepskin use and plastic mattress cover use in combination were significantly associated with HDM sensitization (Table 4.3). The

population attributable fractions for HDM sensitization associated with sheepskin or plastic mattress cover use in infancy, if causal, were as follows: 8.8% for sheepskin; and, 26.2% for plastic mattress cover. The use of a foam mattress in infancy was not prospectively associated with an increased risk of sensitization to HDM. The results in Table 4.3 were not altered when the SPT cut off for positivity was 2mm wheal diameter. Similar patterns to Table 4.3 were also found using *D. pteronyssinus* or *D. farinae* as individual species-specific outcomes, both as dichotomous or continuous variables.

For children exposed only to plastic mattress covers in infancy, there was no significant association with childhood sensitization to the other primarily indoor aeroallergens, cat (unadjusted RR 0.60; 95% CI 0.18, 1.90) or alternaria (unadjusted RR 1.46; 95% CI 0.55, 3.90). Moreover, there was no association with exposure to sheepskin (unadjusted RR 1.51; 95% CI 0.76, 3.02), plastic mattress (unadjusted RR 1.28; 95%CI 0.76, 2.18) or both covers together (unadjusted RR 1.43; 95% CI 0.61, 3.35) as an infant and subsequent ryegrass sensitization. Use in infancy of sheepskin alone or plastic mattress cover alone were significantly associated with hayfever (aRR 2.26; 95% CI 1.19, 4.32) and aRR 1.78; 95% CI 1.09, 2.90), respectively. The use in infancy of both these underbedding items was not significantly associated with hayfever in childhood (adjusted RR 1.91; 95% CI 0.89, 4.07).

Usual infant sleep position was not associated with HDM sensitization. The association between sheepskin and HDM sensitization or plastic cover and HDM sensitization did not vary by whether the infant slept prone or not.



**Table 4.3 The prospective association between sheepskin, plastic mattress cover and foam mattress use in infancy and child sensitization to house dust mite in the 1997 CARHS**

	% HDM sensitized** among exposed	Adjusted*** RR (95% CI) for bedding vs none	p value
<b>Bedding (reference group)*</b>			
Neither sheepskin nor plastic cover	15.8% (22/139)	1.00 (reference)	-----
Only plastic mattress cover	25.6% (55/215)	2.06 (1.22, 3.51)	0.007
Only sheepskin	25.4% (17/67)	2.27 (1.14, 4.55)	0.020
Both sheepskin and plastic cover	35.9% (14/39)	2.25 (1.05, 4.83)	0.038
Foam mattress (other)****	23.6% (56/237)	1.09 (0.72, 1.67)	0.676
<b>Sleep position</b>			
Sleep side vs prone	22.9 (57/249)	0.99 (0.64, 1.52)	0.949
Sleep back vs prone	31.3 (5/16)	0.94 (0.30, 2.89)	0.908

\*Reference group properties not listed for brevity.

\*\*Skin prick reaction of greater than or equal to 3 mm to either mite allergen, *D. pteronyssinus* or *D. farinae*.

\*\*\*The risk ratio has been adjusted for parents with private health insurance at time of child's birth, at-birth family history of asthma, being an only child, whether child was exclusively breastfed by ten weeks of age, home gas heater use in infancy, and use of a feather quilt as a child.

\*\*\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.1).

#### 4.4.4 Prospective association between underbedding and asthma

Prospective associations between the underbedding variables and respiratory symptoms are presented in Table 4.4. There is no association between sheepskin, plastic mattress cover or cotton undersheet use in infancy and asthma symptoms in childhood. The type of infant cot is also not associated with childhood respiratory symptoms of asthma. HDM sensitization was significantly associated with child asthma ever (unadjusted RR 1.65; 95% CI 1.32, 2.06) and hayfever (unadjusted RR 2.57; 95% CI 1.78, 3.72).

**Table 4.4 The prospective association between underbedding and cot type and respiratory symptoms in the 1997 CARHS**

Respiratory symptom in childhood <i>Infant bedding (reference group)*</i>	n/total N	% Children with infant bedding combination with wheeze	Risk ratio	95% CI	p value
<b>Recent Wheeze</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	125/419	29.8	1.00 (reference)		
Only plastic mattress cover	64/215	29.8	1.02	0.77, 1.36	0.875
Only sheepskin	15/66	22.7	0.74	0.47, 1.19	0.217
Both sheepskin and plastic cover	10/40	25.0	0.84	0.48, 1.46	0.534
Cotton	112/380	29.5	1.72	0.82, 3.62	0.154
<i>Cot type</i>					
Plasticaine (wood, steel or other)	58/187	31.0	1.09	0.82, 1.45	0.564
<b>Night Wheeze</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	81/409	19.8	1.00 (reference)		
Only plastic mattress cover	43/209	20.6	1.10	0.75, 1.60	0.627
Only sheepskin	9/65	13.9	0.67	0.36, 1.27	0.223
Both sheepskin and plastic cover	7/40	17.5	0.88	0.44, 1.78	0.729
Cotton	70/370	18.9	0.32	0.57, 3.05	0.515
<i>Cot type</i>					
Plasticaine (wood, steel or other)	35/182	19.2	0.96	0.66, 1.41	0.841
<b>Asthma Ever</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	155/419	36.7	1.14	0.57, 2.28	0.714
Only plastic mattress cover	82/214	38.3	1.10	0.87, 1.41	0.420
Only sheepskin	25/67	37.3	1.03	0.74, 1.44	0.863
Both sheepskin and plastic cover	12/40	30.0	0.81	0.50, 1.32	0.402
Cotton	140/378	37.0	1.21	0.73, 2.02	
<i>Cot type</i>					
Plasticaine (wood, steel or other)	76/188	40.4	1.19	0.94, 1.52	0.147

\*Reference group properties not listed for brevity.

#### 4.4.4.1 The prospective association between mattress type and wheeze

The prospective associations between foam mattress and wheeze are shown in Table 4.5. The positive association between foam mattress use in infancy and subsequent respiratory symptoms found in the unadjusted analysis was reduced following the adjustment for potential confounders, including other infant bedding factors such as sheepskin, plastic mattress cover and synthetic quilt. There was no association between foam mattress and frequent wheeze.

**Table 4.5 Prospective association between foam mattress use in infancy and childhood respiratory symptoms in the 1997 CARHS**

Respiratory symptom in childhood Infant mattress (reference group)*	n/total N	% Children with infant bedding combination with wheeze	Unadjusted RR	p value	Adjusted RR**	p value
<b>Recent wheeze</b>						
Foam mattress (other)***	81/235	34.5	1.41 (1.05, 1.89)	0.021	1.35 (0.98, 1.83)	0.063
<b>Night wheeze</b>						
Foam mattress (other)***	54/230	23.5	1.49 (1.01, 2.20)	0.043	1.28 (0.83, 1.88)	0.289
<b>Asthma ever</b>						
Foam mattress (other)***	96/236	40.7	1.26 (0.99, 1.61)	0.065	1.13 (0.87, 1.46)	0.364

\*Reference group properties not listed for brevity.

\*\*The risk ratio has been adjusted for parents with private health insurance at time of child's birth, at-birth family history of asthma, being an only child, whether child was exclusively breastfed by ten weeks of age, home gas heater use in infancy, use of a sheepskin in infancy, use of a plastic mattress cover in infancy, and use of a synthetic quilt as a child.

\*\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.1).

#### **4.4.4.2 Infant underbedding and child lung function**

In this sample of 499 children, lung function data were available on 495. The mean FEV<sub>1</sub> was 1.70 litres, (standard deviation 0.28), and the mean FVC was 1.88 litres, (standard deviation 0.36). The FEV<sub>1</sub> and FVC volumes were close to volumes predicted for healthy Australian children of a similar height and gender using a previously published normogram (441). The previous study had calculated predicted values of FEV<sub>1</sub> and FVC, based on height and sex, and from normal values obtained for 1,280 Australian children without asthma, not using asthma medications, with no recent respiratory infection, and who were not treated for bronchitis before the age of 2 years (441). The regression equation for normal FVC was calculated as follows (441):

$$FVC = 0.000123 \times \text{height}^2 - 0.261 \text{ (-0.147 for females)}$$

And for FEV<sub>1</sub>:

$$FEV_1 = 0.000106 \times \text{height}^2 - 0.155 \text{ (-0.09 for females)}.$$

Applying these equations to the 1997 CARHS study population, the mean percentage of predicted was 98% for FEV<sub>1</sub> and 97% for FVC. The mean FEV<sub>1</sub>/FVC ratio was 91% (standard deviation 7). Only 6.9% (34/495) children had a FEV<sub>1</sub>/FVC ratio of less than 80%.

I undertook an analysis of the spirometric values to allow an assessment to be made of the clinical importance of a change in respiratory function. I did not demonstrate any significant differences in the mean spirometric values between children with exposure to the different underbedding and mattress types in infancy. These results are shown in Table 4.6 and Table 4.7. Children who were exposed to the listed underbedding items in infancy did not demonstrate a greater reduction in their adjusted difference in mean FEV<sub>1</sub>/FVC ratio when compared to children with either recent or frequent wheeze.

Table 4.6 Unadjusted differences in mean spirometric values between children with different bedding combinations in infancy in the 1997

CARHS

Child respiratory symptoms and bedding exposure	Unadjusted difference in mean FEV <sub>1</sub> (mL) with 95% CI between children with and without characteristic	p value	Unadjusted difference in mean FVC (mL) with 95% CI between children with and without characteristic	p value	Unadjusted difference in mean FEV <sub>1</sub> /FVC (%) with 95% CI between children with and without characteristic	p value
<b>Child respiratory symptoms:</b>						
Recent wheeze	0.95 (-4.5, 6.4)	0.732	3.6 (-3.2, 10.5)	0.301	-1.2 (-2.5, 0.10)	0.070
Frequent wheeze	-19.9 (-34.2, -5.7)	0.006	-16.1 (-33.9, 1.7)	0.077	-3.6 (-6.9, -0.38)	0.029
<b>Bedding exposure variables:</b>						
Sheepskin	4.8 (-2.6, 12.3)	0.202	2.4 (-6.8, 11.6)	0.612	1.31 (-0.46, 3.1)	0.146
Plastic mattress liner	-0.05 (-5.3, 5.2)	0.987	2.9 (-3.7, 9.4)	0.390	-1.1 (-2.3, 0.17)	0.091
Both	3.5 (-6.0, 13.1)	0.466	0.17 (-11.7, 12.0)	0.978	1.5 (-0.79, 3.8)	0.199
Foam mattress (other)**	-6.7 (-11.9, -1.4)	0.013	-8.8 (-15.3, -2.3)	0.008	0.62 (-0.64, 1.9)	0.335

\*All estimates adjusted for child height (cm), child age (years), child sex, season of lung function (3-month periods) and technician.

\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.1).

**Table 4.7 Adjusted differences in mean spirometric values between children with different bedding combinations in infancy in the 1997**

**CARHS**

Child respiratory symptoms and bedding exposure	Adjusted difference in mean FEV <sub>1</sub> (mL) with 95% CI between children with and without characteristic	p value	Adjusted difference in mean FVC (mL) with 95% CI between children with and without characteristic	p value	Adjusted difference in mean FEV <sub>1</sub> /FVC (%) with 95% CI between children with and without characteristic	p value
<b>Child respiratory symptoms:</b>						
Recent wheeze	-0.57 (-4.3, 3.2)	0.767	1.8 (-3.1, 6.7)	0.474	-1.1 (-2.4, 0.16)	0.085
Frequent wheeze	-12.6 (-22.3, -29.5)	0.011	-7.4 (-20.0, 5.2)	0.251	-3.8 (-7.1, -0.57)	0.021
<b>Bedding exposure variables:</b>						
Sheepskin	3.5 (-1.6, 8.6)	0.179	0.72 (-5.8, 7.3)	0.830	1.4 (-0.39, 3.1)	0.127
Plastic mattress liner	-2.4 (-6.1, 1.2)	0.195	0.18 (-4.5, 4.9)	0.939	-1.1 (-2.3, 0.20)	0.099
Both	2.2 (-4.4, 8.3)	0.508	-1.4 (-9.8, 7.0)	0.747	1.5 (-0.78, 3.8)	0.197
Foam mattress (other)**	-2.5 (-6.2, 1.2)	0.190	-3.5 (-8.2, 1.2)	0.149	0.40 (-0.87, 1.7)	0.535

\*All estimates adjusted for child height (cm), child age (years), child sex, season of lung function (3-month periods) and technician.

\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.1).

#### **4.4.5 Family history**

I further examined the role of family history and HDM sensitization and asthma. An at-birth family history of asthma was not significantly associated with subsequent HDM sensitization (unadjusted RR 1.30; 95% CI 0.90, 1.89). There was no evidence that parents of infants with an at-birth family history of asthma were selectively avoiding sheepskins (37.1% use versus 37.0% non-use,  $p=0.953$ ) as part of a bed allergen reduction strategy, nor were they selectively using a plastic mattress cover (38.8% use versus 34.8% non-use,  $p=0.376$ ). Exposures to sheepskin (unadjusted RR 2.12; 95% CI 0.94, 4.80) or plastic mattress cover (unadjusted RR 1.89; 95% CI 1.01, 3.55) tended to be positively associated with HDM sensitization even among the subgroup of those with no at-birth family history of asthma. The positive association with either sheepskin use or plastic mattress cover use in infancy and subsequent HDM sensitization remained significant after adjustment for the child's history of eczema, hay fever and asthma, and also the family history of asthma in 1997. Further adjustment for at-birth family history of asthma did not alter the results in Table 4.3.

### **4.5 STATISTICAL METHODS: THE 1995 CHILDHOOD ASTHMA SURVEY**

#### **4.5.1 The Infant cohort study with 1995 follow-up**

For the children who as infants were part of the TIHS birth cohort and also participated in the 1995 Childhood Asthma Survey, the identical underbedding exposure variables and coding were constructed as for the 1997 CARHS (see Section 4.3.1). The outcomes variables were recent wheeze, night wheeze or asthma ever (see Section 4.3.2). For this prospective data, a generalized linear model with a log link function and binomial error structure was used to control simultaneously for multiple confounders and to obtain confidence intervals for RR estimates (452) as described in Section 4.3.4.

## **4.5.2 The cross-sectional 1995 Childhood Asthma Survey**

The main underbedding exposure variables of interest were the use in childhood at age 7 years of cotton quilted cover, sheepskin, plastic mattress cover, electric blanket, foam mattress and innerspring mattress. Bed types were single, double, top bunk-bed and bottom bunk-bed. All ten variables were dichotomous for exposure or no exposure to the bedding variable. The outcome variables were recent wheeze, night wheeze or asthma ever (see Section 4.3.1).

ORs were estimated by logistic regression analysis (502) (see Section 3.1.5.1). To examine the possible contribution of confounders, multiple logistic regression models that included terms for the exposure and potential confounding variables were used following the procedures described in Section 4.3.4.

## **4.6 RESULTS: THE 1995 CHILDHOOD ASTHMA SURVEY**

### **4.6.1 The Infant cohort study with 1995 follow-up**

#### ***4.6.1.1 Characteristics of the study population***

Among the 863 children in the 1995 Childhood Asthma Survey who were also included in the cohort study, the mean age was 6.9 years (standard deviation 0.3 years). Table 4.8 describes the characteristics of this study population. Similar to the children from the TIHS who were seen in 1997, wheeze was also common. There were 27.0% (222/823) of the children with recent wheeze, 19.2% (160/834) with night wheeze and 32.4% (280/863). The most common type of cots was either plasticaine 39.1% or cots with either wood or steel frames 44.6%. Other cot types included carry cot (1.5%) and other (14.9%).



**Table 4.8 Characteristics of the study population in the Infant cohort study with 1995 follow-up**

<b>Categorical measures</b>	<b>%</b>	<b>n/total N</b>
Male sex	71.3	615/863
<b>Respiratory symptoms</b>		
Recent wheeze	27.0	222/823
Wheeze episodes in past 12 months		
1-3	17.2	125/726
4-12	10.0	67/668
>12	4.8	30/631
Night wheeze	19.2	160/834
Asthma ever	32.4	280/863
<b>Underbedding</b>		
Neither sheepskin nor plastic cover use	35.7	307/859
Only sheepskin use in infancy	34.5	296/859
Only plastic mattress cover	23.3	200/859
Both sheepskin and plastic cover	6.5	56/859
Cotton undersheet use	81.4	699/859
<b>Mattress type</b>		
Foam mattress	62.8	536/854
Natural fibre mattress*	32.4	277/854
Other	4.8	41/854
<b>Cot type</b>		
Plasticaine	39.1	334/855
Wood/steel frame	44.6	381/855
Other	16.4	140/855
<b>Continuous variables</b>		
	<b>Mean</b>	<b>Standard deviation</b>
Age	6.9	0.3

\*Natural fibre comprises ti-tree or kapok mattresses.

#### ***4.6.1.2 Prospective associations between underbedding and asthma***

Prospective associations between the underbedding variables and respiratory symptoms are presented in Table 4.9. There is no association between sheepskin, plastic mattress cover or cotton undersheet use in infancy and asthma symptoms in childhood. No prospective association was found between cot type in infancy and subsequent development of wheeze or HDM. Further analysis of wheeze by sub-group of frequency did not provide different results from Table 4.9.

### **4.6.2 The cross-sectional 1995 Childhood Asthma Survey**

#### ***4.6.2.1 Characteristics of the study population***

The 1995 cross-sectional Childhood Asthma Survey was similar to the Infant cohort study with 1995 follow-up with regard to child age, but the proportion of children experiencing respiratory symptoms was lower. Cotton quilted covers (42.1%), electric blanket (21.4%) and sheepskin (21.1%) were the most common underbedding items. The majority of children in 1995 slept in a single bed (73.4%) whereas 10.8% slept in either the top or bottom bunk-bed. The study characteristics are presented in Table 4.10.

**Table 4.9 The prospective association between underbedding and cot type and respiratory symptoms in the Infant Cohort Study with 1995 follow-up**

Childhood respiratory symptoms <i>Infant bedding (reference group)*</i>	% Children with infant bedding combination with wheeze	n/total N	Risk ratio	95% CI	p value
<b>Recent Wheeze</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	27.1	207/764	1.00 (reference)		
Only plastic mattress cover	27.3	77/282	1.03	0.81, 1.30	0.836
Only sheepskin	27.7	52/188	1.04	0.80, 1.35	0.778
Both sheepskin and plastic cover	23.6	13/55	0.87	0.53, 1.42	0.584
<i>Mattress type</i>					
Foam mattress (other)**	27.1	138/509	1.05	0.83, 1.33	0.706
<i>Cot type</i>					
Plasticaine (vs wood, steel or other)	29.6	93/314	1.19	0.94, 1.49	0.141
<b>Night Wheeze</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	19.2	149/776	1.00 (reference)		
Only plastic mattress cover	18.0	52/289	0.92	0.68, 1.24	0.577
Only sheepskin	18.7	36/193	0.97	0.70, 1.36	0.877
Both sheepskin and plastic cover	16.7	9/54	0.87	0.47, 1.60	0.651
<i>Mattress type</i>					
Foam mattress (other)**	19.0	98/517	1.01	0.75, 1.35	0.965
<i>Cot type</i>					
Plasticaine (vs wood, steel or other)	21.9	70/320	1.24	0.96, 1.69	0.091
<b>Asthma Ever</b>					
<i>Underbedding</i>					
Neither sheepskin nor plastic cover	32.3	259/803	1.00 (reference)		
Only plastic mattress cover	31.8	94/296	0.97	0.79, 1.19	0.783
Only sheepskin	29.5	59/200	0.89	0.70, 1.13	0.331
Both sheepskin and plastic cover	33.9	19/56	1.05	0.72, 1.54	0.794
<i>Mattress type</i>					
Foam mattress (other)**	33.8	181/536	1.12	0.91, 1.37	0.284
<i>Cot type</i>					
Plasticaine (vs wood, steel or other)	33.2	111/334	1.04	0.85, 1.26	0.719

\*Reference group properties not listed for brevity.

\*\*Ti-tree mattresses comprised the majority of other mattresses (see Table 4.8).

**Table 4.10 Characteristics of the study population in the cross-sectional 1995 Childhood Asthma Survey**

<b>Continuous measures</b>	<b>Mean</b>	<b>Standard deviation</b>
Mean age (years)	6.9	0.3
<b>Categorical measures</b>	<b>%</b>	<b>n/total N</b>
Recent wheeze	22.9	1400/6107
Wheeze episodes in past 12 months		
1-3	15.8	880/5587
4-12	7.5	384/5091
>12	2.8	136/4834
Night wheeze	14.4	889/6172
Severe wheeze	3.9	249/6317
Asthma ever	27.1	1710/6307
<b>Type of mattress</b>		
Foam	32.0	2038/6364
Innerspring	66.3	4218/6364
Other	1.7	108/6364
<b>Mattress liners</b>		
No covering	8.3	524/6307
Cotton covered quilted	42.1	2653/6307
Plastic/PVC	12.8	809/6307
Sheepskin	21.1	1331/6307
Electric blanket	21.4	1347/6307
Allergy cover	0.9	54/6307
Other (for example, rugs)	1.1	71/6306
<b>Type of bed</b>		
Single	73.4	4662/6354
Double	2.0	129/6354
Top bunk	10.8	687/6354
Bottom bunk	10.8	686/6354
Other	3.0	190/6354
Bed on the floor	1.4	90/6329
Bed supported by legs or frame	98.6	6239/6329

#### **4.6.2.2 Current underbedding and mattress type and respiratory symptoms**

Associations between the current use of different underbedding and types of mattress are shown in Table 4.11. Current electric blanket use is positively associated with both recent wheeze (OR 1.18; 95% CI 1.02, 1.3) and night wheeze (OR 1.27; 95% CI 1.08, 1.50). The current use of sheepskin is negatively associated with respiratory symptoms. This inverse association was greater for children with frequent wheeze: OR 0.84 (95% CI 0.70, 1.01) for 1-3 episodes; OR 0.75 (95% CI 0.57, 0.98) for 4-12 episodes; and, OR 0.54 (95% CI 0.33, 0.90) for more than 12 episodes of wheeze in the past year (Test for trend,  $p=0.002$ ).

#### **4.6.2.3 Current electric blanket and sheepskin use and respiratory symptoms**

The associations between current electric blanket use and various wheeze outcomes remained significant after the adjustment for potential confounders: recent wheeze (aOR 1.26; 95% CI 1.08, 1.46), night wheeze (aOR 1.35; 95% CI 1.13, 1.61) and asthma ever (aOR 1.17; 95% CI 1.01, 1.35). Compared to no wheeze the association was stronger for children with frequent wheeze: aOR 1.08 (95% CI 0.90, 1.30) for 1-3 episodes; aOR 1.53 (95% CI 1.19, 1.96) for 4-12 episodes; and, aOR 1.79 (95% CI 1.21, 2.65) for more than 12 episodes of wheeze in the past year (Test for trend  $p=0.003$ ). The inverse association between current use of sheepskin as underbedding and wheeze remained greater for more than 12 episodes of wheeze than less episodes of wheeze in the past year after the adjustment for potential confounders. The Test for trend,  $p=0.083$ , was of borderline significance. These results are shown in Table 4.12.

**Table 4.11 Association between underbedding and mattress use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey**

Child respiratory symptom <i>Child bedding (reference group)*</i>	% Children with bedding combination with respiratory symptoms	n/total N	Odds ratio	95% CI	p value
<b>Recent Wheeze</b>					
<i>Underbedding at age 7 (more than one type was recorded)</i>					
No cover (any cover)	23.0	116/505	1.00	0.81, 1.24	0.997
Cotton quilted (other)	23.3	589/2533	1.03	0.91, 1.16	0.649
Plastic (other)	23.3	182/780	1.02	0.86, 1.22	0.792
Sheepskin (other)	19.7	252/1278	0.78	0.67, 0.91	0.002
Electric blanket (other)	25.3	325/1284	1.18	1.02, 1.36	0.024
<i>Mattress type at age 7</i>					
Foam mattress (vs other*)	24.3	475/1953	1.12	0.99, 1.28	0.071
<b>Night Wheeze</b>					
<i>Underbedding at age 7</i>					
No cover (any cover)	16.3	83/510	1.17	0.91, 1.50	0.210
Cotton quilted (other)	14.4	368/2564	0.99	0.86, 1.15	0.917
Plastic (other)	13.2	104/788	0.89	0.71, 1.11	0.300
Sheepskin (other)	12.4	161/1297	0.81	0.67, 0.97	0.021
Electric blanket (other)	16.9	220/1305	1.27	1.08, 1.50	0.005
<i>Mattress type at age 7</i>					
Foam mattress (vs other)**	15.2	299/1966	1.10	0.95, 1.28	0.208
<b>Asthma Ever</b>					
<i>Underbedding at age 7</i>					
No cover (any cover)	29.0	150/517	1.11	0.91, 1.36	0.290
Cotton quilted (other)	26.9	706/2625	0.99	0.88, 1.11	0.835
Plastic (other)	27.5	219/796	1.03	0.87, 1.21	0.744
Sheepskin (other)	23.9	314/1316	0.81	0.70, 0.93	0.004
Electric blanket (other)	28.3	378/1339	1.08	0.94, 1.24	0.266
<i>Mattress type at age 7</i>					
Foam mattress(vs other)**	28.3	570/2011	1.09	0.97, 1.23	0.140

\* Reference group properties not listed for brevity.

\*\*Innerspring mattresses comprised the majority of other mattresses (see Table 4.10).

**Table 4.12 Association between electric blanket and sheepskin use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey**

Child Bedding (reference group)* Child respiratory symptom	% Children with bed item with respiratory symptoms	n / total N	Unadjusted Odds ratio (95% CI)	p value	Adjusted Odds ratio** (95%CI)	p value
<b>Electric blanket</b>						
Wheeze frequency over past year						
None (0 episodes)			1.00 (reference)	----	1.00 (reference)	----
1-3 episodes	16.3	187/1146	1.05 (0.88, 1.25)	0.599	1.08 (0.90, 1.30)	0.390
4-12 episodes	9.4	99/1058	1.37 (1.08, 1.74)	0.011	1.53 (1.19, 1.96)	0.001
>12 episodes	3.9	39/998	1.56 (1.07, 2.29)	0.021	1.79 (1.21, 2.65)	0.004
p value for test for trend				0.024		0.003
<b>Sheepskin</b>						
Wheeze frequency over past year						
None (0 episodes)			1.00 (reference)	----	1.00 (reference)	----
1-3 episodes	14.1	168/1194	0.84 (0.70, 1.01)	0.063	0.89 (0.74, 1.08)	0.229
4-12 episodes	6.0	66/1092	0.75 (0.57, 0.98)	0.038	0.89 (0.67, 1.19)	0.433
>12 episodes	1.7	18/1044	0.54 (0.33, 0.90)	0.017	0.65 (0.39, 1.08)	0.096
p value for test for trend				0.002		0.083

\* Reference group properties not listed for brevity.

\*\*Adjusted for family history of asthma as a child, use of a synthetic quilt as a child, male sex, exposure to cigarette smoke as a child, carpet in the child's bedroom.

#### **4.6.2.4 Bed type and respiratory symptoms**

In the univariate analysis, there was no relationship between the child's current use of a single bed, double bed or the top bunk-bed and recent wheeze, night wheeze and asthma ever (see Table 4.13). Table 4.14 shows that when frequency of recent wheeze was examined, for those children sleeping in the bottom bunk-bed, there was an increased risk of greater than 12 episodes of wheeze (aOR 1.63; 95% CI 1.01, 2.65). Sleeping on the top bunk-bed was not associated with respiratory symptoms.

**Table 4.13 Association between bed type in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey**

Child respiratory symptom Child Bedding (reference group)*	% Children with bedding combination with wheeze	n/total N	Unadjusted Odds ratio	95% CI	p value
<b>Recent Wheeze</b>					
Single bed	22.6	1011/4473	1.00 (reference)		
Double bed	21.3	26/122	0.91	0.59, 1.41	0.677
Top bunk	23.4	153/653	1.04	0.85, 1.25	0.723
Bottom bunk	23.8	156/655	1.06	0.88, 1.28	0.546
Supporting frame	22.3	1370/5976	1.49	0.84, 2.65	0.178
<b>Night Wheeze</b>					
Single bed	14.2	639/4517	1.00 (reference)		
Double bed	12.3	15/122	0.83	0.48, 1.44	0.515
Top bunk	14.3	95/666	0.99	0.79, 1.25	0.951
Bottom bunk	16.7	110/660	1.22	0.98, 1.52	0.072
Supporting frame	14.4	867/6043	0.90	0.50, 1.64	0.734
<b>Asthma Ever</b>					
Single bed	27.0	1247/4612	1.00 (reference)		
Double bed	23.0	29/126	0.80	0.53, 1.22	0.297
Top bunk	27.8	189/679	1.04	0.87, 1.24	0.656
Bottom bunk	27.3	185/678	1.01	0.84, 1.21	0.916
Supporting frame	27.2	1679/6174	1.27	0.77, 2.10	0.350

\*Reference group properties not listed for brevity.



**Table 4.14 Association between bunk-bed use in childhood and respiratory symptoms in the cross-sectional 1995 Childhood Asthma Survey**

<b>Bunk-bed (reference group)*</b> Child respiratory symptom	<b>% Children with bed item with respiratory symptoms</b>	<b>n / total N</b>	<b>Unadjusted Odds ratio (95% CI)</b>	<b>p value</b>	<b>Adjusted Odds ratio** (95%CI)</b>	<b>p value</b>
<b>Bottom bunk-bed (vs top bunk bed)</b>						
Recent wheeze	23.8	156/655	1.06 (0.88, 1.28)	0.546	1.09 (0.89, 1.33)	0.413
Wheeze frequency over past year						
None (0 episodes)						
1-3 episodes	15.3	90/589	0.96 (0.76, 1.22)	0.750	1.03 (0.80, 1.31)	0.838
4-12 episodes	8.1	44/543	1.10 (0.79, 1.52)	0.579	1.06 (0.75, 1.50)	0.743
>12 episodes	4.2	22/521	1.64 (1.03, 2.61)	0.038	1.63 (1.01, 2.65)	0.046
<i>p value for test for trend</i>				<i>0.546</i>		<i>0.413</i>
Night wheeze over past year	16.7	110/660	1.22 (0.98, 1.52)	0.072	1.26 (1.00, 1.59)	0.048
Asthma ever	27.3	185/678	1.01 (0.84, 1.21)	0.916	1.00 (0.82, 1.21)	0.968

\*Reference group properties not listed for brevity.

\*\*Adjusted for family history of asthma as a child, use of a synthetic quilt as a child, cat as a pet as a child, number of household residents as a child, carpet in the child's bedroom.

## 4.7 DISCUSSION

In the 1997 birth cohort, the use of sheepskin or the use of plastic mattress covers in infancy were associated with an increased risk of HDM sensitization in childhood. There was no evidence of a synergistic multiplicative interaction when both sheepskin and plastic mattress cover were together with an aRR 2.25 (95% CI 1.05, 4.83). This aRR was not multiplicative of the two individual risk ratios, that is aRR 2.06 (95% CI 1.22, 3.51) for plastic mattress cover and aRR 2.27 (95% CI 1.14, 4.55) for sheepskin. This may be demonstrating the importance of closer proximity to the airways of one item over another. No association was found between the other types of underbedding nor with foam mattress use and HDM sensitization. The type of infant cot was not associated with HDM sensitization in childhood.

The strengths of this study include prospective infant bedding measures, the ability to examine many potential confounders and the availability of a biological parameter to HDM sensitization among the child sample. The study sample was not representative of all live births in the geographical area, it consisted of infants born at higher risk of SIDS (436) (see Section 3.2.1). However, none of the cohort entry criteria predicted HDM sensitization. After controlling for the factors listed in Table 4.3, additional individual adjustment for any scoring system components did not alter the results. The results are not likely to be influenced by differential follow-up as the proportion of TIHS children followed up from infancy did not differ by the type of bedding to which they were exposed. In addition, I was able to control for other bedding variables that are associated with underbedding plus a large number of potential confounding factors operating in either infancy or childhood. Confounding, including that due to family history of asthma, could not explain the identified associations. In fact, the risk ratio increased in magnitude after adjustment for significant confounders, showing the importance of being able to take these into account.

There was a good follow-up rate and the children in this study should not differ from other children to any large extent with regard to the development of allergic sensitization. Furthermore, there was no recall bias or disease related choice in bedding because the bedding exposure was measured prospectively and was independent of disease awareness. At the time of assessment for HDM sensitization, the research nurse was also unaware of the infant bedding status. The findings of similar results in children with no family history of asthma also argue against a spurious association caused by the non-selection of sheepskin and/or the selection of plastic mattress liners by parents in asthmatic families. However, these findings cannot be conclusive in

an observational study. The generalizability of the results from this cohort is discussed in Chapter 5 (see Section 5.7.6).

Personal exposure measures to HDM allergen levels were not available. However, recent studies have also not used intra nasal sampling to directly measure the inhaled HDM dose. Furthermore, there is uncertainty concerning the most appropriate measures of personal exposure thus, further studies which measure (i) inhaled HDM dose (507), (ii) HDM allergen levels both on the mattress surface (168) and in the bedding (167), and (iii) bedding composition arrangements during early infancy, may be needed to assess to what extent the reported positive association between bedding (for example, sheepskins or bottom bunks) and HDM sensitization is mediated by higher exposure to inhaled HDM allergens.

The 1995 Childhood Asthma Survey relied on parental report of exposures. Thus, reporting bias, which could result in bias of results away from the null value, may be an issue in this study. In addition, due to the cross-sectional nature of the study, the associations demonstrated here may reflect wheeze-induced bedding alterations.

#### **4.7.1 Exposure to sheepskin**

As stated above, in the 1997 CARHS, sheepskin use in infancy was positively associated with subsequent HDM sensitization. Previous work indicates that underbedding may increase the risk of HDM sensitization by allergen loading and/or a potentiation of bedding allergenicity (505) (see Section 1.5.3). Earlier studies have reported a clear biological plausibility for HDM's role in sensitization as the proteolytic activity of their enzymes can actively damage the airway epithelium (508). Infant sheepskins may harbour very high levels of mites and potentially serve as an important source of exposure for infants. Sheepskins have also been found to have higher HDM levels than mattresses (483). Moreover, it has been shown that the high levels of airborne HDM allergens experienced during sleep are generated from the bedding and not from the floor (473). In the absence of experimental or household disturbance, most investigators have been unable to detect airborne mite (183). Thus, most exposure is likely to occur when the individual contacts and disturbs the dust on the surfaces and in the materials where the mites breed (509), such as bedding items. In this study, the exposure to sheepskin in infancy tended to be positively associated with HDM sensitization even among the sub-group of those with no at-birth family

history of asthma, suggesting that the avoidance of sheepskin should not be guided by only a family history of atopic disease.

As previously discussed, inhalant allergen sensitization is an important determinant of childhood asthma (167, 170, 175) (see Section 2.2.1.3). The 1997 CARHS and the Infant cohort study with 1995 follow-up did not demonstrate an association between sheepskin use in infancy and subsequent asthma. However, an earlier case-control study of children from the New Zealand arm of the ISAAC, found an increased risk of asthma associated with the recalled use of sheepskin bedding in infancy (aOR 1.91; 95% CI 1.11, 3.33) (179). In the 1995 cross-sectional Childhood Asthma Survey, there was an inverse association between current use of sheepskin as underbedding and wheeze. There was a significant dose-response trend for increasing wheeze frequency for the unadjusted analysis which remained greater for more than 12 episodes of wheeze compared with less episodes of wheeze in the past year after the adjustment for potential confounders. This result may be considered to be most likely due to reverse causality. By age 7 years, as in this Survey, children with asthma may be avoiding sheepskins in agreement with current recommendations (498, 499). The inverse association was greater for those children with frequent wheeze possibly because those with severe disease would be most likely to make disease-related changes to their bedding.

#### **4.7.2 Exposure to plastic mattress liner**

The increased risk of sensitization to HDM associated with plastic mattress covers in infancy demonstrated in this study is unexpected. No other study has previously reported an association between plastic mattress liner and HDM sensitization. Previous studies have shown mattress covers to be effective in reducing the amount of HDM allergen in the bed (487, 510) of asthmatics who were already sensitized to HDMs. However, the threshold level of HDM required to cause sensitization in susceptible persons is much lower than the level needed to trigger an asthma attack (see Section 2.2.1.2). Occlusive bedding covers are advocated as an important avoidance measure to mite allergens (183, 485, 486). Far fewer mites have been collected from the surface of cot mattresses which were either vinyl topped or covered with a plastic coverslip than were collected from a cot mattress with a cotton top alone (479). Yet, despite allergen levels being dramatically reduced in the weeks after the introduction of such covers (487), long-term effectiveness is unknown.

A recent Cochrane meta-analysis (488) of 29 RCTs from 1980 until 1996, found that bedding changes aimed at reducing exposure to allergens from HDMs seem to be ineffective in improving the symptoms of asthma in asthmatic people known to be sensitive to HDMs. Overall, the Cochrane review found there was no statistically significant difference in improvement of asthma (RR 1.04; 95% CI 0.83, 1.31), asthma symptom scores (standardized mean difference  $-0.07$ ; 95% CI  $-0.35, 0.22$ ), medication usage (standardized mean difference  $-0.14$ ; 95% CI  $-0.43, 0.15$ ), or peak flow in the morning (standardized mean difference  $0.04$ ; 95% CI  $-0.13, 0.21$ ), even among the sub-group on whom effective allergen reduction was documented (488). The findings of two subsequent randomized, double-blind, placebo controlled studies of allergen-impermeable bed covers are in accordance with the meta-analysis. The mite-proof bedding covers did reduce the level of exposure to mite allergens but did not lead to a significant improvement of clinical symptoms in 1,122 adult patients with asthma (511) or 279 adult patients with allergic rhinitis (512). This could be because even though beneficial in relation to HDM allergen reduction (513), if the trials did not specifically assess the effect in the sub-group of mite-sensitive asthmatics sensitized to HDM, but assessed across all asthmatics, there would be a dilution of the ability to detect the mattress cover effect if other causes of non-HDM sensitized asthma were operating. Also, these two trials were in adults. An earlier study (15) has reported that when mite avoidance measures are taken in the bedroom, mite-sensitive asthmatics appear to improve more quickly, and to a greater degree, if they are children than if they are adults: bronchial responsiveness to histamine improves 4-fold within 2-4 months in children, but in adults there is only a 2-fold improvement after 12 months. These authors postulated that the magnitude of the response may be greater in children because they spend more time in bed, than adults, in contact with the high concentration of mite allergen that is found in bedding. In addition, HDMs are not the only agent that can influence lung function. The home environment, apart from the mattress, is an important source of non-specific irritants as well as other allergens. For example, endotoxin and cat allergen have been demonstrated to affect nasal and bronchial symptoms (514) (see Section 2.3.6 and Section 2.2.2).

The use of plastic mattress liner in infancy was not associated with sensitization to other indoor or outdoor allergens. The number of children with sensitization to other indoor allergens was very small in this study, but in addition, an allergen-specific interaction may be responsible for the results reported here. The lack of an association between exposure to infant bedding and subsequent ryegrass sensitization is consistent with an exposure effect acting principally on inhalant allergens present in the bedding environment. There was no association of infant bedding with ryegrass, which demonstrated a prevalence of sensitization similar to HDM (see

Table 4.1). Furthermore, bedding is known to contain high concentrations of HDM allergen, with HDM allergen thus being in larger amounts close to the nasal passages of infants than other aeroallergens. One interpretation of this is that the concomitant exposure of the infant to both allergen and, for example, VOCs from bedding in early life could be critical, and exposure to ryegrass being outdoors and not necessarily occurring in the early months of life might not be expected to be influenced by indoor VOCs. Also, the age of sensitization is generally younger for HDM than for ryegrass (515), hence infant bedding may be more important for the former. Sensitization to other indoor allergens is less prevalent in this study and therefore numbers are decreased, with reduced statistical power to detect any effect. In addition, similar considerations to variability in early infant exposure could apply.

There may be other adverse effects from the barrier method used. Plastic mattress covers release VOCs close to an infants breathing zone. Therefore, the finding that exposure to plastic mattress covers is not associated with other indoor allergen sensitization, only HDM, does not mean that HDM loading is the only possible mechanism. Plastic mattress covers release VOCs which in animal models produce airway inflammation and airflow limitation after a brief one-hour exposure (492). Furthermore the presence of these compounds in the bedroom has been associated with Th2 deviation and increased allergen sensitization in children (496). This could specifically affect HDMs. One possibility is that VOC and HDM interaction at the bedding site is greater than at other locations. Sleeping infants whose airway is in close proximity to such covers may be exposed to high concentrations of these compounds for considerable periods of time (492). Sensitization to inhaled allergens such as HDM could thus be enhanced either by airway inflammation resulting in increased airway permeability and enhanced allergen presentation to the immune system (491, 492, 516-519), by VOC-induced Th2 deviation (238, 496, 520) or a combination of both.

There is a growing body of work to support the proposition that organic or other components affecting infant air quality may induce sensitization to allergens (521). In this Tasmanian birth cohort, recently published work reported an increased risk for home gas appliance use at one month of age and HDM sensitization (RR 1.98; 95% CI 1.04, 3.79) with confounder matching (504). And, also in this cohort, it was previously demonstrated that infant exposure to indoor gas cooking, gas heating and frequent hairspray use in the bedroom were all significantly associated with subsequent childhood asthma (245), again implicating organic compounds in the air as a factor to be considered.

Furthermore, in a matched pair case-control study based on the Oslo Birth Cohort, the risk of bronchial obstruction during the first two years of life was related to the presence of plasticizer (VOC)-emitting (491) surface materials: PVC flooring (aOR 1.89; 95% CI 1.14, 3.14) and textile wall materials (aOR 1.58; 95% CI 0.98, 2.54) (522). This relation was modified by household ventilation. The relation of bronchial obstruction to plasticizer-emission was considerably stronger when there was low air exchange (aOR 12.6; 95% CI 1.00, 1.59) than when it was high (aOR 2.6; 95% CI 1.02, 6.58) (523). A subsequent population-based cross-sectional study (524) of 2,568 Finnish children aged 1 to 7 years, found that persistent wheezing was strongly related to the presence of plastic wall materials (aOR 3.42; 95% CI 1.13, 10.36). And, Jaakkola et al., 2004, recently reported in a cross-sectional study of Russian 8-12 year old schoolchildren, that risks of current wheeze were associated with recent renovation and the installation of materials with potential chemical emissions, such as PVCs: aOR 1.36 (95% CI 1.00, 1.86) with new linoleum flooring; and aOR 1.70 (95% CI 1.21, 2.40) with new synthetic carpet. Overall, the findings reported here support the proposition that chemical emissions may play a role in the development of sensitization to allergens and child asthma, and indicate that it would be appropriate to consider the type of materials present in bedding items and their potential to emit organic chemicals.

#### **4.7.3 Exposure to different mattress type**

In the 1997 CARHS, infant mattress type was not associated with HDM sensitization or with wheeze in childhood. As discussed earlier, the evidence regarding one mattress type reducing allergen exposure over another type is inconclusive, as previous studies report conflicting levels of HDM allergen when mattress types are compared (see Section 4.1). Further, the age of the mattress may be important and data on mattress age has not been collected here. Custovic et al., 1996 (484), however, reported that new mattresses can become a significant source of exposure to mite allergens after a short period of time (<4 months). Moreover, some earlier studies have reported findings as mattress samples, which were in fact composite samples that included dust from pillows, mattresses, quilts and underbedding (480, 525), therefore making it difficult to attribute HDM levels to any one particular bedding item. Notwithstanding, a number of studies have demonstrated a strong correlation between the current level of HDMs in children's mattresses (type not specified) and specific IgE sensitization (168, 169). Also, in a large population survey (478) in Ethiopia, foam mattress use was positively associated with sensitivity to *D. pteronyssinus* (OR 2.09; 95% CI 1.22, 3.57). In regions of New South Wales, Australia,

where mattress Der p I levels were high, in a cross-sectional study (167), more children were sensitized to HDMs, and these children had significantly more AHR and recent wheeze. The risk of HDM-sensitized children having current asthma doubled with every doubling of Der p I level. There was a modest correlation between Der p I exposure in individuals and AHR ( $r = 0.23$ ,  $p < 0.03$ ) (167). Even so, the results reported in this Chapter are in agreement with those from other studies that have not found an association with mattress type and HDM sensitization or respiratory symptoms. A cross-sectional study in Spain found no significant difference in mite sensitization levels related to the type of mattress (foam or innersprings) in 94 subjects (526). Also, when data from a New Zealand birth cohort of 677 children was examined retrospectively, there was only a slight tendency for the prevalence of any atopy to common allergens to differ by different mattress types: 48.2% of children who had an innerspring mattress were atopic compared to 34.7% of the children who had not used an innerspring mattress ( $p=0.09$ ) (497). And, the case-control study of children from the New Zealand arm of the ISAAC found no association between asthma and current mattress characteristics: kapok versus foam mattress (OR 0.35; 95% CI 0.09, 1.33); and innerspring versus foam OR 0.87; 95% CI 0.57, 1.33) (179).

Furthermore, it has been reported that the recording of mattress type is not a good surrogate for measuring actual exposure to HDM allergens as the mattress itself is not a direct source of allergen exposure, as mattress dust contains allergens which have filtered down from the upper bedding (527). And, as such, it is argued, mattresses are only a proxy for the measurement of other allergen sources closer to the subject (527), suggesting that proximity of the bedding to the infant's airways may play a major role in allergen inhalation. The results reported in this Chapter may in part support this proposal as I was unable to demonstrate any association, after adjusting for confounders, between exposure to certain mattress types in infancy and HDM or wheeze. It can be postulated that mattresses contain larger reservoirs than underbedding items yet the effect on sensitization to HDM is stronger for the latter. This may indicate that not only is the HDM reservoir important but other factors, for example proximity to the airway, may play a significant role. In this study, the potential confounders adjusted for included other bedding items known to harbour HDM and/or be associated with HDM sensitization in this cohort.

#### **4.7.4 Exposure to different bed type**

In the 1997 CARHS, no difference in childhood HDM sensitization or respiratory symptoms by bed type in infancy was found. However, in the 1995 cross-sectional Childhood Asthma Survey,



those children sleeping in the bottom bunk-bed were found to have an increased risk of frequent wheeze (aOR 1.63; 95%CI 1.01, 2.65) compared with children sleeping in the top bunk-bed. Categorizing bottom bunk-bed versus top bunk-bed in the analysis, ensured there was no “bunk” effect and restricted the variability of other potential confounders such as the number of residents and sibling effect, as both resident and sibling numbers were considered to be high if families were using bunk-beds.

This finding is consistent with results from a cross-sectional study (526) in Spain, of 94 consecutive bunk-sleeping subjects (47 pairs of siblings). In that study, asthma was found to be more prevalent in subjects sleeping on the bottom bunk-bed than those sleeping on the top bunk-bed ( $p < 0.05$ ). 60% of subjects showed mite sensitization, but differences between bottom bunk-bed and top bunk-bed subjects were not found. A tendency was found towards higher Der p 1 levels in the bottom bunk-bed compared with the top bunk-bed 11.9 (95% CI 0.4, 562.29)  $\mu\text{g/g}$  versus 7.84 (95% CI 0.27, 140.59)  $\mu\text{g/g}$  respectively), although the difference did not reach statistical significance (526). As previously stated, measurement of mattress mite levels do not necessarily encompass all the mattress reservoirs within the bedding environment (513) and, in addition, measurement at a particular moment does not reflect the dynamics of exposure during sleep, when movements of the top bunk-bed sleeper may cause particles of top-mattress house dust to be released over the bottom bunk-bed sleeper who is also being exposed to allergens within his/her own bedding items. Also, sleeping in the bottom bunk-bed may expose the child to greater allergen exposure than if sleeping in the top bunk-bed owing to the “sandwich” position between two mite infested sets of mattresses and beddings (526).

#### **4.7.5 Exposure to electric blanket**

In the cross-sectional 1995 Childhood Asthma Survey, a positive association was found between the current use of electric blanket and wheeze. This association was stronger for children with more frequent wheeze, particularly for more than 12 episodes of wheeze in the past year, though I was unable to demonstrate a significant test for trend for wheeze frequency, possibly reflecting inadequate statistical power. At first, these results appear contrary to our understanding of conditions favourable for HDM microclimates. A combination of high temperatures (above 30 deg C) and a low relative humidity is known to be detrimental to the survival of HDM (528), and such conditions may be reached in beds by heating the mattress with the aid of electric blankets at times that they are not being slept on (528, 529). An earlier study (529) observed a median

reduction in concentration to 60% of the initial value concentration of HDMs on mattress surfaces in the beds with electric heating blankets compared to an increase to 119% in the beds without the blankets ( $p>0.05$ ) after one year (529). However, another study (528) has reported that despite a reduction of between 19% to 84% of the HDM populations in the part of the mattress that was covered by the electric blanket, HDMs in the non-heated portions of the mattress were much more abundant than in the treated areas (528). Moreover, both these two studies concluded that complete elimination of HDMs from already infested mattresses does not seem possible with electric blankets. And, from a clinical point of view, it was considered that a reduction in the concentration of mites or mite allergen of about 40% such as one of the studies had achieved, would probably not be sufficient to benefit HDM-allergic patients (529).

Also, in normal household use, electric blankets are not left on for a period of up to 12 hours when not being slept on as occurred in these two studies (528, 529). Normal usage would further reduce the time when the heat from the blanket could influence the microclimate of the mattress underneath. It has subsequently been reported that the presence of an electric blanket on the bed did not influence bed Der p 1 levels in 467 beds of children participating in the New Zealand arm of the ISAAC (525). Thus, even with the use of electric blankets, the HDM level may be high enough to trigger wheeze in HDM sensitized children. Moreover, higher levels of HDM in other parts of the mattress not underlying the electric blanket may migrate to the overlying pillows or quilts thereby increasing the HDM allergen load close to the child's airways. The density of mite populations is the highest near the surface (528) and laboratory studies have reported mites tend to move towards areas of high humidity and low temperature, finding the best locations within their microenvironment (530).

There have been no previous cross-sectional or prospective studies reporting an association between electric blanket use and either HDM sensitization or wheeze. Moreover, there are no current recommendations regarding the use of electric blankets for children at risk of, or suffering from, atopic diseases. The results presented in this Chapter are, to my knowledge, the first to identify an association between current use of an electric blanket and wheeze in children. This study has found a dose-response trend between electric blanket use and increasing wheeze frequency. This may be reflecting HDM sensitization as it has been suggested that symptoms such as frequent wheeze may be better markers of HDM-allergen related airway disease than a history of asthma or milder symptoms (196) (see Section 2.2.1.6) and, in addition, atopic individuals are over-represented at the severe end of the asthma spectrum (181, 195, 196). However, this does not mean that a casual relationship must be present. One or more factors

might be strongly associated with both exposure and disease to give rise to the pattern found here without there being any causal connection between them (456). As electric blankets are not used in infancy, it is not possible to exclude reverse causality: the dose-response trend may be as a result of children with frequent wheeze being given electric blankets, whereas children with no or lesser wheeze were not.

## 4.8 CONCLUSION

In the cross-sectional 1995 Childhood Asthma Survey, the current use in childhood of an electric blanket or sleeping in a bottom bunk-bed are associated with frequent wheeze. A proposed role of HDMs contributing to the increased association of frequent wheeze and the use of electric blankets or sleeping on a bottom bunk-bed is speculative. The reporting of wheeze episodes as outcome measures should reduce the level of disease misclassification by identifying sub-groups of children with more frequent episodes of wheeze in the past year that are more likely to reflect allergen-induced airway disease rather than airway disturbance due to viral infection or other non-atopic factors (195) (see Section 2.2.1.6). Thus, these findings may be related to HDM sensitization and as such suggest new areas which might be the subject of further consideration and study. In future work, prospective study designs which exclude disease-related changes in bedding are required.

This Chapter has reported that an infant's underbedding in the form of sheepskins and the use of plastic mattress covers are associated with the development of HDM sensitization in childhood. Infants spend a significant proportion of their time in bed (15) with consequent opportunity for prolonged exposure to adverse environmental influences. Furthermore, bedding is a readily modifiable environmental factor. Sheepskins are commonly used in infant bedding in Australia and New Zealand, although they may have a more restricted use worldwide. However, due to their high content of HDM allergen (479, 483), they indicate a likelihood of a high infant exposure to HDM allergen when in the bed. The results in this Chapter support current recommendations (183, 498, 499) that the use of sheepskins as infant bedding in atopic families is inappropriate because they are responsible for significantly greater exposures to HDM allergens. A novel finding in this study also included that exposure to sheepskin in infancy tended to be positively associated with HDM sensitization even among the sub-group of those children with no at-birth family history of asthma. Thus indicating that it may be appropriate to review the current

recommendation, with a view to extension for all infants, and not only those infants at high-risk of acquiring asthma, to avoid the use of sheepskins in infancy.

The results reported here also suggest that greater attention and further study should be given to other potentially adverse environmental factors related to the bedding environment such as VOCs. Plastic mattress covers are used throughout the world as part of infant bedding, largely for the protection against bedwetting. Current New South Wales Health recommendations to minimize exposure to HDM state “consideration should be given to encasing children’s mattresses and pillows with high quality impermeable mattress covers” (498), and the National Asthma Council, Australia recommends encasing of mattresses in mite-proof covers (499). However, there is no specific recommendation regarding the actual material composition of the mattress cover. Moreover, as demonstrated by the Cochrane review, there is conflicting evidence regarding the efficacy of using mattress covers in the prevention of asthma symptoms despite a reduction in HDM levels. The results presented in this Chapter are not consistent with the use of plastic/vinyl mattress covers to be recommended for infants at high-risk of atopic disease, and in addition, further studies should be undertaken considering potential factors other than HDM, for example VOCs, that may initiate and/or trigger asthma in those individuals exposed to plastic mattress covers.

The role of bedding manipulation in primary prevention of atopy and wheeze may not yet have been fully assessed and future RCTs addressing these issues could prove worthwhile. Observational studies of bedding are potentially complicated by selection bias: children with asthma may preferentially use one type of bedding rather than another. Selection bias cannot be fully excluded in this observational study: it is unlikely, but children at risk of atopy may have been given bedding items such as sheepskin. Bedding is a feasible intervention for a RCT to confirm the causal nature of these findings. And, identification of modifiable factors contributing to the burden of asthmatic disease would have considerable public health benefit.

## **4.9 POST-SCRIPT**

This Chapter provides new information which will increase the evidence base for recommendations on bedding and asthma prevention. Current recommendations may not be addressing all environmental factors that are associated with the development and/or triggering of asthma. Consideration needs to now be given to other bedding items, in addition to the proximity

of these materials to the nasal passages. The following Chapter 5 will consider both the composition of bedding materials and the bedding item's relative proximity to the airways as it examines the role of infant cocoon and sleeping bags in allergic sensitization and respiratory health.

## Chapter 5

# Infant cocoons and sleeping bags: allergic sensitization and respiratory health

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## 5.0 PREFACE

This Chapter examines the relationship between two specific bedding items in infancy, cocoons and sleeping bags, and the development of child wheeze and HDM sensitization. The two prospective studies, the Infant cohort study with 1995 follow-up and the 1997 CARHS have been analysed and the findings described in this Chapter.

The findings from the Infant Cohort Study with 1995 follow-up have been reported in a recently published paper (see Appendix 4):

Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. A prospective association between cocoon use in infancy and childhood asthma. *Paediatric and Perinatal Epidemiology* 2004; 18(4):281-189.

## 5.1 INTRODUCTION

HDM levels have been shown to vary within the different bedding materials, and significantly higher levels of dust mite allergens (9, 531-534) are found in synthetic bedding than in feather bedding. Der p allergen levels (in terms of geometric means) have been found to be 5 to 8 times greater in synthetic pillows than in feather pillows (9, 532, 534). Over a 12 month period, new synthetic pillows accumulated higher concentrations of Der p 1 (19.28  $\mu\text{g/g}$ ; 95% CI 9.76, 38.07) than new feather pillows (6.45  $\mu\text{g/g}$ ; 95% CI 2.96, 14.05) (535). Also, synthetic quilts have been found to have 15-fold higher Der p 1 levels compared to feather quilts (ratio geometric mean Der p 1  $\mu\text{g/m}^2$ : 15.45; 95% CI 4.28, 55.8) (9).

Prospective studies have not previously examined the role of synthetic bedding and HDM sensitization. Two cross-sectional studies have reported differing results: one study finding mite sensitization levels were not related to the type of mattress bedding material (526) and the other,

that foam (synthetic) mattress use was associated with an increased risk of sensitization to *D. pteronyssinus* (478) (see Section 4.1).

There have been, however, numerous studies reporting, from both developing and first world environments, that the use of synthetic bedding (foam mattresses, pillows, and blankets) is associated with a significantly increased risk of childhood wheeze. As of April 2004, seven cross-sectional studies (136, 197, 478, 505, 536-538) and two prospective studies (12, 13) have reported associations between synthetic bedding and wheeze, and in addition, two cross-sectional studies have reported an association between synthetic bedding and rhinitis (539, 540).

Two population-based case-control studies (136) investigated the association between childhood wheeze in schoolchildren 7-8 years of age and changes in the home environment between 1978 and 1991 in Croydon, London (see Section 2.6). The study found that of the potential indoor environmental risk factors examined, the increasing use of non-feather pillows (from 44% in 1978 to 67% in 1991 among control children) explained greater than half of the 20% increase in the population prevalence odds of current wheeze (OR 1.20; 95% CI 1.04, 1.39) in 1991 compared to 1978. The use of non-feather pillows was positively associated with childhood wheeze (OR 1.54; 95% CI 1.13, 2.10). A subsequent population based case control study of schoolchildren in Sheffield, UK, compared secondary schoolchildren with frequent or severe wheeze with children with no wheeze, and found that pillows with synthetic fillings were a risk factor for severe childhood asthma (OR 2.78; 95% CI 1.89, 4.17), after the exclusion of asthmatic subjects whose bedding had been changed because of their disease (197). This association remained evident when the children with severe asthma was restricted to those children whose parents denied making changes in the bedroom because of allergy. The results from these studies prompted speculation that the increase in the use of non-feather pillows contributed to the increasing exposure to HDM, which in turn could have been partly responsible for the increase in childhood wheezing (198).

In a recent cross-sectional study of children in Canberra, Australia, synthetic quilt use was associated with asthma (aOR 1.67; 95% CI 1.05, 2.65) and recent wheeze (aOR 2.11; 95% CI 1.33, 3.34) among SPT-positive to aeroallergens, including Der p, children but not SPT-negative children (505). These results support the view that if the adverse respiratory effect of synthetic bedding, is mediated by the previously documented higher HDM allergens found in synthetic bedding (9, 531-534), this adverse effect would be more evident among children who were sensitized to aeroallergens rather than among non-sensitized children.

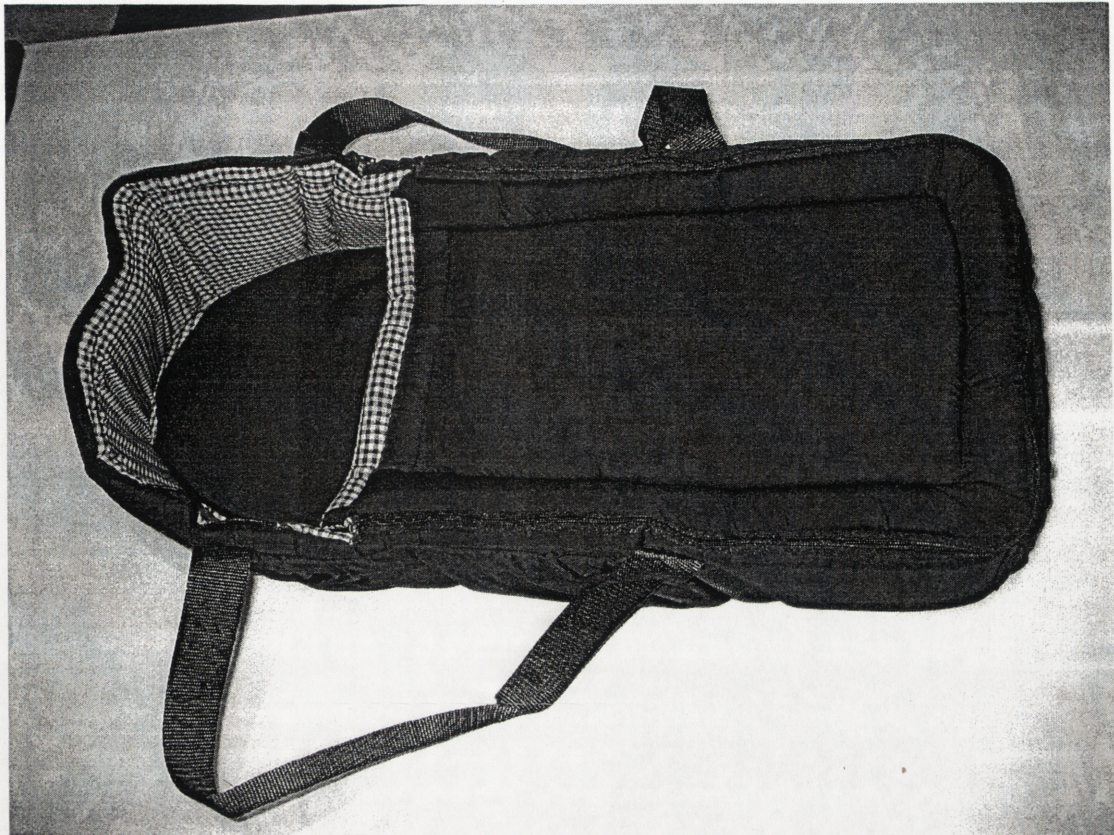
The Oslo Birth Cohort (12) explored the association between early life exposure to feather versus non feather (synthetic and other) bedding (quilts) and found that the aOR for bronchial obstruction in children from 0 to 2 years of age, by exposure to feather quilt at age 6 months was 0.59 (95% CI 0.41, 0.86); and for asthma at the age of 4 years was aOR 0.38 (95% CI 0.23, 0.64). When parallel analyses were performed including only children with either feather or synthetic quilt (excluding the 'other' category), equal risk variation between feather and synthetic quilt as between feather and non-feather quilt were obtained. In addition, in children from the TIHS birth cohort, synthetic pillow use at one month of age has recently been reported to be associated with frequent wheeze (>12 episodes wheeze in the past year) at age 7 (aRR 2.5; 95% CI 1.2, 5.5) independent of childhood exposure (13).

These studies, described above, have reported on the association between the synthetic bedding items of mattresses, quilts and pillows and increased risk of childhood wheeze. Thus, other synthetic bedding items such as cocoons or sleeping bags, might also influence asthma development or symptoms.

Cocoons are similar to a padded sleeping bag with a hood that comes close to the sides of the baby's head, fully encasing the infant, leaving only the face exposed (see Figure 5.1). While lying within the cocoon, the infant is then placed on a flat surface or in the cot or pram. A pillow is usually not used in conjunction with a cocoon nor, unless it is exceptionally cold, would it be necessary to place an additional covering on top of an infant lying within a cocoon. If attached, straps allow the cocoon to be hand carried or tied against the mother's chest. Infants placed in cocoons or baby nests may spend prolonged periods of time with their airways in closer proximity to the cocoon material than if placed on other thinner composite bedding, for example compared to cotton blankets which are washed more frequently, potentially increasing any adverse effect on respiratory health mediated by close proximity. There is currently no specific health advice available regarding the respiratory health effects of the use of cocoons or sleeping bags containing synthetic materials in infancy.



Figure 5.1 Infant Cocoon



This Chapter describes the prospective relationship between an infant's use of cocoons or sleeping bags and HDM sensitization and asthma in childhood. The aim of this Chapter is to test the hypothesis that the use of, predominantly synthetic, cocoon/baby nests or sleeping bags in infancy is associated with the respiratory symptoms of wheeze in childhood and/or HDM sensitization.

## 5.2 METHODS

At the home interview in the TIHS data collected as part of the infant's sleeping environment included the infant's use of a cocoon or a sleeping bag as an item of bedding, not clothing. The use of a cocoon at the time of interview or intention to use a cocoon in cold weather was recorded, thereby avoiding the effect of current season when interviewed. In 1994, further details regarding cocoons and sleeping bags were collected. At least 84% of cocoons were noted by the research nurse at the one month home interview, to be either quilted or padded. In addition, infant cocoons manufactured and sold in Southern Tasmania during the cohort study period most commonly comprised outer coverings of cotton or polycotton with a polyester (synthetic) filling.

Sleeping bags that were used as bedding items tended to be padded similar to the cocoons but with a lesser quantity of material.

For this Chapter, only prospective data using the TIHS birth cohort was analysed. The two study sample populations are: (i) the 863 children for whom a home interview had occurred at one month of age in 1988 as part of the TIHS and who also took part in the 1995 Childhood Asthma Survey (see Figure 3.1, Section 3.2.2); and (ii) the 499 children in the CARHS.

## **5.3 STATISTICAL METHODS: THE 1995 CHILDHOOD ASTHMA SURVEY**

### **5.3.1 Exposure variables**

The bedding exposure variables of interest were (i) cocoon use in infancy and (ii) sleeping bag use in infancy. Both variables were dichotomous for exposure or no exposure.

### **5.3.2 Outcome variables**

The dichotomous outcome variables were the child's recent wheeze or night wheeze in the past 12 months and asthma ever. Wheeze frequency over the past year was also examined. Wheeze over the past year was defined as 1-3 episodes; 4-12 episodes; or greater than 12 wheeze episodes compared with no wheeze as the baseline group (see Section 4.3.2).

### **5.3.3 Generalized linear modeling**

A generalized linear model with a log link function and binomial error structure was used to control simultaneously for multiple confounders and to obtain confidence intervals for relative risk (RR) estimates (452) (see Section 3.1.5.3).

To identify potential confounders, the association between a large number of factors and childhood wheeze was examined (see Table 5.4). More than 40 confounders were further examined to see how they each related separately to cocoon use and wheeze. A generalized linear model was then constructed as follows. Each potential confounder (330) was individually

added to the model as a covariate if the variable was associated with wheeze in the exposure to outcome analysis, or had been reported to be related to asthma in the literature. Change-in estimate methods (466) was used to examine the confounding effect of these factors on the exposure-disease association. Those factors that altered the point estimate for the exposure-wheeze association by 10 percent or more were included in the final model. In addition, the remaining variables in Table 5.4 were added as individual factors into the final model. None of these factors altered the adjusted risk ratios reported in Table 5.5 and were not retained in the final confounder set. Pearson chi-square test was used to further explore the possible associations between the explanatory variables.

### 5.3.4 Discrete-time proportional hazards modeling

The relation between infant cocoon use and age of onset of asthma symptoms was assessed using discrete-time proportional hazards modeling (541). Discrete-time proportional hazards model estimates, by maximum likelihood estimation, two discrete time (grouped duration data) proportional hazards regression models, and can be estimated as a regression model for a binary dependent variable. Discrete-time models estimate both time-varying covariates and flexible specifications of duration dependence, where multiple occurrences of tied failure times are also easily handled (542). This approach was used to model the length of time (in years) up to the age of onset of asthma for each child because age of onset was only recorded in complete years, thus the ages of 12.1 to 12.9 would have been recorded as '12'. This method is in contrast to the proportional hazard modeling used in Section 4.3.3.1 where a small time interval ( $\Delta t$ ) was used in contrast to complete years (0, 1, 2, ..., 7) examined here. The distribution of durations until the age of onset of asthma is modeled via the probabilities of having asthma at each value  $t$ . There is a one-to-one relationship between these probabilities – 'hazard rates' – and the probabilities of having completed durations of different lengths until the onset of asthma – summarized by the 'survivor function'. More precisely, the discrete-time hazard rate  $h_{it}$  is:

$$h_{it} = \text{prob}(T_i = t | T_i \geq t; X_{it})$$

where  $X_{it}$  is a vector of regressor variables (covariates) which may vary with time.  $T_i$  is a discrete random variable representing the time at which the onset of asthma occurs. In this study, it is the difference in  $T_i$ 's distribution by cocoon exposure which is of primary interest (541).

### 5.3.5 Matched cohort analysis

As the numbers of children who used a cocoon in infancy were small, a matched cohort analysis was also conducted to evaluate the effect of cocoon use in infancy on asthma. Matching can prevent confounding (see Section 3.3.4). In a cohort study with matching by exposure status, none of the potentially confounding variables that have been matched are likely to be confounding the exposure-disease association because none will be associated with the exposure in the study population. Potentially confounding factors are thus similarly distributed in those children exposed to cocoons and those children without cocoon exposure.

A matched pair stratified analysis with exposed matched to non-exposed on confounder status, optimizes the amount of information obtained per child (448) and addresses the difficulty in controlling for multiple confounders with rare exposures. The confounder status here refers not to a single confounder, but to a set of confounders. In a cohort study that compares risks, no additional action is usually required in the analysis to control confounding by the matching factors; the process of matching has eliminated confounding by the matching factors (448). However, care has to be taken to consider whether any residual confounding exists by also adjusting for the matched factors in the analysis stage. This is particularly an issue where the matched factor is broadly categorized (for example, smoking or not) and thus residual variation within each matched group can occur. For example, the exposed child may be matched by parental smoking status but some parents may smoke lightly, whereas others heavily. Matching on exposure can be undertaken without regard to the disease status which is unknown at the start of follow-up, thereby preventing selection and recall bias (448).

Fourteen strata were constructed based on 7 possible confounder combination sets. Each of the 19 children with cocoon use was matched with non-exposed children in relation to: at-birth family history of asthma, any gas heating as infant, synthetic quilt use in infancy, only child at age 7, mother smoked during pregnancy, low maternal education at birth, and air freshener used in bedroom as infant. Mantel-Haenszel methods were used for the analysis of the matched-pairs (330). The 14 confounder sets are shown at Table 5.1.

**Table 5.1 Confounder sets by strata for the Infant cohort study with 1995 follow-up for the assessment of infant cocoon use and subsequent wheeze**

Strata	Confounder status						
	Family history of asthma at birth	Gas heating as infant	Synthetic quilt use in infancy	Only child at age 7	Mother smoked during pregnancy	Low maternal education at birth	Air freshener used in bedroom as infant
1	0	0	0	0	√	•	0
2	0	0	0	0	0	0	0
3	√	0	0	0	√	√	√
4	√	√	0	0	√	•	0
5	0	0	0	0	√	√	√
6	√	0	0	0	√	√	0
7	0	0	√	0	√	√	√
8	√	0	0	0	√	•	0
9	√	0	√	0	0	√	0
10	0	0	0	0	0	•	√
11	0	0	0	0	√	√	0
12	0	0	√	0	√	•	0
13	√	0	0	0	0	•	0
14	0	0	0	0	0	•	0

Legend: √ = confounder present;  
 0 = confounder absent;  
 • = no data available.

### 5.3.6 Population attributable fraction

The aetiologic fraction of asthma in childhood attributable to cocoon use in infancy was calculated as  $p(aRR-1)/aRR$ , where  $p$  denotes the proportion of children with cocoon use in infancy among those with the outcome of asthma and  $aRR$  equals the relative risk estimate for cocoon use and asthma, after adjustment for the confounders listed in Table 5.4 (see Section 4.3.3.4).

## 5.4 RESULTS: THE INFANT COHORT STUDY WITH 1995 FOLLOW-UP

### 5.4.1 Characteristics of the study population

The study population is the same as that described in Section 4.6.1. Data were available for recent wheeze, night wheeze and asthma ever on 823, 834 and 863 children respectively (see Table 4.8 Section 4.6.1.1). Data on use of cocoon in infancy was available on 802 children. Cocoon use in infancy of 2.4% (19/802) was low. And, only 0.85% (7/823) of children used sleeping bags as a form of bedding in infancy. The additional study sample characteristics are presented at Table 5.2 (additional to Table 4.8 in Section 4.6.1.1).

**Table 5.2 Additional characteristics of the study population in the Infant cohort study with 1995 follow-up**

Categorical measures	%	n/total N
<i>Bedding exposure variable</i>		
Infant cocoon	2.4	19/802
Infant sleeping bag	0.85	7/823

## 5.4.2 Univariate analysis

### 5.4.2.1 Cocoon use and its association with childhood wheeze

Cocoon use in infancy was associated with recent wheeze in childhood (RR 2.00; 95% CI 1.29, 3.12). The use of a cocoon in infancy was associated with both night wheeze (RR 2.27; 95% CI 1.31, 3.93) and history of asthma ever (RR 1.63; 95% CI 1.05, 2.53) in childhood. Analysis by frequency of wheeze episodes is presented in Table 5.3. Cocoon use in infancy was associated with an increased risk of more episodes of wheeze (Test for trend,  $p=0.015$ ) however, the number of infants in each category of wheeze was very small and no further analysis was undertaken using the outcome measures of wheeze frequency.

**Table 5.3 Cocoon use in infancy and asthma symptoms by number of wheeze episodes for the Infant Cohort Study with 1995 follow-up**

Respiratory symptom in 1995	N	Cocoon use in infancy	%	Unadjusted RR (95% CI) for cocoon use and wheeze	p value
No wheeze	559	9	1.6	1.00 (reference)	-----
1-3 episodes of wheeze	117	5	4.3	2.11 (1.02, 4.35)	0.043
4-12 episodes of wheeze	61	4	6.6	3.28 (1.40, 7.68)	0.006
>12 episodes of wheeze	28	1	3.6	2.14 (0.32, 14.22)	0.432
<i>Test for trend</i>					<i>0.015</i>

### 5.4.3 Confounder identification

To identify potential confounders, how each factor related separately to the use of cocoon in infancy and also to recent wheeze was examined. The infant factors of most relevance are summarized in Table 5.4. Potential confounders included: small sibling size (543), infant and child exposure to tobacco smoke (245) and home gas heating (245), infant synthetic pillow use (13), sheepskin use and season of birth.

**Table 5.4 Identification of potential confounders: unadjusted relative risk for selected factors and infant cocoon use and recent wheeze in the Infant cohort study with 1995 follow-up**

	Cocoon use in infancy Unadjusted RR (95% CI)	p value	Recent wheeze in 1995 Unadjusted RR (95% CI)	p value
<b>Exposure variables</b>				
Cocoon	-----*		2.00 (1.29, 3.12)	0.002
<b>Potential confounding variables</b>				
<i>Parental factors</i>				
Mother smoked during pregnancy	2.33 (0.89, 6.07)	0.083	1.41 (1.12, 1.77)	0.003
Teenage motherhood**	0.86 (0.26, 2.93)	0.814	1.19 (0.90, 1.56)	0.225
Family history of asthma at child's birth	1.31 (0.53, 3.22)	0.557	1.50 (1.20, 1.88)	<0.001
Family history of asthma in 1995	3.55 (1.03, 12.26)	0.045	2.27 (1.72, 2.99)	<0.001
Low maternal education at child's birth	0.66 (0.14, 3.16)	0.602	1.13 (0.63, 2.03)	0.678
Low paternal education at child's birth	0.77 (0.27, 2.18)	0.618	1.24 (1.04, 1.93)	0.023
Maternal postnatal smoking at 1month	2.66 (1.02, 6.92)	0.037	1.38 (1.10, 1.73)	0.006
Maternal smoking at child age 7	4.42 (1.45, 13.44)	0.004	1.45 (1.15, 1.81)	0.001
Duration of second stage labour (5, 15 vs 0, 5 mins)**	2.15 (0.88, 5.22)	0.084	1.09 (0.85, 1.39)	0.497
Duration of second stage labour (CS*** vs 0, 5 mins)**	0.25 (0.03, 1.84)	0.136	1.00 (0.75, 1.34)	0.989
Season of birth (May-Jun vs Mar-Apr)**	0.62 (0.21, 1.86)	0.393	1.12 (0.88, 1.43)	0.344
Season of birth (Aug-Feb vs Mar-Apr)**	2.80 (1.07, 7.29)	0.028	1.02 (0.81, 1.28)	0.854
<i>Infant factors</i>				
Male sex**	0.90 (0.35, 2.33)	0.825	1.42 (1.08, 1.88)	0.010
Infant first born	0.50 (0.18, 1.37)	0.166	1.06 (0.85, 1.33)	0.604
Low birth weight**	0.64 (0.19, 2.17)	0.467	0.99 (0.75, 1.30)	0.916
Intention to bottle feed at birth**	1.79 (0.73, 4.40)	0.199	1.26 (1.01, 1.58)	0.045
Multiple births**	0.77 (0.18, 3.30)	0.726	0.89 (0.62, 1.27)	0.504
Prematurity	0.53 (0.12, 2.27)	0.382	1.06 (0.80, 1.41)	0.673
Solid food introduced by phone interview at 10 weeks	1.36 (0.56, 3.31)	0.494	1.30 (1.04, 1.72)	0.024
Infant exclusively breast fed by phone interview at 10 weeks	0.18 (0.02, 1.36)	0.060	0.67 (0.49, 0.92)	0.009
<i>Childhood factors</i>				
History of eczema	1.76 (0.68, 4.56)	0.240	1.75 (1.39, 2.20)	<0.001
History of hay fever	2.03 (0.79, 5.26)	0.137	2.87 (2.34, 3.52)	<0.001
History of bronchitis	1.46 (0.55, 3.89)	0.452	2.58 (2.08, 3.21)	<0.001



**Table 5.4 continued**

	Cocoon use in infancy Unadjusted RR (95% CI)	p value	Recent wheeze in 1995 Unadjusted RR (95% CI)	p value
History of pneumonia	----*		1.87 (1.40, 2.50)	<0.001
Child's fish consumption vs none	0.75 (0.22, 2.54)	0.642	0.76 (0.57, 1.02)	0.082
No siblings in 1995	----*		1.68 (1.18, 2.38)	0.009
<i>Household factors</i>				
Private health insurance at birth	0.90 (0.36, 2.27)	0.827	0.71 (0.55, 0.91)	0.005
Home gas appliance use in infancy	1.79 (0.25, 12.89)	0.559	1.25 (0.73, 2.16)	0.439
No-one smoking in same room as infant	0.60 (0.22, 1.65)	0.317	0.72 (0.56, 0.93)	0.009
More than six residents in household at birth	0.68 (0.16, 2.90)	0.599	0.90 (0.65, 1.26)	0.549
Cat as pet during infancy	0.53 (0.18, 1.59)	0.249	1.09 (0.86, 1.37)	0.491
Paternal full time employment at child age 7	0.77 (0.31, 1.93)	0.573	0.91 (0.72, 1.15)	0.446
<i>Bedroom factors - infant</i>				
Infant sleeping in bedroom alone	0.44 (0.13, 1.49)	0.171	0.84 (0.65, 1.09)	0.180
Carpet in infant's bedroom	0.30 (0.11, 0.80)	0.013	0.89 (0.62, 1.28)	0.535
Humidity in infant's bedroom >75%	0.87 (0.12, 6.35)	0.888	1.22 (0.79, 1.88)	0.389
Window in infant's bedroom open at night	1.26 (0.52, 3.05)	0.616	1.05 (0.83, 1.32)	0.690
Sheepskin underbedding	0.12 (0.02, 0.91)	0.014	0.99 (0.78, 1.27)	0.962
Plastic mattress liner	0.88 (0.35, 2.22)	0.792	0.99 (0.79, 1.25)	0.933
Foam mattress as infant	1.58 (0.58, 4.35)	0.367	1.05 (0.83, 1.33)	0.705
Use of feather quilt as infant	----*		0.74 (0.21, 2.57)	0.619
Use of synthetic quilt as infant	0.19 (0.06, 0.65)	0.003	1.05 (0.84, 1.33)	0.654
Use of feather pillow as infant	3.98 (0.58, 27.28)	0.141	0.94 (0.35, 2.51)	0.894
Use of synthetic pillow as infant	1.51 (0.51, 4.48)	0.455	1.29 (0.97, 1.72)	0.086
Use of air freshener in infant's bedroom	4.25 (1.47, 12.30)	0.005	1.52 (1.04, 2.22)	0.047
<i>Bedroom factors - child</i>				
Sleeping on bottom bunk as child	----		1.11 (0.81, 1.52)	0.509
Use of feather quilt as child	0.51 (0.20, 1.33)	0.158	0.85 (0.68, 1.07)	0.166
Use of synthetic quilt as child	3.06 (1.18, 7.97)	0.016	1.29 (1.03, 1.61)	0.027
Use of feather pillow as child	0.70 (0.09, 5.14)	0.722	0.86 (0.53, 1.38)	0.516
Use of synthetic pillow as child	0.58 (0.17, 1.95)	0.375	1.04 (0.71, 1.54)	0.825
Carpet in child's bedroom	0.49 (0.12, 2.06)	0.322	0.93 (0.58, 1.49)	0.755

\*Indicates insufficient data for analysis.

\*\*The cohort entry scoring system was based on a composite score derived from these factors (437). Multiple births were automatically included.

\*\*\*CS represents caesarian section.

### **5.4.3.1 Cocoon use and family history**

An at-birth family history of asthma was not significantly associated with cocoon use in infancy (RR 1.33; 95% CI 0.53, 3.22), however, a family history of asthma in 1995 was significantly associated with cocoon use (RR 3.55; 95% CI 1.03, 12.26).

### **5.4.3.2 Cocoon use and maternal smoking**

Both childhood and infant exposure to maternal smoking were associated with wheeze (see Table 5.4). In fact, 88% (311/354) of mothers who smoked when their infant was one month of age, were still smoking when their child was aged 7 years. The association between infant and childhood maternal tobacco smoke exposure was highly significant (Pearson's  $\chi^2$  (1 df) = 470.12;  $p < 0.001$ ). The association between cocoon use and recent wheeze remained significant after adjustment for maternal smoking (aRR 1.88; 95% CI 1.21, 2.93) indicating that exposure to cocoons is not just a marker of the mother's smoking but is independently associated with wheeze. Maternal smoking is significantly associated with recent wheeze (RR 1.38; 95% CI 1.10, 1.73). The association between cocoon use and recent wheeze remained significant when adjusted for both maternal smoking and a family history of asthma at birth (aRR 1.71; 95% CI 1.12, 2.62). Maternal smoking was not associated with family history of asthma at birth (Pearson's  $\chi^2$  (1 df) = 0.31;  $p=0.579$ ).

### **5.4.4 Univariate analysis of sleeping bag use and its association with childhood wheeze**

There was a tendency for sleeping bag use in infancy to be associated with recent wheeze in childhood but the association was not statistically significant (RR 1.60; 95% CI 0.67, 3.78). Similarly, the use of a sleeping bag in infancy was not significantly associated with either night wheeze (RR 1.50; 95% CI 0.46, 4.87) or a history of asthma ever (RR 1.32; 95% CI 0.56, 3.13).

## 5.4.5 Multivariate analysis of cocoon use and its association with childhood wheeze

### 5.4.5.1 Generalized linear models

The association between cocoon use and recent wheeze remained after adjustment for the perinatal entry criteria as either individual factors or as a set. These results are shown at Table 5.5. Adjustment for mattress type and mattress cover type, including sheepskin or plastic mattress cover, had little effect. Additional adjustment for synthetic quilt or pillow use in infancy further increased the association between cocoon use and childhood wheeze (aRR 4.33; 95% CI 2.08, 9.02). The association remained significant between the use of cocoon in infancy and night wheeze (aRR 3.35; 95% CI 1.52, 7.39), and with a history of asthma (aRR 2.56; 95% CI 1.33, 4.92). The population attributable fraction for recent wheeze in childhood associated with cocoon use in infancy was 4.3%.

**Table 5.5 The association between cocoon use in infancy and asthma symptoms in childhood in the Infant cohort study with 1995 follow-up**

Respiratory symptom in 1995	N	Cocoon use in infancy	%	RR (95%CI) for cocoon use and respiratory symptom	p value	aRR (95%CI) for cocoon use and respiratory symptom	p value
No wheeze*	559	9	1.6	1.00 (reference)	-----	1.00 (reference)	-----
Recent wheeze	196	10	5.1	2.00 (1.29, 3.12)	0.002	4.33 (2.08, 9.02)	<0.001**
No night wheeze*	626	11	1.8	1.00 (reference)	-----	1.00 (reference)	-----
Night wheeze	148	8	5.4	2.27 (1.31, 3.93)	0.003	3.35 (1.52, 7.39)	0.003**
No asthma ever*	539	9	1.7	1.00 (reference)	-----	1.00 (reference)	-----
Asthma ever	262	10	3.8	1.63 (1.05, 2.53)	0.029	2.56 (1.33, 4.92)	0.005**

\*Reference category.

\*\*Adjusted for at-birth family history of asthma, home gas appliance use in infancy, synthetic quilt use in infancy, synthetic pillow use in infancy, maternal education at birth, maternal smoking at infant one month age, no other siblings in 1995.

The association with family and childhood history of atopic disease was examined. Further adjustment for at-birth family history of asthma did not alter the results in Table 5.5, and the positive association with cocoon use in infancy and recent wheeze remained significant after adjustment for the child's history of eczema, hay fever and asthma, and also the family history of asthma in 1995. These positive associations persisted after adjustment for the factors listed in Table 5.5 and individual adjustment for over 40 possible confounders including those listed above. The parents of infants with an at-birth family history of asthma were not selectively using cocoons (42.1% use versus 35.6% non-use,  $p=0.556$ ). Exposure to cocoon was positively associated with recent wheeze (RR 2.56; 95% CI 1.45, 4.51) even among children without an at-birth family history of asthma.

#### ***5.4.5.2 Matched cohort analysis***

The matched estimate was obtained using data on 383 children in 14 matched sets, based on the 7 possible confounder combinations. The number of children, exposed and non-exposed to cocoon as an infant, within each confounder combination are tabulated by each outcome variable and presented in Table 5.6. The RR for cocoon use in infancy and subsequent recent wheeze in this matched analysis was 2.72 (95% CI 1.06, 6.95). The relative risks for subsequent night wheeze and a history of asthma ever were 2.73 (95% CI 1.11, 6.75) and 2.44 (95% CI 0.85, 6.97) respectively.

**Table 5.6 Matched cohort analysis for the Infant cohort study with 1995 follow-up**

Strata	Recent wheeze		Night wheeze		History of asthma	
	Children using cocoons in infancy	Children non-exposed to cocoons in infancy	Children using cocoons in infancy	Children non-exposed to cocoons in infancy	Children using cocoons in infancy	Children non-exposed to cocoons in infancy
1	3	58	3	58	3	64
2	2	11	2	12	2	12
3	1	1	1	1	1	1
4**	1	2	1	2	1	2
5	1	3	1	3	1	3
6	1	10	1	10	1	10
7	1	2	1	2	1	2
8	3	33	3	34	3	35
9	1	13	1	13	1	13
10	1	3	1	2	1	3
11	1	20	1	20	1	21
12	1	57	1	57	1	61
13	1	44	1	46	1	46
14	1	89	1	89	1	91
<b>Total</b>	<b>19</b>	<b>346</b>	<b>19</b>	<b>349</b>	<b>19</b>	<b>364</b>

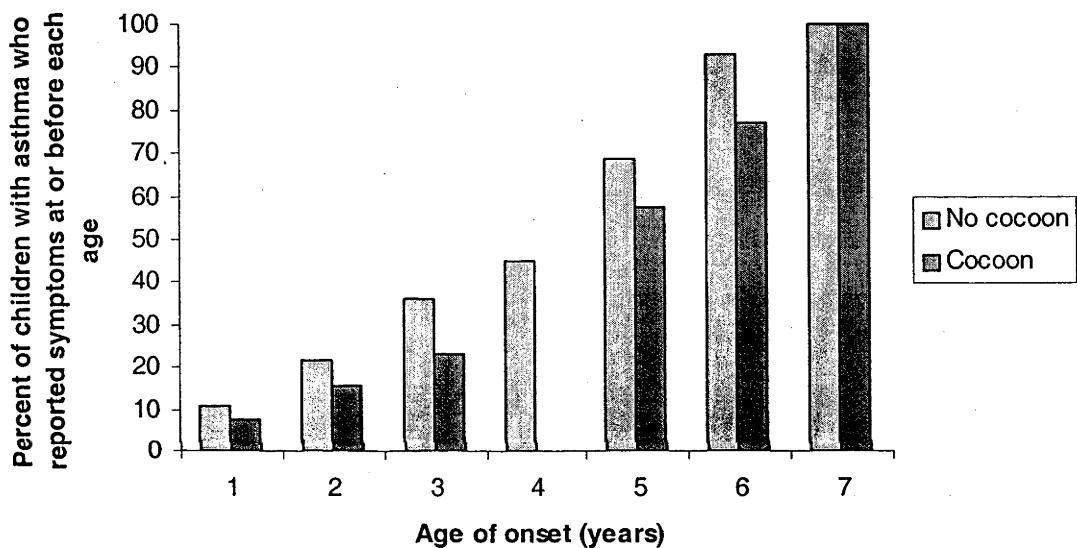
\*Potential confounders in each set: at-birth family history of asthma, any gas heating as infant, synthetic quilt use in infancy, only child at age 7, mother smoked during pregnancy, low maternal education at birth, air freshener used in bedroom as infant.

\*\*In stratum 4, for one exposed child, synthetic quilt in childhood data was not available, so this child was matched with two non-exposed children with the same confounder profile who also had missing synthetic quilt data.

## 5.4.5 Age of onset of wheeze

The use of cocoon in infancy did not relate to the age of onset of wheeze (aRR 0.61; 95% CI 0.23, 1.63). There was insufficient data to determine the association between cocoon use and wheeze frequency by sub-groups. Figure 5.2 shows the age of onset of asthma by cocoon use.

Figure 5.2 Age of onset or wheezy breathing by cocoon use in the Infant cohort study with 1995 follow-up



## 5.5 STATISTICAL METHODS: THE 1997 CARHS

### 5.5.1 Exposure variables

The two dichotomous bedding exposure variables were the same as Section 5.3.1: cocoon use in infancy and sleeping bag use in infancy.

### 5.5.2 Outcome variables

HDM sensitization refers to a positive SPT (wheal size  $\geq 3$  mm diameter) (see Section 4.3.2). The dichotomous outcome variables for wheeze were the same as Section 5.3.2, that is, the child's recent wheeze or night wheeze in the past 12 months and asthma ever. As the number of

children who used cocoons as infants is small, there was insufficient data to assess outcome variables for wheeze frequency of the number of episodes over the past year.

### **5.5.3 Study population and method of analysis**

In this study population of 499 children, described in Section 4.4.1, only 1.22% (5/406) of these children used cocoons in infancy. There was only one child (1/411; 0.24%) who used a sleeping bag as bedding in infancy. No further analysis was undertaken on sleeping bags.

As the sample of infants with cocoon use is small ( $n=5$ ), Fisher's exact test was used. For dichotomous variables with an expected frequency of  $<5$ , more chance variation must be allowed for, and a Fisher's exact test will calculate a significance test of the null hypothesis that the means are equal (544). Fisher's exact test allows computation of the exact probability of the occurrence of the observed frequencies (545). Here in this study, the Fisher's exact test indicates results with very small numbers for each outcome variable which are non-significant, so it was not appropriate to use more sophisticated methods of analysis.

### **5.5.4 Lung function tests**

#### ***5.5.4.1 Simple linear regression***

Simple linear regression models were used to examine the effect of exposure on the continuous outcomes of FEV<sub>1</sub>, FVC and the ratio of FEV<sub>1</sub> to FVC. The simple linear regression equation (545):

$$y = \alpha + \beta x$$

explains the change in one variable, denoted  $y$ , the outcome variable, corresponding to the change in the other explanatory variable, denoted  $x$ . Multiple linear regression models are discussed in Section 3.1.5.2.

## 5.6 RESULTS: THE 1997 CARHS

### 5.6.1 Cocoon use, HDM sensitization and child wheeze

There was no increased risk of subsequent HDM sensitization for children who used a cocoon in infancy (Fisher's exact test,  $t = 0.193$ ,  $p=0.847$ ). No statistically significant association was found between cocoon use in infancy and the respiratory symptoms in childhood of recent wheeze ( $p=0.569$ ), night wheeze ( $p=0.927$ ) or asthma ever ( $p=0.868$ ). These results are presented in Table 5.7.

**Table 5.7 Association between cocoon use in infancy and wheeze in childhood for the 1997 CARHS**

Respiratory symptom	% children with cocoon with wheeze	Fisher's exact t for cocoon use and respiratory symptom	P value
Recent wheeze	40.0% (2/5)	-0.570	0.569
Night wheeze	20.0% (1/5)	-0.092	0.927
Asthma ever	40.0% (2/5)	-0.167	0.868

There were no significant differences in the mean spirometric values between children exposed to cocoons in infancy compared to children who did not use cocoons in infancy. Children who used a cocoon in infancy did not demonstrate a greater reduction in their unadjusted difference in mean FEV<sub>1</sub>/FVC ratio when compared to children with recent wheeze or frequent wheeze, but they did have lower FEV<sub>1</sub> and FVC volumes. These results are presented in Table 5.8.

**Table 5.8 Unadjusted mean difference (95% CI) in spirometric values for children using a cocoon in infancy in the 1997 CARHS**

Variable	Unadjusted difference in mean FEV <sub>1</sub> (mL) with 95% CI between children with and without variable		Unadjusted difference in mean FVC (mL) with 95% CI between children with and without variable		Unadjusted difference in mean FEV <sub>1</sub> /FVC (%) with 95% CI between children with and without variable	
		p value		p value		p value
Recent wheeze	0.95 (-4.5, 6.4)	0.732	3.6 (-3.2, 10.5)	0.301	-1.2 (-2.5, 0.10)	0.070
Frequent wheeze	-19.9 (-34.2, -5.7)	0.006	-16.1 (-33.9, 1.7)	0.077	-3.6 (-6.9, -0.38)	0.029
Cocoon	-31.3 (-56.5, -6.2)	0.015	-37.8 (-68.2, -7.3)	0.015	1.1 (-4.8, 7.1)	0.711



## 5.7 DISCUSSION

In the Infant cohort study with 1995 follow-up, the use of cocoon was associated with a more than 2-fold increased risk of recent wheeze, nocturnal wheeze and asthma ever at age 7 years. There was a non-significant tendency for sleeping bags to also be associated with wheeze.

For the 1997 CARHS, there was no increased risk of subsequent HDM sensitization for children who used a cocoon in infancy. No statistically significant association was found between cocoon use in infancy and the respiratory symptoms in childhood of recent wheeze, night wheeze or asthma ever.

The findings reported in this Chapter are based on a small number of exposed individuals to the use of either cocoons or sleeping bags in infancy, and the findings may have been a result of chance (330). The positive findings in regards to cocoon use and wheeze need to be confirmed in other studies. In the Infant cohort study with 1995 follow-up, the small number of children exposed to sleeping bag in infancy ( $n=7$ ) may have contributed to the failure to detect a statistically significant effect in this cohort, arising in a Type II error (448). The most common reason for a Type II error is that the number of observations are too few and have failed to demonstrate a difference between the two groups (that is exposed and non-exposed to sleeping bags). Similarly, in the 1997 CARHS, the number of children exposed to either cocoon or sleeping bag in infancy may have been too small to reveal any significant association between subsequent wheeze, changes in lung function or HDM sensitization (see Section 3.2.4.2).

The internal validity (330) of this inference (that is, the adverse role of infant cocoon use on wheeze) as it pertains to the members of the source population should be considered. Internal validity is a study where “the index and comparison groups are selected and compared in such a manner that the observed differences between them on the dependent variables under study may, apart from sampling error, be attributed only to the hypothesized effect under investigation” (461). Three general types of bias can detract from internal validity: selection bias, information (measurement) bias, and confounding (330).

### **5.7.1 Selection bias**

The positive results reported in this Chapter are not likely to be influenced by differential follow-up as the proportion of TIHS children followed up from infancy did not differ by whether they used a cocoon or not. This prospective cohort study has collected standard information over time and has a high response rate, both factors minimizing selection bias (461). Moreover, the findings indicate that atopic children were not preferentially using or avoiding the use of cocoons as evidenced by the lack of association with eczema and rhinitis in infancy and an at-birth family history of asthma.

### **5.7.2 Measurement bias**

Limitations of this study included the use of a parental questionnaire and the absence of a biological or physician assessment of asthma. The ISAAC questionnaire, however, is considered a valid instrument for the determination of current asthma symptoms in the past 12 months and has been previously validated (440) (see Section 3.2.2.1). As the exposure was measured prospectively and was independent of disease awareness, there was no recall bias. In addition, at the time of assessment for wheeze, the research nurse was also unaware of the infant bedding status, thus minimizing observer bias, another sub-type of measurement bias. Differences in health care utilization between cocoon users and non-users, and the potential for increased reporting of symptoms should not influence the findings of this study.

Cocoons manufactured and sold during the study period most commonly comprised synthetic materials. Reporting of the material composition of cocoons was undertaken in 1994. And, at that time, no cocoon was described by the research assistants as having a non-synthetic material. It is considered that during the study period, cocoons contained polyester/synthetic filling, with/without synthetic-containing outer fabric. However some infants may have been exposed to cocoons made of natural materials. This could lead to misclassification of the record of cocoon taken to indicate synthetic cocoons. This misclassification would likely be non-differential (330). That is, the proportion of children misclassified on exposure (synthetic cocoon or no synthetic cocoon use) is unlikely to depend on disease status and thus the bias would be toward the null value (of no relation). Therefore, if this non-differential misclassification was present, it would reduce the study's ability to detect the effect of cocoon use on wheeze.

### 5.7.3 Confounding

The association between cocoon and wheeze was increased in magnitude after the negative association between cocoon and other synthetic bedding use was taken into account. It is noteworthy that the prospective association persisted after adjustment for many possible confounding factors by individual stratification and a matched cohort analysis. These confounders included bedding variables and other potential confounding factors operating in either infancy or childhood. Matching was used as a further mechanism to both control confounding and to improve the precision with which information was obtained regarding those children who as infants used cocoons, and as a means to confirm the estimates of the relative risks obtained from the individual stratified analysis (464). Confounding, including that due to infant or child exposure to maternal smoking or family history of asthma, could not explain the identified associations. Only one variable for maternal smoking, when infant aged one month, was included as a potential confounder in the final model due to the high collinearity between this variable and the variable for maternal smoking when child aged 7 years.

Cocoon use is not associated with an at-birth family history of asthma, however, cocoon use is associated with a family history of asthma in 1995. This may mean that the family is still using cocoons or other similar bedding, and that as cocoon use is now associated with a family history of asthma in 1995, perhaps it is the younger siblings also using cocoons who develop asthma that contribute to this positive family history in 1995, which is not evident at the index case's birth as the association with asthma is not only with the index child.

It is not possible to clearly associate one particular population with use or non-use of cocoons. A search of the literature did not identify any other studies detailing factors associated with cocoon use in other populations. However, in this study the role of potential indicators of socioeconomic status such as private health insurance, level of maternal education, level of paternal education, and father's unemployment at the time of birth were explored. None of these factors showed any association with cocoon use. Exposure to environmental tobacco smoke and less breastfeeding at 10 weeks were controlled for in the final model and their inclusion did not alter the positive association between cocoon use and wheeze.

#### **5.7.4 A causal role for cocoon and childhood wheeze**

The adverse role of synthetic bedding on asthma has been demonstrated in previous studies (12, 478, 536, 538) (see Section 5.1). And, the findings in this Chapter add to the causal inference of synthetic bedding causing asthma. These results meet the Bradford-Hill criteria (546) of consistency but as they are based on only one observational study, I am unable to report that the role of cocoon use in the development of child wheeze is causal. Moreover, the prospective findings in this study were based on a small number of exposed children and further studies are required to confirm these findings.

It is important to note that no study to date has shown a lower wheeze prevalence with exposure to synthetic bedding (12, 478, 536, 538). Moreover, it has previously been reported (13) in the 1995 Childhood Asthma Survey that the association between synthetic upper bedding and frequent wheeze in childhood displayed the features of high strength of association, temporality, dose-response and consistency (330). These features when considered with the results from the previous studies (see Section 5.1) indicate that the association between infant cocoon use and childhood wheeze may be causal in nature. If causal, the population attributable fraction for recent wheeze in childhood associated with cocoon use in infancy was low, 4.3%, reflecting the rarity of the exposure.

#### **5.7.5 Possible biological and physical mechanisms for the observed results**

Cocoons provide an intimate and prolonged relationship between the cocoon material and the infant's breathing zone. Thus one possibility for the effect reported in this study is that exposure to HDM allergen in synthetic cocoons could contribute to the increased development of wheeze in children (see Section 2.2.1). However, cocoon use did not appear to predict HDM sensitization. A full investigation of mechanisms, including whether bedding-asthma associations are mediated through HDM sensitization, is beyond the scope of this current thesis. There are also mechanisms related to bedding items, other than HDM allergen loading, that may be contributing to childhood wheezing. These mechanisms are discussed in Chapter 4. An increased risk of asthma related to the indoor emissions of VOCs has been demonstrated in children and adults (495, 522, 547), and VOCs released in low concentrations from synthetic materials close to the breathing zone might increase mucosal permeability to inhaled allergens (197) or promote

sensitization to HDM within the household environment similar to that which has been observed for indoor gas heating (504) or other infant bedding materials, such as plastic mattress covers (548) (see Section 4.7.2).

Reduced exposure to bacterial endotoxin levels is another environmental factor that has been postulated to contribute to the development of child wheeze. Exposure to house dust endotoxin may protect against the development of atopy by enhancing Th1 responses during perinatal life (270) (see Section 2.3.6). A study in a community hospital in the Netherlands, found synthetic pillows harboured fewer bacterial products than feather pillows (549). However, a recent report (11) from New Zealand that endotoxin levels were not significantly different between synthetic and feather pillows (synthetic: feather ratio [endotoxin units per gram of dust] 0.78; 95% CI 0.54, 1.15) may make this a less likely mechanism of action in regards to synthetic bedding items, including cocoons. This study was, however, based on only eight pairs of pillows, each pair consisting of a synthetic and feather pillow from each bed, indicating that further studies are required to clarify endotoxin levels in bedding items.

The length of exposure to the bedding environment may be further increased as the infant is often transported from the bed to other locations while still remaining within the cocoon. In addition, with the close proximity of the synthetic cocoon material to the infant's airway it is likely that exposure to bedding related factors such as allergens, VOCs or endotoxins may occur in a continuous low dose fashion.

### **5.7.6 Generalizability of the study findings**

As previously discussed, there is no prior evidence with regard to an infant's use of cocoons containing synthetic materials and adverse respiratory effects in childhood. It is important to determine if the results reported in this Chapter are generalizable beyond the study sample. "A study is externally valid or generalizable if it can produce unbiased inferences regarding a target population (beyond the subjects in the study)" (461). This is meaningful only with regard to a specific external population (461). And, a study's results must be true for the subjects studied, that is internally valid, before the findings are considered for generalization to different settings (330). The internal validity of this cohort study has been considered above (see Section 5.7). The small number of infants exposed to cocoons or sleeping bags does potentially impact on the

study's internal validity because chance cannot be excluded as being responsible for the observed results.

The TIHS cohort is not representative of the general infant population of Australia. This cohort comprised one-fifth of live births in the defined geographical area of Tasmania, but weighting in selection of individual infants was given to risk factors for SIDS (436). However, the lack of representativeness of the cohort should not be considered as affecting external validity. In order for the results of an analytical cohort study to be generalized to other populations it is not necessary for the cohort to be representative of the community from which it was selected (330, 550). The key concerns with regard to a study base are that the eligible participants are well defined, that there is good distribution of determinants, confounders and modifiers in the study and adequate sample size (550). The TIHS cohort fulfils the criteria that would support the generalization of the findings of this birth cohort. The eligible participants have been well defined, all satisfy the cohort-entry selection criteria and there is sufficient variability in exposure and potential confounders. Moreover, the potential effects of the entry scoring system components were taken into account in the multivariate analyses. After controlling for the factors listed in Table 5.5, further adjustment for these perinatal entry criteria did not alter the results. Thus, the TIHS cohort entry criteria are unlikely to affect the generalizability of these results. The children in this study should not differ from other children to any large extent with regard to the biological development of asthma. However, the bedding items used in Tasmania in 1988 may not be similar to modern cocoons in other settings thus making the applicability of these results less.

## **5.8 CONCLUSION**

In conclusion, the results of this study add to the increasing evidence for a role for infant bedding items in the development of childhood asthma. This study is unique. There are no other studies, especially no prospective studies on infant cocoon use and child wheeze. The findings suggest that synthetic cocoon use in infancy is associated with an increased subsequent risk of child asthma. The use of cocoons in infancy is an easily modifiable environmental factor but currently there is no clear evidence base regarding possible health effects. No study to date, moreover, has shown a lower prevalence of wheeze with exposure to synthetic bedding. However, the number of children exposed to cocoons in this cohort study was small and further studies are now required to confirm these findings.

## 5.9 POST-SCRIPT

Bedding items, and more specifically their material composition, are gaining recognition for their possible role in childhood asthma. Chapter 4 and Chapter 5 have postulated that the adverse effect of different types of underbedding, such as sheepskin and plastic mattress covers, and cocoons with subsequent HDM sensitization and child asthma may be mediated through mechanisms that may be enhanced by proximal airway exposure. In Chapter 6, the issue of proximity to airway exposure is explored as the interaction between bedding and different sleep positions with regard to child wheeze is examined, with specific reference to synthetic quilts.

## Chapter 6

# The association between childhood sleep position, bedding and respiratory health

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## 6.0 PREFACE

This Chapter examines the relationship between synthetic quilt use and sleep position in childhood and child asthma. The cross-sectional study, the 1995 Childhood Asthma Survey, has been analysed and the findings described in this Chapter.

The findings from this Chapter have been reported in a recently published paper (see Appendix 5):

Ponsonby AL, Dwyer T, Trevillian L, Kemp A, Cochrane J, Couper D, Carmichael A. The bedding environment, sleep position, and frequent wheeze in childhood. *Pediatrics* 2004; May 113(5):1216-22.

## 6.1 INTRODUCTION

Chapters 4 and 5 have reported associations between both underbedding, sheepskin and plastic mattress liners, and cocoon use in infancy with subsequent HDM sensitization or childhood wheeze. The adverse effect of these bedding items may be mediated through some mechanism that involved proximal airway exposure. And, as discussed, higher allergen loading near a child's airway has also been proposed as one possible explanation (9, 532, 534) for the numerous cross-sectional and prospective associations between synthetic bedding and childhood wheeze (see Section 5.1). These reported associations may, however, reflect selection bias. Studies of bedding are potentially complicated by selection bias as children with asthma may preferentially use synthetic rather than feather bedding, based on the concept that they are non-allergenic (as opposed to feather pillows) (198). The majority of these studies reporting an association between synthetic bedding and childhood wheeze were based on exposure to pillows alone. It is less recognized that upper bedding, such as quilts, can also be a source of HDM exposure during sleep. Recently, synthetic quilts have been shown to have a markedly higher Der p content than feather quilts (9, 551): the ratio (synthetic: feather) of the geometric mean for Der p ( $\mu\text{g}/\text{m}^2$ ) was 15.45 (95% CI 4.28, 55.8) (9). In addition, a 10-fold reduction of airborne HDM allergen near the face during sleep was obtained by replacing used overlying quilts with new quilts (473). The



authors in that study, concluded that the HDM airborne allergens near the face during sleep were generated from the used bedding, and not from the bedroom floor (473). Moreover, other studies (444, 481) have reported poor correlation between HDM allergen levels in the bed and the floor, supporting the view that measuring antigen levels in carpet is not a good indicator of inhaled antigen load (552).

Personal aeroallergen exposure may be influenced by the level of reservoir allergens, the nature of the allergen source, proximity of airways to the source, level of dust disturbance, level of ventilation and indoor humidity, the size of particles carrying the allergen and the rate of breathing of the individual (507, 553). Inhalation of HDM allergen is believed to occur principally through airborne allergen inhaled into the nose. Bedding is proximal to the human airway and will contribute to the airborne allergen load if physically disturbed (474). Moreover, high levels of airborne allergen are generated if the bedding is infested with mites as a person's normal movement during sleep probably renders surface allergen airborne and available for inhalation (473). In addition it has been reported that uptake of a dust mite allergen particle-surrogate from allergen-containing surfaces, such as pillows, also occurs by direct nose transfer (554).

Specificity of association, refers to the extent to which a single well-characterized factor can be shown to be responsible for a single disease (9, 555) It is one of the criteria for proving causality between an environmental exposure and non-infectious illness defined by Bradford-Hill (9, 546). The validity that specificity confers on any causal inference regarding the exposure effect has been questioned (9, 330, 556). However, there are instances in which specificity can be used in support of a causal hypothesis (556, 557). According to Weiss, 2002 (557), one such circumstance applies to the specificity of exposure, that is, where only the exposure initially predicted to be associated with an outcome actually is observed to be associated with it.

The bedding environment is ideal to examine whether an expected specificity of association is in fact observed as one can study the influence of bedding for different sleep positions. This approach has previously been used to examine the interaction between bedding environment and sleep position in sudden infant death research (558). For example in the SIDS research study, an adverse effect of quilt use was observed among infants who slept supine or on the side (aOR 6.16; 95% CI 2.01, 18.87)) but not among prone sleeping infants (difference in effect,  $p=0.01$ ) (559).

This Chapter reports a novel approach to assess the role of bedding in asthma by examining the interaction between bedding and different sleep positions with regard to child wheeze. Specifically, if it could be demonstrated that synthetic quilt use, for example, conferred a different risk if a child slept in a different sleep position then the case for synthetic quilt use being causally related to asthma would be strengthened. If the adverse effect was mediated through some mechanism that involved the bedding being in close proximity to the airway one would postulate that the association between overlying synthetic quilt use and adverse respiratory outcomes would be specifically observed among children sleeping supine, where the face would be closer to overlying bedding. This aim of this Chapter is to consider specificity of exposure as it pertains to synthetic quilt use and its association with frequent wheeze. The hypothesis is that the association between synthetic quilt use and frequent wheeze is significantly stronger among children who slept supine compared with children who slept non-supine.

## **6.2 METHODS**

For this Chapter, the cross-sectional data from the 1995 Childhood Asthma Survey was analysed. The child's current bedding and usual sleep position were recorded by parental questionnaire for the 6,378 seven year children participating in the 1995 Childhood Asthma Survey (see Section 3.2.2).

## **6.3 STATISTICAL METHODS**

### **6.3.1 Exposure variables**

#### ***6.3.1.1 Child bedding***

Overbedding refers to any bedding items that covered the child's body above the sheet and was classified into three categories: any synthetic quilt, feather quilt, and other bedding (that is, neither feather nor synthetic quilt) used. The most common type of bedding in the other category was blankets. Quilts, doonas or duvets of dacron, polyester or other synthetic composition were classed as synthetic quilts. A small number of children in childhood (n=23) were excluded because the pillow was described as "anti-allergy" but information on composition was not available. Synthetic pillows were those reported as foam/sponge/tontine/polyester/dacron. Sheepskin was any wool fleece under-bedding with either hide or material backing. Dichotomous

exposure variables, synthetic versus feather quilt use (the main measure of bedding exposure); and, other overbedding versus feather quilt use were created.

### **6.3.1.2 Usual sleep position**

Sleep position was classified as supine if the parents reported that the child usually slept on the back in response to the question "What position does your child usually sleep in?" Children usually sleeping on the side or on the stomach were termed non-supine sleepers. A dichotomous variable, children who slept supine versus children who slept non-supine was the main indicator of sleeping position.

## **6.3.2 Outcome variables**

### **6.3.2.1 Respiratory wheeze and measures of lung function**

Frequent wheeze was defined as children with greater than 12 wheeze episodes over the past year compared to children with no wheeze as the baseline group (see Section 4.3.2).

Disease misclassification within the broad spectrum of asthma has been a large problem in asthma epidemiology (see Section 2.2.1.6). For this bedding study, we were interested in identifying children who would be more likely to have HDM-triggered airway disease rather than those with asthma due to other mechanisms. We chose to compare children with frequent wheeze for the following reasons. Firstly, as a better marker of HDM-related airway disease revealing more bedding-wheeze patterns: (i) children with asthma who are also sensitized to HDM are more likely to have severe or frequent asthma (181); (ii) feather pillow and quilt use has been inversely associated with severe wheeze (197); and (iii) it has been previously reported using the 1997 CARHS that HDM-sensitized children are much more likely ( $p < 0.0001$ ) to have frequent wheeze than non-sensitized children in this setting (Prevalence Ratio 19.6; 95% CI 6.9, 55.6) (196). Secondly, in this 1995 Childhood Asthma Survey, current synthetic overbedding (pillow and quilt) use has been reported previously to show a strong association with frequent wheeze (aRR 5.2; 95% CI 1.3-20.6, for 12 episodes or more) but not with moderate wheeze (1-12 episodes) (13).

The continuous outcome variables of lung function were FEV<sub>1</sub>: both baseline and post-exercise spirometric measures were used, the latter after six minutes of free running (442). Post-exercise FEV<sub>1</sub>, is a lung measure previously observed to be lower in children with recent wheeze or asthma (442) (see Section 3.2.2.1). Exercise challenge lung function was obtained on a subset of children (n=414) from randomly selected schools (see Section 3.2.2).

## **6.4 STATISTICAL METHODS: THE 1995 CHILDHOOD ASTHMA SURVEY**

### **6.4.1 Logistic regression**

The Breslow Day test, a test of homogeneous association across the strata, was first used to examine differences in the association between synthetic versus feather quilt use and severe wheeze by sleep position strata (452).

Univariate odds ratios were calculated using simple logistic regression (560). The logistic regression equation (330) is given by:

$$p(\text{probability}) = \frac{\exp(\alpha + \beta x)}{1 + \exp(\alpha + \beta x)}$$

This logistic model is equivalent to an exponential odds model (see Section 5.5.4).

The reference group chosen for upper bedding was feather quilts because this bedding type (i) has lower HDM levels (532, 534), and (ii) has been previously associated with reduced wheeze compared to synthetic quilts (196, 198). We examined the interaction between quilt type and sleep position by comparing synthetic to feather quilts. Most children (88.1%) slept under these two overbedding types (see Table 6.1). For sleep position, children who slept supine were compared to non-supine sleeping children and children with no usual sleep position were excluded.

## 6.4.2 Matched case-control analysis

A nested case-control study with each child with frequent wheeze, matched to control children with no wheeze over the past year, among the children who were reported to have a usual sleep position was utilized to increase efficiency. In total, 117 children with frequent wheeze were matched to 1,162 controls with up to 10 controls per case (452). Each index child was matched to the nearest controls by date of birth and to those who had the same status as the index child with regard to four characteristics: gender, foam mattress or not, electric blanket or not and sheepskin or not (see Section 5.3.5). More than 80% of controls were born within a month of the index case. Conditional logistic regression was used in the matched analysis where each matched set was standardized with regard to underbedding except for pillow type. As feather pillows and allergen-occlusive mattress covers were too uncommon to allow adequate matching, they were considered as additional confounders in the matched analyses.

## 6.4.3 Multiple logistic regression modeling

Multiple logistic regression models were used to examine the relation between quilt use, sleep position and reported respiratory outcomes with control for confounders (560). The difference in the quilt-wheeze associations by sleep position was examined by the log likelihood ratio test for the reduction in deviance associated with the addition of an interaction term into the logistic model (561). The risk estimates for each factor and the interaction term were adjusted for the confounding effect of the other components in the model.

The term *statistical interaction* denotes the interdependence between the effects of two or more factors within the confines of a given model of risk (562). Here, the interaction is based on a multiplicative model. This is using a logistic model in which the excess incidence rate of a disease in the population exposed to, say, two agents (measured as the difference with respect to the non-exposed population) is equal to the sum of the excess in the population exposed only to the first agent, plus the excess in the population exposed only to the second, plus a third term expressing the interaction effect of the two agents when both are present (563). Within this frame of reference, the key feature of the multiplicative model is that its interaction term is an explicit and easily computable function of the other two terms (the two relative rates) so that, when the multiplicative model holds, no independent estimation of this term is required (563). Any

interactions observed would also be present in an additive model but negative or absent findings can not be taken to mean that additive interactions are not present (564).

#### **6.4.4 Lung function tests**

The lung function sample was relatively small so synthetic quilt use was examined as a dichotomous exposure to maximize the numbers within each category for analysis. Multiple linear regression models were used to examine FEV<sub>1</sub> as a continuous outcome with adjustment for relevant confounders (447) (see Section 3.1.5.2).

### **6.5 RESULTS: THE 1995 CHILDHOOD ASTHMA SURVEY**

#### **6.5.1 Characteristics of the study population**

The study population has been reported in Section 4.6.2 and comprised 6,378 children who turned seven years of age in 1995. Synthetic pillow or quilt use was common. Feather quilt use was also common but feather pillow use was not. Most parents were able to report a usual child sleep position with 86% of children with either frequent wheeze (117/136) or no wheeze (4,048/4,707) reported to have a usual position. More than a third of the children slept supine. Among non-supine children, the side position (n=2,564) was much more common than the prone sleep position (n=484). Although many children had recent wheeze (23%), only 2% (n=136) of children were reported to have had frequent wheeze with more than 12 episodes in the last year. The additional study sample characteristics (see Table 4.10) are presented below in Table 6.1.

**Table 6.1 Distribution of sleeping environment characteristics and respiratory wheeze in the 1995 Childhood Asthma Survey**

Characteristic	Total N	n	% with variable
<i>Usual sleep position:</i>	6355		
Supine (on back) sleep position		2431	38.3
Non-supine (on side or prone)		3048	48.0
No usual sleep position or other		876	13.8
 <i>Overbedding type:</i>	 6345		
Any synthetic quilt use		2649	41.7
Feather quilt use		2941	46.4
Other overbedding		755	11.9
 <i>Pillow type:</i>	 6340		
Any synthetic pillow		5709	90.0
Feather pillow		231	3.6
Other pillow		400	6.3
 Sheepskin underbedding	 6307	 1331	 21.1
 Electric blanket	 6307	 1347	 21.4
 Allergen-occlusive mattress cover		 54	 0.86
 Foam mattress		 2038	 32.0
 <i>Bed type:</i>	 6354		
Single bed		4662	73.4
Bottom bunk bed		686	10.8
Other		1006	15.8
 <i>Wheeze frequency over the past year:</i>	 6107		
None (0 episodes)		4707	77.1
Moderate (1-12 episodes)		1264	20.7
Frequent (12 episodes or more)		136	2.2
 Recent wheeze		 1400	 22.9
 Asthma ever	 6307	 1710	 27.1

## 6.5.2 Univariate analysis

### ***6.5.2.1 Sleeping environment and other characteristics associated with frequent wheeze or sleep position***

The univariate analysis is shown in Table 6.2. Usual supine sleep position (versus usual side or prone) was not significantly associated with frequent wheeze (OR 0.90; 95% CI 0.61, 1.33). Frequent wheeze was positively associated with synthetic quilt, synthetic pillow, electric blanket and sleeping in a bottom bunk. A supine sleep position was associated with electric blanket or foam mattress use but not with frequent wheeze, rhinitis or eczema. Asthma medication type and use over the past year did not relate to sleep position. In Australia in 1997, bedding advice to children with asthma included the use of an allergen-occlusive mattress cover and sheepskin avoidance (565). Consistent with the recommendation, children in this study with frequent wheeze were more likely (OR=18.39;  $p<0.0001$ ) to sleep on allergen-occlusive covers but less likely (OR=0.54;  $p=0.02$ ) to sleep on a sheepskin. There was no difference in the association between allergen-occlusive cover use or sheepskin use and recent wheeze by sleep position.



**Table 6.2 The univariate association between sleeping environment, child characteristics and frequent wheeze or supine sleep position**

Characteristic (reference group)	Odds Ratio (95% CI) For frequent wheeze	p value	Odds Ratio (95% CI) For supine sleep position	p value
<b>Sleeping environment</b>				
Usual supine position (usual side or prone)	0.90 (0.61, 1.33)	0.585	-----	
Synthetic quilt (feather quilt)	1.74 (1.20, 2.51)	0.004	1.03 (0.92, 1.16)	0.427
Other overbedding (feather quilt)	1.37 (0.78, 2.39)	0.27	0.92 (0.77, 1.10)	0.546
Synthetic pillow (feather pillow)	3.24 (1.03, 10.24)	0.045	0.98 (0.78, 1.23)	0.813
Other pillow (feather pillow)	3.07 (0.68, 13.85)	0.145	1.14 (0.81, 1.61)	0.457
Sheepskin underbedding (no sheepskin)	0.54 (0.33, 0.90)	0.017	1.06 (0.93, 1.20)	0.400
Electric blanket (no electric blanket)	1.56(1.07, 2.29)	0.021	1.17 (1.02, 1.33)	0.039
Foam mattress (no foam mattress)	1.35 (0.95, 1.92)	0.095	1.21 (1.08, 1.36)	0.001
Bottom bunk bed (other type of bed)	1.76 (1.08, 2.88)	0.039	0.96 (0.81, 1.15)	0.812
Allergy occlusive cover (non-use)	18.39 (8.10, 41.74)	<0.0001	1.37 (0.77, 2.46)	0.283
Feather pillow (no feather pillow)	0.26 (0.08, 0.82)	0.021	1.12 (0.92, 1.38)	0.266
<b>Child characteristics</b>				
Male sex	1.31 (0.93, 1.85)	0.119	1.07 (0.96, 1.20)	0.208
Premature (<37 wks) birth	2.19 (1.31, 3.64)	0.003	0.83 (0.68, 1.02)	0.078
Breastfed in infancy	0.65 (0.45, 0.95)	0.025	0.94 (0.83, 1.07)	0.385
No siblings	1.31 (0.66, 2.62)	0.436	0.95 (0.75, 1.20)	0.650
Family history of asthma	5.43 (3.50, 8.41)	<0.001	1.05 (0.94, 1.17)	0.386
<b>Child's history of:</b>				
Eczema	3.69 (2.60, 5.23)	<0.001	1.15 (1.01, 1.31)	0.030
Hayfever	9.05 (6.37, 12.86)	<0.001	1.14 (1.00, 1.30)	0.057
Pneumonia	6.11 (4.00, 9.33)	<0.001	1.23 (0.99, 1.52)	0.056
Bronchitis	6.09 (4.30, 8.62)	<0.001	1.06 (0.93, 1.20)	0.385
Father fulltime employment	0.69 (0.49, 0.98)	0.040	0.91 (0.81, 1.02)	0.103
Low maternal education (<12 years)	1.67 (1.16, 2.42)	0.006	1.11 (1.00, 1.24)	0.056
Maternal smoking	1.58 (1.11, 2.25)	0.011	1.12 (1.00, 1.26)	0.055
Exposed to indoor smoking in same room	1.62 (1.15, 2.29)	0.006	1.08 (0.97, 1.20)	0.171
Cat as family pet	0.89 (0.63, 1.26)	0.512	1.03 (0.93, 1.15)	0.562
Bedroom carpet	0.52 (0.30, 0.90)	0.019	1.22 (0.99, 1.52)	0.063
Exposure to gas used in cooking or heating	0.81 (0.42, 1.56)	0.532	0.91 (0.76, 1.10)	0.330
Fish consumption >/1/week	0.78 (0.34, 1.79)	0.563	0.94 (0.75, 1.18)	0.595
Household residents >5	0.98 (0.85, 1.13)	0.808	1.00 (0.96, 1.05)	0.974

### 6.5.2.2 The relation between overbedding composition and frequent wheeze by usual sleep position

The association between quilt use and severe wheeze after stratification by sleep position was examined. These results are shown in Table 6.3. We found the association between sleep position and frequent wheeze varied by the type of overbedding used. Among supine sleepers, synthetic (versus feather) quilt use was associated with frequent wheeze (OR 3.75; 95% CI 1.78, 8.63). However, this apparent adverse effect was not evident among non-supine children (OR 1.12; 95% CI 0.65, 1.93). The difference in synthetic quilt effect by sleep position was significant; test for interaction,  $p=0.007$ .

**Table 6.3 The univariate association between overbedding composition and frequent wheeze by sleep position**

Characteristic (reference group)	Odds Ratio (95% CI) For frequent wheeze	p value
<i>Overbedding by sleep position</i>		
Among supine sleepers, synthetic (feather) quilt	3.75 (1.78, 8.63)	<0.0001
Among non-supine sleepers, synthetic (feather) quilt	1.12 (0.65, 1.93)	0.654
<i>Difference in effect by sleep position</i>	$p = 0.007$	
Among supine sleepers, other overbedding (feather) quilt	2.76 (0.89, 7.90)	0.038
Among non-supine sleepers, other overbedding, (feather) quilt	0.99 (0.39, 2.21)	0.970
<i>Difference in effect by sleep position</i>	$p = 0.10$	

### 6.5.3 Confounder identification

To examine the potential contribution of confounding factors, we identified factors which were associated with severe wheeze or sleep position. Factors significantly associated with severe wheeze are shown in Table 6.2. Children with hay fever, a history of eczema, bronchitis, pneumonia, or a family history of asthma was also significantly over-represented in the severe wheeze group. The following factors did not relate significantly to severe wheeze: male sex, family pet cat, child exposure to any active smoking in the same room, gas heater use, gas cooking, foam mattress use, plastic mattress liner use, recalled age of introduction of solid food, fish consumption >1 a week, younger, older or total sibling number, resident number, and regular child care at less than or one year of age. We then examined how the factors in Table 6.2 related to child sleep position among children with no recent wheeze. Children were more likely to sleep supine if they slept on a foam mattress (OR 1.21; 95% CI 1.06, 1.39), slept on an electric blanket (OR 1.23; 95% CI 1.05, 1.44) or used a feather pillow (OR 1.29; 95% CI 1.02, 1.63). The other factors showed little association with sleep position. Among children with frequent wheeze, type of medication use in the past year or frequency of use did not relate to child sleep position.

### 6.5.4 Multivariate analysis

#### ***6.5.4.1 The relation between overbedding composition and frequent wheeze by usual sleep position***

We examined the nested case-control sample where each child with frequent wheeze was matched to controls without wheeze with regard to age, sex, foam mattress use, electric blanket use and sheepskin use. Again, a similar pattern was evident, with a difference in the likelihood of severe wheeze by overbedding apparent among supine sleeping children but not non-supine children. Synthetic compared to feather quilt use was associated ( $p=0.02$ ) with severe wheeze among supine sleepers (OR 2.54; 95% CI 1.18, 5.48) but this association was absent for children sleeping on the side or prone (OR 1.09; 95% CI 0.62, 1.92); test for interaction,  $p=0.005$ . Further adjustment for synthetic pillow use provided matched odds ratios from conditional logistic regression of 2.37 (95% CI 1.08, 5.23) and 1.06 (95% CI 0.60, 1.88) respectively; Test for interaction,  $p=0.005$ . Among non-supine children, the effect of synthetic versus feather quilt use did not vary between side and prone children ( $p=0.86$ ). The significant difference in quilt effect by sleep position persisted after adjustment for premature (<37weeks) birth, breastfeeding history,

sibling number, allergen-occlusive mattress cover use, overlying sheet use, home gas use or child exposure to tobacco smoke or the other factors listed in Table 6.2. The interaction effect also persisted after adjustment for child hayfever, eczema and family history of asthma (Test for interaction,  $p=0.01$ ).

Six different sleep position-overbedding combinations with regard to frequent wheeze were examined. These results are shown in Table 6.4. The baseline group for each pair-wise comparison was sleeping supine under a feather quilt. All other sleep combinations were associated with a higher risk of frequent wheeze and the difference in risk for synthetic quilt use was significant regardless of sleep position used under a synthetic quilt. In particular, children sleeping under synthetic quilts were at a higher risk of severe wheeze. These findings were not altered by further individual adjustment for feather pillow use, premature birth, family history of asthma, breastfeeding history, parental smoking, sibling number or any of the factors listed in Table 6.2.

#### ***6.5.4.2 The relation between pillow composition and frequent wheeze by usual sleep position***

The effect of pillow composition on frequent wheeze by sleep position was not able to be examined due to low numbers: there were only three children who slept supine on a non-synthetic pillow who were reported to have frequent wheeze.

**Table 6.4 The risk of frequent wheeze for various combined sleep arrangements compared to sleeping supine under a feather quilt in nested case-control study.**

Combined sleeping arrangement		Cases (%) n=117	Matched Controls (%) n=1144	Matched Odds Ratio* (95%CI)	p value
Sleep position	Overbedding				
Supine	Feather quilt	8.5	20.6	1.00 (reference)	----
Supine	Other overbedding	6.0	4.9	2.88 (0.83, 10.03)	0.10
Supine	Synthetic quilt	26.5	17.7	2.67 (1.23, 5.80)	0.01
Non-supine	Feather quilt	27.4	26.0	1.87 (0.86, 4.08)	0.12
Non-supine	Other overbedding	6.8	6.5	6.84 (0.82, 56.75)	0.08
Non-supine	Synthetic quilt	24.8	24.4	2.38 (1.09, 5.18)	0.03

\* Cases matched to controls with regard to age, sex, foam mattress use, electric blanket use and sheepskin use.

### 6.5.5 Lung Function

Lung function results were available on 96.7% (414/428) children. The median FEV<sub>1</sub> in this sample was 1.44 L (inter-quartile range; 1.30 L to 1.59L). Increasing wheeze frequency over the past year was associated with lower post-exercise FEV<sub>1</sub> measures, after adjustment for child age, sex, height, distance run, ambient humidity during exercise, family history of asthma, child exposure to active smoking and whether asthma medications were taken within six hours of testing. Children with any wheeze episodes over the past year had a lower FEV<sub>1</sub> post-exercise than children with no wheeze. Among children who slept non-supine, synthetic quilt use was not associated with a significant FEV<sub>1</sub> reduction post-exercise compared to children not using this item. However, among children who did sleep supine, synthetic quilt use was associated (p=0.05) with a lower post-exercise FEV<sub>1</sub> compared to supine sleepers under feather or other bedding. Synthetic quilt use was associated with lower post-exercise FEV<sub>1</sub> measures among supine (p=0.05) but not non-supine children (p=0.61) (see Table 6.5). An adverse effect for synthetic quilt use particularly among supine sleepers was observed for this measure of lung function, similar to the findings reported above for frequent wheeze.

**Table 6.5 Change in FEV1 post-exercise by wheeze frequency and sleep arrangement**

Factor	Number of children with Lung Function Tests and data available	Adjusted* FEV <sub>1</sub> change in ml post-exercise (95% CI)	p value
<i>Number of wheeze episodes in the past year:</i>			
None (reference)	320	0% (reference)	----
1-3	48	-5.5 (-8.80 to -2.2)	0.001
4-12	16	-5.5 (-11.1 to 0.05)	0.05
More than 12	2	-16.6 (-30.9 to -2.21)	0.02
Supine sleep position	349	-0.1 (-2.6 to 2.4)	0.94
Synthetic quilt use	406	-1.3 (-3.6 to 1.00)	0.27
For children with non-supine sleep position, synthetic quilt use	196	-1.0 (-4.7 to 2.8)	0.61
For children with supine sleep position, synthetic quilt use	151	-3.6 (-7.0 to 0.03)	0.05

\*Lung function measures adjusted for child height, age, sex, distance run, ambient humidity during exercise, family history of asthma, child exposure to active smoking and whether asthma medications were taken within six hours of testing. Children using beta agonists on the day of testing were excluded (n=6).

## 6.6 DISCUSSION

In the cross-sectional and nested case-control assessment, an interaction between quilt use and sleep position on respiratory function was observed. There was an adverse effect associated with synthetic quilt use on frequent wheeze and post-exercise lung function among children who slept supine but not among children who did not sleep supine. Among children who slept supine, synthetic (versus feather) quilt use was associated with frequent wheeze. However, among non-supine sleepers, overlying synthetic quilt use was not associated with frequent wheeze. This difference in quilt effect by sleep position was highly significant. Similarly, synthetic quilt use was associated with lower post-exercise FEV<sub>1</sub> measures among supine but not non-supine children.

The strengths of this study are a high participation rate, the availability of lung function as well as symptom report data and the use of frequent wheeze as a study outcome. As previously discussed, frequent wheeze may be a better marker of HDM allergen-related wheeze than the global term "asthma" because HDM atopy is strongly related to frequent wheeze (196) (see

Section 6.3.2.1). The use of a nested case-control analysis with matching on underbedding reduced the likelihood that underbedding variability contributed to the observed interaction.

The cross-sectional design study does not limit the study materially because the postulated interaction is based on short-term, not long-term disease processes. Synthetic bedding has been postulated to induce adverse effects through HDM allergen loading (534), the release of VOCs (197), or altered endotoxin exposure (13) (see Section 5.7.5). Bronchial provocation with aeroallergen can produce either an immediate or late response with wheeze and FEV<sub>1</sub> reduction (566, 567). VOCs can induce a decline in FEV<sub>1</sub> in asthmatic subjects within 1.5 hours of exposure (568). Inhaled endotoxin can produce a dose-related bronchoconstriction with a decrease in FEV<sub>1</sub> within six hours, which is more accentuated among asthmatic subjects (569, 570). Thus, bedding-induced bronchoconstriction could occur over a short time period.

### **6.6.1 Measurement bias**

A potential weakness of the study is that frequent wheeze, bedding and sleep position were based on parental report only and therefore may introduce measurement bias. The report of wheeze frequency showed good agreement with measures of post-exercise lung function. Further, the findings for synthetic quilts and lung function were similar to those for reported frequent wheeze. The lung function decrement associated with synthetic quilt use among supine sleepers was only small but it was two-thirds the magnitude of the decrement associated with recent wheeze and thus may be of clinical relevance.

Previously, the parent report of infant bedding has been shown to agree well with interviewer observations at home interview. The validity of a parental report of usual sleep position in children of this age group has not been established. In addition, studies have shown that child sleep position is likely to change during the night (571, 572). This could lead to misclassification of usual sleep position. This misclassification would be likely to be non-differential and thus reduce the study's ability to detect sleep position effects. However, the important issue is that the interaction between synthetic bedding and sleep position is unlikely to be explained by such misclassification. Sleep position was classified as a binary factor (supine/non-supine) and both differential and non-differential misclassification of a binary environmental factor will, if it has any effect, bias a multiplicative interaction effect toward the null value when the following conditions are met (573), as they are here. First, the two binary factors should be independent. The lack of

association between synthetic quilt use and supine sleeping in Table 6.2 satisfies the criteria that the two binary factors should be independent (573). A second condition is that the measures must classify the true exposures better than random (573). Past validation work shows a high level of agreement between parental report and research nurse observation of infant bedding (13). Thus, parental report is likely to classify bedding correctly, certainly better than random.

To our knowledge, the parental report of child usual sleep position at age seven has not been validated. However, the study findings provide some indirect evidence that parental classification of usual sleep position is likely to be better than random. Children sleeping on electric blankets were significantly more likely to sleep supine, consistent with past thermal work on sleeping infants that indicates that the non-prone position assists the loss of excess body heat (574). That is, the sleep position data does provide a pattern of results consistent with past work on thermal balance (574) which would predict children with electric blankets to avoid the prone position, which provides a reduced capacity to lose body heat. Thus, the usual sleep position by parental report, although likely not to classify all true sleep positions correctly, is likely to classify sleep position more correctly than chance.

### **6.6.2 Causal inference**

There is growing evidence that synthetic bedding materials are associated with increased childhood wheeze (198, 472, 575). It is now a high priority to establish if the association is causal in nature. Epidemiologic research identifying an effect modification or interaction can assist in our understanding of the causal process of disease. Effect modification occurs when the estimate of the effect of one factor depends on another factor in the study base (576). The term statistical interaction denotes a similar phenomenon (577) but does not establish biological interaction. In this study, for the issue of overlying synthetic quilts and child wheeze, if the adverse effect was mediated through some mechanism that involved the bedding being in close proximity to the airway (such as, but not restricted to, HDM allergen transfer) one would postulate that the association between overlying synthetic quilt use and adverse respiratory outcomes would be specifically observed among children sleeping supine, where the face would be closer to overlying bedding as was observed in the present study. In contrast, the adverse effect of an overlying synthetic quilt would be less evident for side or prone sleeping children because other bedding items such as the mattress would be closer to the airway and thus relatively more



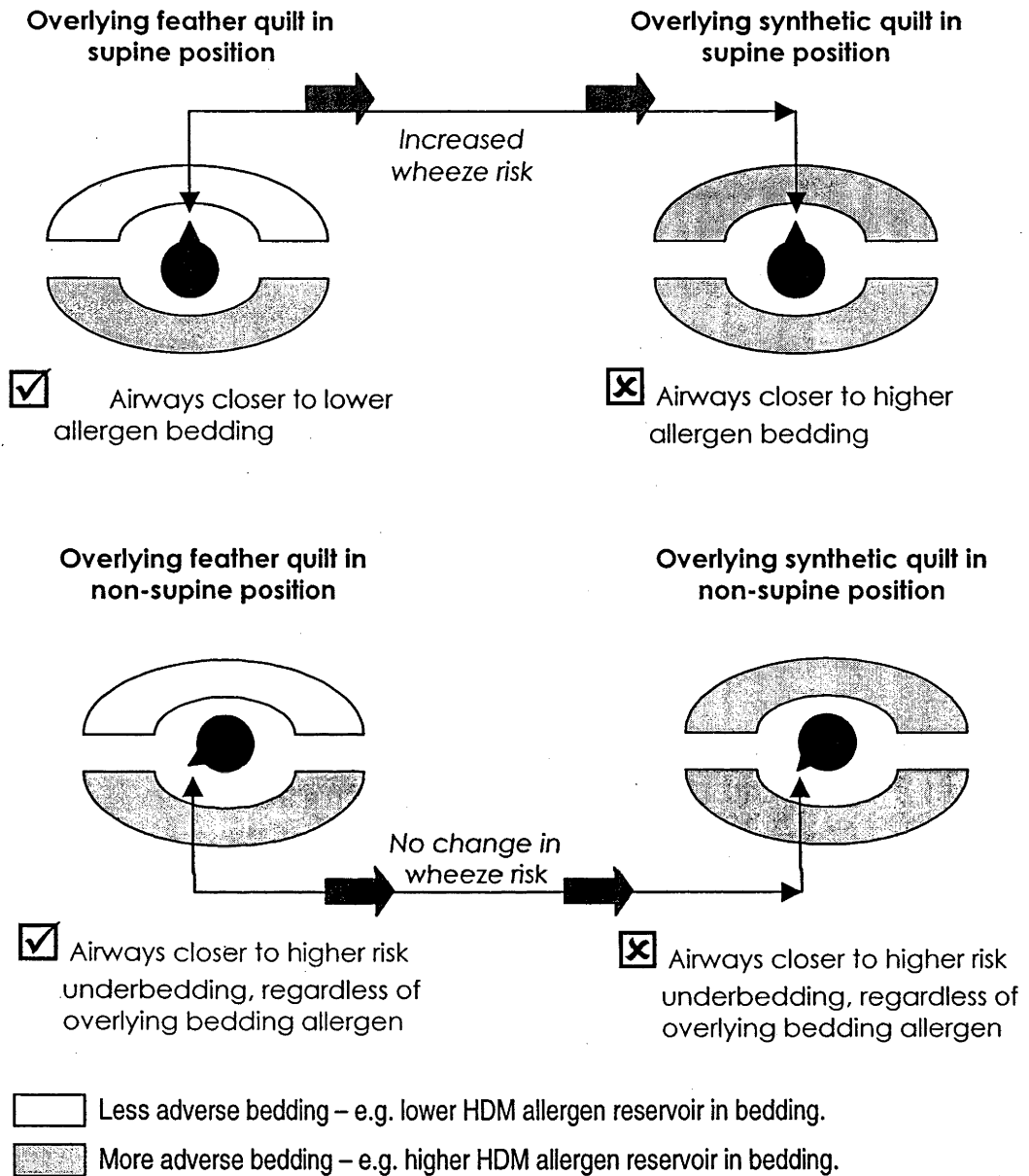
important than any overlying items such as quilts. A diagrammatic representation of this is shown in Figure 6.1.

Previous studies have shown that the association between synthetic upper bedding and severe wheeze has a high strength of association (13, 197), a dose-response relationship (13), biological plausibility (532) and ecological coherence (198, 472, 575). And, two recent birth cohorts have reported that a prospective relationship is evident (12, 13) (see Section 5.1). However, experimental evidence is not available and may be difficult to obtain because of the ethics of applying a potentially deleterious exposure (synthetic bedding) to children with asthma in a RCT.

One of the counter-arguments against a causal role for synthetic bedding with childhood wheeze was that the association may merely reflect selection bias even prior to wheeze development: that is, synthetic bedding was preferentially selected for children at risk of subsequent wheeze. However, the finding that the adverse effect of synthetic quilts was restricted to supine-sleeping children only is evidence against this because it is unlikely that this selection bias differs by sleep position. This is further supported by the findings of no interaction between sleep position and the two bedding items (sheepskin and allergen-occlusive mattress cover) that do appear to reflect selection according to the asthma recommendations existing at the time of the study. In 1997, Australian asthma recommendations were to avoid sheepskins and use impermeable mattress covers (565).

The interaction reported here provides further support for the causal criteria of specificity (557) because the adverse effect of synthetic quilts was most evident in children who would be more likely to be sleeping face-up near the quilt. That is, these results show specificity of exposure where only one type of exposure is related to a given outcome (557). In contrast, as predicted, the adverse effect of an overlying synthetic quilt was less evident for side or prone sleeping children because other bedding items such as the pillow or mattress would be closer to the face and thus relatively more important than overlying quilts. The exact mechanisms that underlie this interaction are not yet understood, but possible mechanisms in relation to synthetic bedding have been previously discussed in Chapter 5.

**Figure 6.1 Schematic representation of a hypothesised mechanism involving close proximity of bedding to the child's airway**



**Note:** The hypothesis is that the adverse effect of an overlying synthetic quilt is mediated by a mechanism involving close proximity to the airway. For example, inhaled HDM allergen dose into a child's airways could be less if the airway is in close proximity to lower HDM allergen bedding, such as feather quilts (9, 551), compared to higher HDM bedding such as synthetic quilts (532, 534, 551, 575), underbedding (551, 578) or mattress (9, 556).

## **6.7 CONCLUSION**

This Chapter has provided further evidence of the importance of the role played by specific bedding items and their material composition in childhood asthma. To our knowledge, this is the first report on the interaction between the effect of an overlying synthetic quilt and sleep position on wheeze risk. We found a positive interaction between overlying synthetic quilt use and the supine sleep position. The interaction is consistent with an adverse effect of synthetic quilt use that is mediated by close physical proximity. Thus, these findings indicate that an increasing focus on the bedding environment immediately adjacent to the nose and mouth of children during sleep is required.

## **6.8 POST-SCRIPT**

Chapters 4, 5 and 6 have considered the adverse association of individual infant bedding items and HDM sensitization and child wheeze. These bedding exposures, however, do not occur singly but in combination with other environmental factors, including additional bedding items. Chapter 7 examines the associations between composite bedding, bedding environmental factors and child asthma.

## 7.0 PREFACE

This Chapter presents an additional approach to investigate the infant bedding and bedroom environment in asthma. This approach is based on a theoretical model of HDM loading in different bedding items and is used to investigate infant sleeping environment and subsequent childhood wheeze. Specifically, the analyses in this Chapter seeks (i) to extend bedding exposure measurement by considering bedding not as single items but as a composite and (ii) to investigate bedding-home environment interactions. The two prospective studies, the 1997 CARHS and the Infant cohort study with 1995 follow-up, and the cross-sectional study, the 1995 Childhood Asthma Survey, have been analysed and are described in this Chapter.

The findings from the Infant cohort study with 1995 follow-up, discussed in this Chapter, are reported in a paper currently 'in press' (see Appendix 6):

Trevillian LF, Ponsonby AL, Dwyer T, Kemp A, Cochrane J, Lim LL-Y, Carmichael A. The infant bedroom environment and asthma at 7 years: a prospective cohort. *Am J Public Health* 2005; 95(8):(In press).

## 7.1 INTRODUCTION

Difficulty in measuring indoor exposures during early life has been one of the problems that have hampered aetiology research in childhood asthma. Exposures such as infant sheepskins, discussed in Chapter 4, do not occur singly but in combination with other environmental factors, including additional bedding items. HDM allergen levels in bedding have been shown to be more important than bedroom floor HDM levels in determining (i) airway responsiveness (190) or (ii) asthma severity (187). A longitudinal study (190) of 30 children aged 8-12 years, demonstrated that the natural changes in HDM levels, as measured in the childrens' bedding can lead to significant reductions in PEFr in children who are allergic to HDMs; whereas in an earlier study (187) mite allergen levels in the mattress were a more important determinant of asthma severity in children with HDM allergy, than levels in floor samples.

The majority of previous studies that have recorded bedding HDM allergen levels have used composite bedding samples, for example mattress and upper bedding combined. Yet the appropriateness of such an approach is questioned. Marks et al., 1995 (578), found that Der p 1 allergen concentrations in the upper bedding and mattress did not differ significantly from those in the whole bed ( $p>0.15$ ), implying that mattress or upper bedding Der p 1 levels can be taken as representative of the whole bed. This was despite the concentration of Der p 1 in the pillow being 2.78-fold lower than that in the whole bed ( $p=0.011$ ); yet no distinction was made between the different material compositions of the individual bedding items (578). And as previously discussed, it is well recognized that the bedding material itself influences HDM allergen levels within individual items (9, 14, 479, 532, 535, 556) (see Section 5.1). Furthermore, a recent study (9) in New Zealand has also reported a wide variation in Der p 1 levels in individual components of bedding. Reservoir dust samples from bedding items showed Der p 1 geometric mean levels were 13.4  $\mu\text{g/g}$  (95% CI 9.5, 18.9) in pillows; 29.4 (95% CI 19.8, 43.5) in duvets; and 53.8  $\mu\text{g/g}$  (95% CI 39.4, 73.4) in mattresses (9). These results also suggest that the contribution of each individual bedding item to HDM allergen inhalation load warrants consideration.

Furthermore, dust collected from pillows and upper bedding might be an important indicator of HDM allergen exposure, given the more intimate, prolonged relationship between pillows and upper bedding, and the airway. These items are also more likely to be physically disturbed during sleep, generating airborne HDM. In addition, these items (pillows and upper bedding) can influence mattress levels, as mattress dust contains allergens that have filtered down from the upper bedding, and may be seen as a proxy only for the measurement of other allergen sources closer to the subject (527) (see Section 4.7.3). HDM allergen levels on mattresses were found to be significantly higher when synthetic pillows (12.22; 95% CI 7.34, 14.63  $\mu\text{g/g}$  dust) were used compared with feather or wool pillows (7.33; 95% CI 3.07, 8.68  $\mu\text{g/g}$  dust) (490). Thus, it is likely that allergen levels are influenced by the nature of the bedding, both type (for example, quilt or pillow) and composition (for example, wool or synthetic), by laundry routine, and by the environmental climate of the room (527, 579).

In addition to bedding, other conditions in individual homes within the same climatic region vary sufficiently such that dust samples from the same site in different houses in a single locality have a wide distribution of HDM allergen levels (513). These variations between homes have prompted the identification of modifiable housing factors to create conditions less conducive to mite growth. Several recently published studies have reported residential and environmental

factors that are associated with high indoor HDM allergen levels within bedroom and living room floor dust and mattress dust. These household factors may impact on humidity and/or temperature levels within the home and as a consequence affect HDM microclimate and levels (580). The critical humidity for HDM survival is temperature dependent, ranging from 55% to 75% relative humidity over the temperature range from 15°C to 35°C (581). The presence and age of carpets, the type and age of residential buildings, the presence of damp in the home, older mattresses and increasing number of household residents have all been shown to influence indoor HDM allergen concentrations (580). Furthermore, bedroom heating increases the HDM levels in bedding (481, 582, 583). The Childhood Asthma Prevention Study measured HDM allergen levels in the homes of 616 participants in Sydney, Australia, and reported that the mean Der p 1 concentration ( $\mu\text{g/g}$ ) was significantly greater in the beds of participants whose rooms were heated than in the beds of homes not heated (20.39; 95% CI 14.14, 29.39 versus 14.05; 95% CI 12.48, 15.81) (481). As of April, 2004, there are 23 published papers (updated from Simpson et al., 2001) (580) that have investigated the relationship between household characteristics and HDM allergen levels. The findings of these studies are summarized in Table 7.1.

Thus, with regard to childhood asthma, the environmental model for infant HDM exposure may not be one of single major risk factors operating independently, but rather one of environmental determinants operating synergistically to increase infant HDM exposure.

The aim of this Chapter is to test the hypotheses:

(i) The association between bedding items and child wheeze is of a greater magnitude for composite bedding than for individual bedding items; and

(ii) Other home environmental factors interact with bedding items to influence the bedding-wheeze association.

Table 7.1 Results from 23 published studies of the analysis of household factors associated with higher indoor HDM allergen levels

Study	No. of homes	Older home	Carpet vs smooth floor	Mould/Damp	Increasing no. of Residents	Indoor Humidity	Heating/heating type	Foundation	Structure	Older mattress
Norwich, UK (Luczynska et al. 1998) (584)	158	Yes†	Yes (older carpets)	NM	NM	NM	No	Yes (concrete; high in mattress)	NM	Yes
Kent, UK (Atkinson et al. 1999) (585)	643+	No	Yes	Yes	Yes	NM	NM	NM	NM	Yes
France, 2 towns (Dornelas de Andrade et al. 1995) (586)	98^	No	NM	No	NM	No	No	NM	NM	NM
Holland, 2 towns (Van Strien et al. 1994) (587)	516^	Yes	Yes	Yes*	Yes	Yes <sup>ns</sup> in sub-group	NM	Yes (timber)	Yes (brick)	Yes
Germany, 3 towns (Kuehr et al. 1994) (588)	1291	No	NM	Yes	Decreased levels	Yes	Yes	NM	NM	Yes
Stockholm, Sweden* (Wickman et al. 1991) (589)	160^	NM	NM	No	No	Yes <sup>ns</sup>	NM	NM	NM	NM
Sweden*, 3 towns (Munir et al. 1995) (590)	130^	NM	No	Yes	NM	Yes <sup>ns</sup>	NM	NM	NM	NM
Spain*, 2 towns (Alvarez et al. 1997) (591)	65	No	NM	Yes	NM	NM	NM	NM	NM	NM
Portugal* (Placido et al. 1996) (592)	59	Yes	Yes	Yes	No	NM	No	NM	NM	NM
Estonia (Julge et al. 1998) (593)	197+	Yes	Not clear	Yes	No	NM	Yes	NM	Yes (Timber)	NM
USA, National survey (Arbes et al., 2003) (583)	831	Yes	No	Yes	No	Yes	Yes	NM	NM	NM
Northern Norway (Schei et al., 2002) (482)	152	NM	No	Yes	NM	Yes	Yes	NM	No	Yes

Table 7.1 continued

Study	No. of homes	Older home	Carpet vs smooth floor	Mould/Damp	Increasing no. of Residents	Indoor Humidity	Heating/heating type	Foundation	Structure	Older mattress
Canada, 2 cities (Chan-Yeung et al. 1995) (582)	120	Yes	No	No (non sig. trend)	Yes	No	Yes	NM	NM	NM
New Zealand (Wickens et al. 1997) (525)	474 <sup>^</sup>	NM	Yes	N (non-sig. trend)	Yes	Yes	No	NM	NM	No
Melbourne, Australia (Dharmage et al. 1999) (579)	485	Yes	Yes (older carpet)	Yes	NM	Yes (mattress only)	Yes	Yes (timber)	Yes (timber)	Yes
Tasmania, Australia (Couper et al. 1998) (444)	72+	NM	Yes	Yes	No	Yes <sup>^*</sup>	No	No	No	NM
Hong Kong* (Leung et al. 1998) (594)	40	No	NM	NM	NM	No	NM	NM	NM	No
Christchurch, New Zealand*(Martin et al. 1997) (595)	59	No	NM	Yes	NM	Yes	NM	Not clear	Not clear	No <sup>^*</sup>
Boston, USA (Chew et al., 1998) (596)	499	No	Yes	NM	No	NM	NM	NM	NM	No
Victoria, Australia (Garrett et al. 1998) (480)	80	Yes	Yes	Yes	No	Yes	NM	Yes (concrete)	Yes (brick)	Yes <sup>^*</sup>
Moree, Wagga Wagga, Australia* (Vanlaar et al. 2001) (551)	50 <sup>^</sup>	No	NM	NM	NM	Yes	NM	No	NM	Yes
Manchester, UK (Simpson et al. 2002) (597)	564	Yes	Yes	Yes	No	NM	No	NM	NM	Yes
Sydney, Australia (Mihshahi et al. 2002) (481)	616	Yes	Yes	Yes <sup>*</sup>	No	NM	Yes <sup>*</sup> (timber)	Yes <sup>*</sup> (timber)	Yes <sup>*</sup> (timber, fibro)	Yes

NM = not measured-

<sup>^</sup>Yes if p<0.05; \* if univariate analysis only; <sup>^\*</sup> if linear correlation; # if subjects asthmatic; <sup>^\*</sup> Inner spring mattress; + if subjects infants; <sup>^</sup> if subjects children



## 7.2 METHODS

### 7.2.1 Sources of data

The role of composite bedding and wheeze was examined in the three Tasmanian studies. The 1997 CARHS provided data for assessment of HDM sensitization and lung function in childhood, but was too small to examine bedding-home environment interactions. The potentiation effect of home environmental factors on composite bedding was examined in the Infant cohort study with 1995 follow-up and the 1995 Childhood Asthma Survey. The use of the three studies allows an assessment of the consistency of the findings.

### 7.2.2 Exposure variables

#### *7.2.2.1 Selection and classification of bedding items*

Four bedding items: synthetic pillow, synthetic quilt, cocoon and sheepskins were selected as exposure variables based on their capacity to contain high HDM allergen loads as reported in previous studies (see Section 4.1 and Section 5.1). Also, in this Tasmanian cohort, sheepskin use was associated with HDM sensitization (see Chapter 4) (548). And, synthetic bedding items such as pillow, quilt and cocoon (see Chapter 5) were associated with child wheeze (13, 196, 598). In addition, as reported in Chapter 4, the role of infant mattress type in HDM sensitization, (foam mattress aRR 1.09; 95% CI 0.72, 1.67), and recent wheeze (foam mattress aRR 1.35; 95% CI 0.98, 1.83) appeared less important (548) than the selected bedding items so it was not included here as an exposure variable. Cocoon use occurred in infancy, not in childhood, and thus was not in the 1995 Childhood Asthma Survey.

Sheepskins comprised the animal hide with the natural wool fibres attached. Infant cocoons manufactured and sold in Southern Tasmania during the study period most commonly comprised outer coverings of cotton/polycotton with a polyester (synthetic) filling (598). Pillows reported as foam/sponge/tontine/polyester/Dacron were classified as synthetic and a synthetic quilt in infancy was defined as the use of a synthetic quilt over the infant during cold weather. The parental report of infant synthetic pillow use showed high agreement with the research nurse observation of infant pillow used in the last night in 1995 (13).

### **7.2.2.2 Composite bedding classifications**

For the TIHS data, there were 16 possible combinations of an infant's exposure to these four bedding items. There were 9 possible bedding exposure combinations for children exposed to the three bedding variables in the 1995 Childhood Asthma Survey. In all three studies, the composite bedding exposures were collapsed to six combinations due to sparse data in some exposure combination strata. This six-level composite bedding classification was ordered from 0 to 5 based on the magnitude of previous associations with wheeze and the volume of HDM reservoir:

Combination 0: No synthetic quilt, pillow, sheepskin or cocoon

Combination 1: Sheepskin only

Combination 2: 1 synthetic item

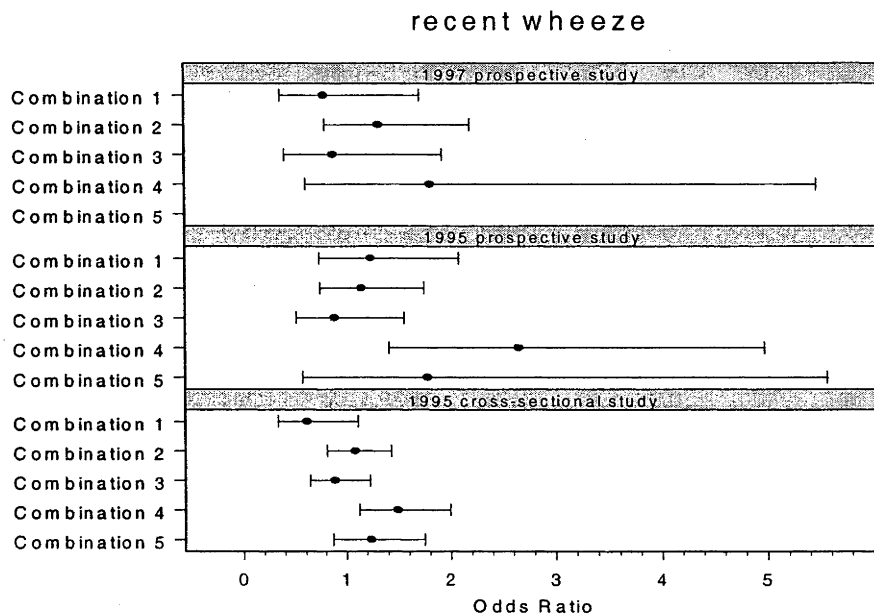
Combination 3: Sheepskin and 1 synthetic item

Combination 4: 2 or more synthetic items

Combination 5: 2 synthetic items and sheepskin

Preliminary analysis showed similar trends for the association between the six-level composite bedding classification and wheeze in all three data sets. Figure 7.1 shows these associations for recent wheeze. Test for linear trend in the 1997 CARHS, Infant cohort study with 1995 follow-up, and the 1995 Childhood Asthma Survey were  $p=0.673$ ,  $p=0.068$ , and  $p<0.001$ , respectively. Similar results were found for night wheeze and asthma ever. However, due to small numbers for some of the exposure categories, this six-level composite bedding classification was further collapsed to a three-level composite bedding classification in each of the data sets.

**Figure 7.1 Graphical representation of unadjusted odds ratios for recent wheeze and the six-level composite bedding classification in the three Tasmanian data sets**



The three-level composite bedding classification was then made based on past work and the distribution of bedding exposures to the HDM allergen-rich synthetic pillows, synthetic quilts, cocoons or sheepskin (9, 479, 532, 556). The reference group *Bedding Combination 0* ( $B_0$ ) represented infants with no synthetic items and no sheepskin (548). *Bedding Combination 1* ( $B_1$ ) comprised either one synthetic item only ( $n=279$ ) or one sheepskin only ( $n=121$ ) or one synthetic item and one sheepskin ( $n=113$ ). *Bedding Combination 2* ( $B_2$ ) comprised two or more synthetic items without sheepskin ( $n=57$ ) or with sheepskin ( $n=14$ ). This classification put more emphasis on synthetic bedding items than sheepskin because of the previous reported associations with wheeze in this cohort (13, 196, 598) (see Section 7.2.2.1). In this Chapter, the term composite bedding refers to the average increase per category from  $B_0$  to  $B_1$  to  $B_2$ . The  $B_2$  effect is  $B_2$  versus  $B_0$ , and the  $B_1$  effect is  $B_1$  versus  $B_0$ .

### 7.2.2.3 Classification of home environmental factors

Environmental exposure variables were coded as binary. Baby's bedroom heated was in response to current use at time of interview and also intended use of any type of heating in cold weather. Validation of the parent's response to the question "What heating is used in the baby's bedroom?" was undertaken by the research nurse at the home interview ( $\kappa=1.00$ ) (see Section 7.2.2.4). Recent painting refers to the infant's bedroom having been painted within the previous

12 months from the time of home interview. Absence of carpet means no wall-to-wall carpet in the infant's bedroom. The research nurse also validated the type of floor covering in the baby's bedroom at the time of the home interview ( $\kappa=1.00$ ). Home gas appliance use in infancy is defined as the positive report of gas cooking or gas heater use in the living room. A 1985-86 survey reported that 86% of the gas-heated Tasmanian homes used bottled gas for heaters of portable or fixed type (599). Infant exposure to tobacco smoke refers to people smoking in the same room as the infant. Biological validation of questionnaire data on infant exposure to tobacco smoke was provided by a 1995 sub-study using infant urinary cotinine levels (600). The absence of bedroom carpet, home gas use during childhood and child exposed to indoor tobacco smoke are the environmental exposure variables I examined for the cross-sectional 1995 Childhood Asthma Survey study.

#### ***7.2.2.4 Validation of exposure variables***

Inter-observer (rater or interviewer) agreement may be an important source of measurement error. The kappa coefficient ( $\kappa$ ) measures pairwise agreement among a set of raters making category judgements, correcting for expected chance agreement. In assessing the amount of agreement among raters of category distinctions, the kappa statistic normalizes for the amount of expected chance agreement and allows a single measure to be calculated over multiple coders (601). Cohen's kappa (602) is also a measure of validity for binary outcomes (603). And, for two raters, the formula is the same (604) for Cohen's kappa (602) and for Fleiss's kappa (605). Measurement validity is defined as "the degree to which a measurement measures what it purports to measure" (461). In this study, the kappa coefficient is used to determine the level of assessment of the dichotomous response to the presence of an infant variable, for example baby's bedroom heating or infant pillow use, between the parental questionnaire and the research nurse's observation at the home interview. The latter is considered the gold standard. The principal weakness of kappa stems from it being a measure of the frequency of exact agreement rather than a measure of the degree of approximate agreement. This is not, however, a weakness with dichotomous data as in this Chapter, since observations then either agree exactly or they totally disagree (604).

$\kappa$  has a maximum of 1.00 when agreement is perfect, and a value of zero indicates no agreement better than chance. The thresholds for evaluation of inter-rater agreement can be interpreted using the following guidelines (606).

**Table 7.2 Guidelines for interpretation of kappa**

Value of K	Strength of agreement (606)
<0.00	Poor
0.00 - 0.20	Slight
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Substantial
0.81 - 1.00	Almost perfect

$\kappa$  is defined as (602, 605):

$$\kappa = \frac{(P_o - P_e)}{(1 - P_e)}$$

where  $P_o$  is an observational probability of agreement, and  $P_e$  is a hypothetical expected probability of agreement under an appropriate set of baseline constraints such as total independence of observer classifications (606).

In a typical experimental design of two raters making dichotomous decisions on the same population of subjects, the distribution of data can be displayed in a 2 x 2 contingency table (607).

The respective cell proportions are given by

$$P(x) = \frac{x}{N}$$

Where the cell count,  $x = a, b, c,$  or  $d$  and  $N = a + b + c + d$  is the total number of observations.

The proportion of agreements is given by

$$P_o = \frac{(a + d)}{N}$$

The expected agreement,  $P_e$ , is calculated from the marginals by the equation

$$P_e = \left\{ \left[ P\left(a + \frac{c}{N}\right) * P\left(a + \frac{b}{N}\right) \right] + \left[ P\left(b + \frac{d}{N}\right) * P\left(c + \frac{d}{N}\right) \right] \right\}$$

From the observed  $P_o$  and the derived  $P_e$ :

$$K = \left( \frac{P_o - P_e}{1 - P_e} \right) = 1 - \left[ \frac{(1 - P_o)}{(1 - P_e)} \right]$$

Here, kappa is used to assess the validity of parental report of exposures compared to the research nurse observations.

### 7.2.3 Outcome variables

The outcome variables HDM sensitization, recent wheeze, night wheeze, asthma ever and wheeze frequency were coded as previously described in Section 4.3.2. The validity of these measures is discussed in Section 3.2.2.1.

## 7.3 STATISTICAL METHODS

Pair-wise correlations were obtained by Spearman's rank order correlation. Univariate ORs and 95% confidence intervals were logit-based and calculated by logistic regression. To assess the role of the composite bedding combination exposures in infancy as risk factors for asthma at the age of 7 years, multivariate logistic regression models were calculated to control for multiple confounders simultaneously, providing adjusted ORs (503) for the categorical outcome variables recent wheeze, asthma ever and night wheeze. Those factors found in univariate analysis, or a priori, to be associated with wheeze were examined as potential confounders. Using a change-in-estimate methods (466) those factors that altered the point estimate for the exposure-wheeze association by 10 percent or more, were included in the final model. I examined the confounding effect of a large number of factors including sibling number, in utero exposure to maternal smoking, air freshener use in infant's bedroom, cat or dog as a family pet during infancy, visible indoor mould and plastic mattress liner use in infancy, which were eliminated according to the 10% rule during modeling. The cohort entry criteria, either separately or as a set did not alter any

of the reported associations. Factors that could operate on the causal pathway between bedding and asthma or could modify the association were not included as routine confounders. Those potential confounders selected were not considered to physically influence bedding or host response to bedding and thus modify the bedding effect. I used the Wald test (608) for linear trend of the categorical bedding variables ( $B_1$  vs  $B_0$  or  $B_2$  vs  $B_0$ ) by replacing the binary predictors with a single predictor, taking category rank scores.

To assess whether an association between a composite bedding combination and a respiratory outcome differed by environmental factor status after controlling for confounders, a model was first built with terms for composite bedding and each confounder and the dependent variable was one of the respiratory outcomes examined. A second model was then built in the same way as the first but also with a term for the environmental factor and an interaction term between composite bedding and environmental factor. The resulting deduction in deviance obtained by using the second model compared to the first was then assessed using the p value associated with the log likelihood ratio test (503). Tests for interaction often use a higher significance than  $p=0.05$  (560). Here, interaction terms that improve the model by  $p \leq 0.1$  are considered important. Stratified multivariate logistic regression was used to explore the potentiation of more than one environmental factor on the bedding-wheeze effect. Stratification was made on the number of environmental factors present (0, 1, 2 or 3). Discrete proportional hazard modeling (541) was used to examine age of onset of asthma or wheezy breathing by bedding. The potentiation of age of onset by environmental factors was determined by a stratified log rank test (467).

Multiple linear regression models were used to examine the effect of exposure on continuous outcomes, such as the lung function measures of FEV<sub>1</sub>, FVC and the ratio of FEV<sub>1</sub> to FVC with adjustment for relevant covariates (see Section 3.1.5.2).

## **7.4 RESULTS: THE INFANT COHORT STUDY WITH 1995 FOLLOW-UP**

### **7.4.1. Characteristics of the study population**

The characteristics of the study population, including wheeze prevalence, are shown in Table 7.3. Infant bedding data for all bedding combinations was available on 800 children. The percentage of infants exposed to each composite bedding category was 27.0%, 64.1% and 8.9% for  $B_0$ ,  $B_1$  and  $B_2$  respectively. The majority of infant's bedrooms were carpeted (90.6%) whereas less

infants were exposed to the two other environmental factors: infant bedroom heated (34.3%) or bedroom recently painted within the previous 12 months (33.5%).



**Table 7.3 Characteristics of the study population in the Infant cohort study with 1995 follow-up**

	%	n/total N*
Mean age (years)	6.9 (standard deviation=0.3)	
<b>Respiratory symptoms</b>		
Recent wheeze over past year	27.0	222/823
Night wheeze over past year	19.2	160/834
Asthma ever	32.4	280/863
<b>Infant bedding</b>		
Synthetic pillowcase use at 1 month age	14.8	127/857
Synthetic quilt use at 1 month age	44.9	396/802
Cocoon use at 1 month age	2.4	19/802
Sheepskin use at 1 month age	29.8	256/859
<i>Six-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or cocoon, or sheepskin	27.0	216/800
Combination 1: Sheepskin only	15.1	121/800
Combination 2: 1 synthetic item	34.9	279/800
Combination 3: Sheepskin and 1 synthetic item	14.1	113/800
Combination 4: 2 or more synthetic items	7.1	57/800
Combination 5: 2 synthetic items and sheepskin	1.8	14/800
<i>Three-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or cocoon, or sheepskin	27.0	216/800
Combination 1: 1 Synthetic and/or 1 sheepskin item	64.1	513/800
Combination 2: 2 or more synthetic items	8.9	71/800
<b>Environment</b>		
Heating in infant's bedroom	34.3	294/857
Carpet in infant's bedroom	90.6	767/847
Infant's bedroom painted within previous 12 months	33.5	287/856
Any gas appliance use in infant's house	3.3	28/856
Infant exposed to tobacco smoke in house	65.6	558/851

\*Small N for some characteristics: bedding items (N=800).

#### **7.4.2 Risk of childhood wheeze associated with increasing numbers of bedding items in infancy**

Infants exposed to a composite bedding arrangement of two or more synthetic items in infancy, had a more than two-fold risk of subsequent wheeze by age 7 years compared with children who had none of these bedding items in infancy aOR 2.10 (95% CI 1.15, 3.82) (Table 7.4). There was a dose-response relationship between exposure to increasing number of bedding items in infancy and the risk of recent wheeze in childhood (Test for linear trend,  $p=0.053$ ) (Table 7.4). This trend for a higher number of HDM allergen-rich bedding items and increasing risk of subsequent wheeze was also found for asthma ever (Test for linear trend,  $p=0.072$ ) and night wheeze (Test for linear trend,  $p=0.034$ ).

**Table 7.4 Prospective association between infant composite bedding classifications and childhood wheeze in the Infant cohort study with 1995 follow-up**

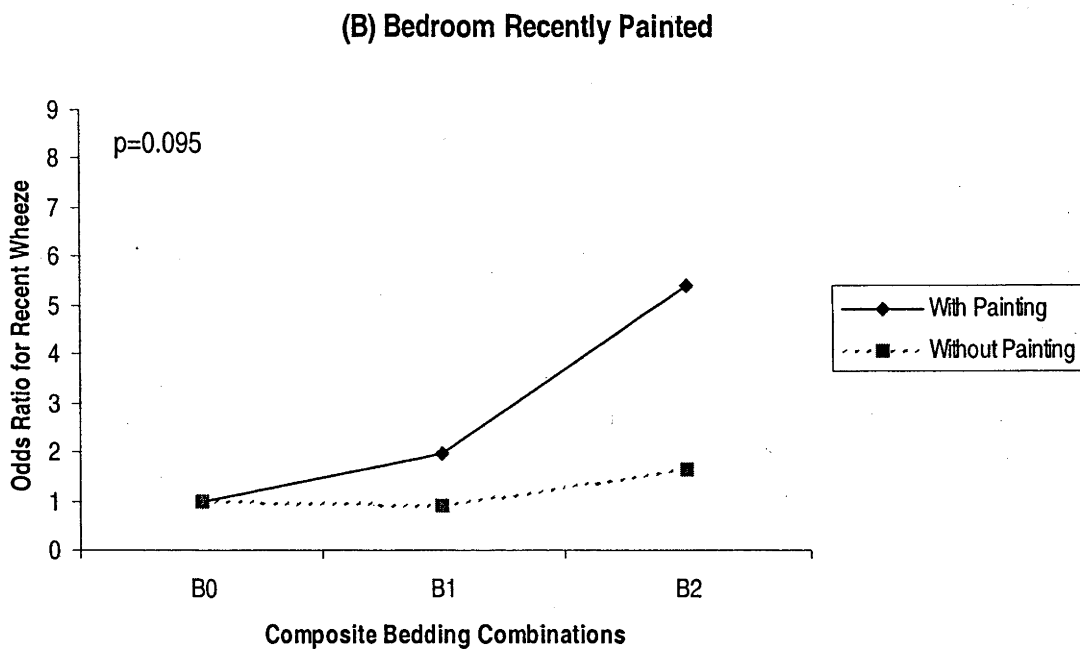
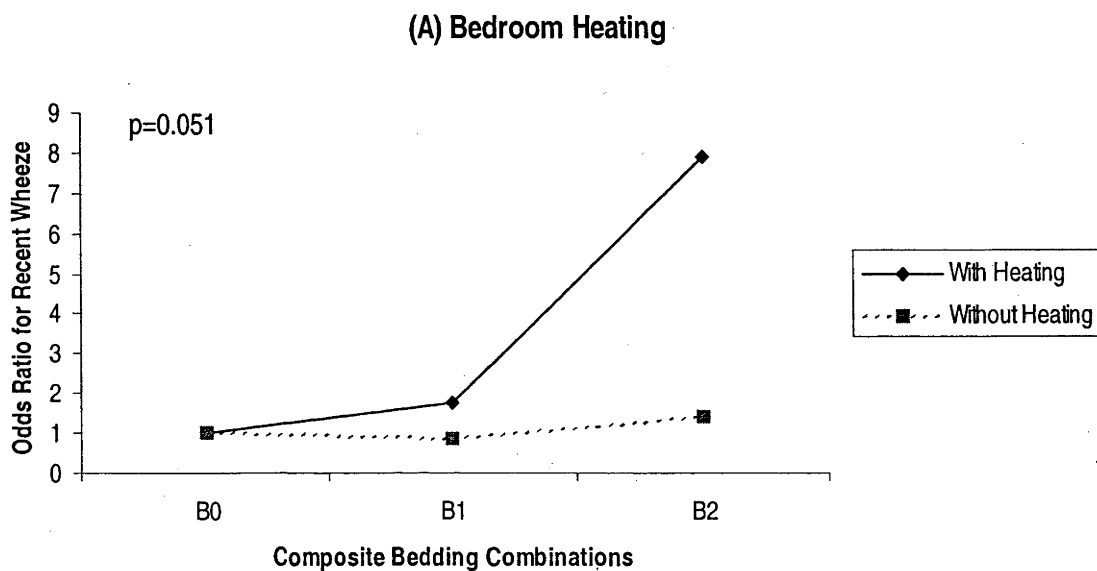
Bedding combinations by respiratory symptoms	% Children with infant bedding combination with wheeze		Unadjusted odds ratio			Adjusted odds ratio*		
	%	n/ total N	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
<b>Recent wheeze</b>								
Combination 0	23.8	49/206	1.00 (reference)			1.00 (reference)		
Combination 1	25.7	126/490	1.11	0.76, 1.62	0.593	1.07	0.72, 1.57	0.744
Combination 2	43.3	29/67	2.45	1.37, 4.37	0.003	2.10	1.15, 3.82	0.015
<i>Linear Trend</i>					<i>p = 0.014</i>			<i>p = 0.053</i>
<b>Night wheeze</b>								
Combination 0	16.9	35/207	1.00 (reference)			1.00 (reference)		
Combination 1	17.6	88/499	1.05	0.68, 1.62	0.817	1.02	0.66, 1.57	0.940
Combination 2	21.6	24/66	2.81	1.51, 5.22	0.001	2.43	1.29, 4.59	0.006
<i>Linear Trend</i>					<i>p = 0.011</i>			<i>p = 0.034</i>
<b>Asthma ever</b>								
Combination 0	29.6	64/216	1.00 (reference)			1.00 (reference)		
Combination 1	32.6	167/513	1.15	0.81, 1.62	0.439	1.15	0.81, 1.64	0.437
Combination 2	45.1	32/71	1.95	1.12, 3.38	0.018	1.80	1.01, 3.18	0.045
<i>Linear Trend</i>					<i>p = 0.039</i>			<i>p = 0.072</i>

\*Adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.

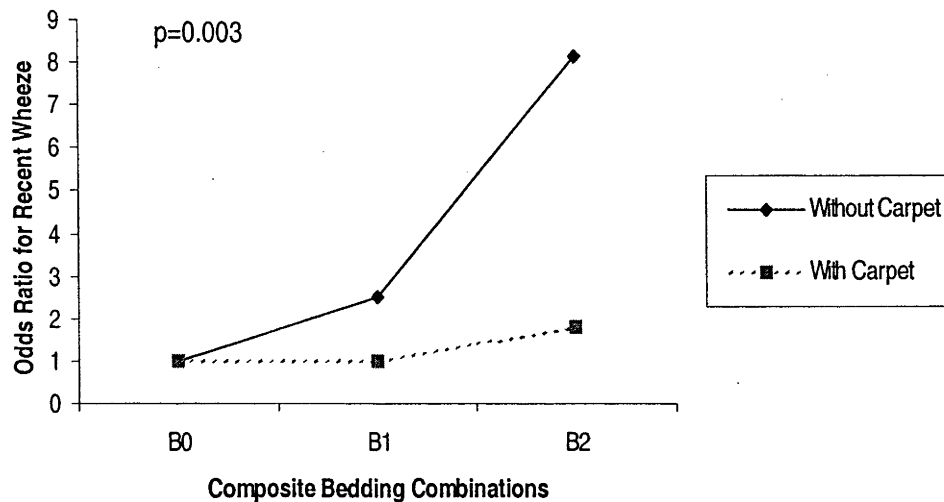
### 7.4.3 Bedding and home environmental factors

No associations were found between the composite bedding classifications, B<sub>1</sub> versus B<sub>0</sub> or B<sub>2</sub> versus B<sub>0</sub>, and any of the three home environmental factors. There was no relationship between bedroom heating and bedroom carpet (*Spearman*  $r = 0.052$ ); bedroom heating and recent painting (*Spearman*  $r = 0.078$ ); bedroom carpet and recent painting (*Spearman*  $r = -0.029$ ). Nor were these factors associated with the composite bedding combinations (*Spearman*  $r = -0.015$ ;  $-0.002$  and  $-0.083$  for bedroom heating, recent bedroom painting or bedroom carpet respectively). Bedroom heating, recent bedroom painting and the absence of bedroom carpet did not significantly predict wheeze with: OR 1.08 (95% CI 0.85, 1.37); OR 0.82 (95% CI 0.63, 1.05); and OR 1.12 (95% CI 0.78, 1.61) respectively. However, Figure 7.2 shows that each of these three environmental factors did potentiate the composite bedding effect on wheeze.

Figure 7.2 Difference of potentiation of composite bedding effects on recent wheeze by environmental factors in the Infant cohort study with 1995 follow-up.



(C) Bedroom Carpet



In (A) the p value is for the difference in the potentiation of the composite bedding effect on recent wheeze by room heating; (B) the p value is for the difference in the potentiation of the composite bedding effect on recent wheeze by recent bedroom painting; and, (C) the p value is for the difference in the potentiation of the composite bedding effect on recent wheeze by absence of carpet. The analysis was adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.

### **7.4.3.1 Risk potentiation of composite bedding effect by room heating**

The dose-response relationship of composite infant bedding on the risk of subsequent wheeze was particularly evident when the infant slept in a heated room (Test for trend,  $p=0.004$ ) than in a non-heated room (Test for trend,  $p=0.653$ ). These results are shown in Table 7.5. In particular, a high number of HDM allergen-rich bedding items in infancy ( $B_2$ ) was strongly associated with recent wheeze in childhood (aOR 7.87; 95% CI 2.17, 28.51) when the infant's bedroom had been heated; but, this association was not found in a non-heated room. The difference in the potentiation of the composite bedding effect by room heating was significant (Likelihood ratio test,  $p=0.051$ ) (see Figure 7.2(A)). This potentiation of the composite bedding effect by room heating was also evident for asthma ever or night wheeze (see Table 7.5).

**Table 7.5 Potentiation of composite bedding effects on wheeze by infant bedroom heating in the Infant cohort study with 1995 follow-up**

Bedding combinations by environmental factors	Recent wheeze			Night Wheeze			Asthma ever					
	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value
<b>Without room heating</b>												
Combination 0	27.0	37/137	1.00 (reference)		19.9	27/136	1.00 (reference)		33.8	49/145	1.00 (reference)	
Combination 1	24.2	74/306	0.84 (0.2, 1.34)	0.454	17.1	53/310	0.81 (0.48, 1.36)	0.420	32.6	105/322	0.91 (0.59, 1.40)	0.673
Combination 2	38.5	20/52	1.39 (0.69, 2.79)	0.354	33.3	17/51	1.68 (0.81, 3.52)	0.166	41.8	23/55	1.14 (0.59, 2.21)	0.703
<i>Linear Trend</i>				<i>p=0.653</i>				<i>p=0.405</i>				<i>p=0.898</i>
<b>With room heating</b>												
Combination 0	17.4	12/69	1.00 (reference)		11.3	8/71	1.00 (reference)		21.1	15/71	1.00 (reference)	
Combination 1	28.0	51/182	1.77 (0.86, 3.65)	0.120	18.2	34/187	1.68 (0.73, 3.89)	0.226	32.3	61/189	1.90 (0.97, 3.73)	0.063
Combination 2	60.0	9/15	7.87 (2.17, 28.51)	0.002	46.7	7/15	8.32 (2.18, 31.67)	0.002	56.3	9/16	7.07 (2.09, 23.85)	0.002
<i>Linear Trend</i>				<i>p=0.004</i>				<i>p=0.008</i>				<i>p=0.003</i>
<b>Difference in bedding effect by room heating</b>												
				<i>p = 0.051</i>								<i>p = 0.181</i>
				<i>Likelihood ratio test</i>								<i>Likelihood ratio test</i>

\*Adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.



### **7.4.3.2 Risk potentiation of composite bedding by bedroom painting**

The greater increase on risk of subsequent wheeze by composite bedding for infants sleeping in a recently painted bedroom (Test for trend,  $p=0.013$ ) was not shown in children who as infants slept in a bedroom that had not been recently painted (Test for trend,  $p=0.383$ ). These results are shown in Table 7.6. Among infants in recently painted rooms, those infants exposed to a composite bedding arrangement of two or more high HDM allergen-rich items ( $B_2$ ), had a more than five-fold increase in risk of recent wheeze by age 7 years (aOR 5.39; 95% CI 1.44, 20.25) than those infants not exposed to this bedding combination (see Table 7.6). There was a greater adverse effect for bedding in a room recently painted than in a non-painted room (Likelihood ratio test,  $p=0.095$ ) (see Figure 7.2(B)). Thus, recent bedroom painting appears to potentiate the adverse effect of bedding. This potentiation of the composite bedding effect by recent bedroom painting was also evident for asthma ever or night wheeze (see Table 7.6).

### **7.4.3.3 Risk potentiation of composite bedding in the absence of bedroom carpet**

The effect of infant HDM-rich composite bedding on wheeze was particularly evident when there was no floor carpet in the infant's bedroom (Test for linear trend,  $p=0.032$ ) rather than when the bedroom was carpeted (Test for linear trend,  $p=0.200$ ). These results are shown in Table 7.7. The potentiation of composite bedding effect on subsequent wheeze was significant when bedroom carpet was absent in an infant's bedroom compared with the presence of carpet (Likelihood ratio test,  $p=0.003$ ) (see Figure 7.2 (C)). This potentiation of the composite bedding effect by the absence of bedroom carpet was also evident for asthma ever or night wheeze (see Table 7.7).

**Table 7.6 Potentiation of composite bedding effects on wheeze by recent infant bedroom painting in the Infant cohort study with 1995 follow-up**

Bedding combinations by environmental factors	Recent wheeze			Night Wheeze			Asthma ever					
	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value
<b>Without painting</b>												
Combination 0	27.2	39/141	1.00 (reference)		18.6	25/140	1.00 (reference)		32.4	48/148		
Combination 1	26.5	82/310	0.89 (0.57, 1.41)	0.633	18.7	59/315	0.98 (0.58, 1.64)	0.927	31.5	103/327	0.98 (0.64, 1.51)	0.944
Combination 2	43.1	22/51	1.65 (0.82, 3.31)	0.162	34.0	17/50	1.87 (0.88, 3.99)	0.104	37.7	20/53	1.20 (0.60, 2.40)	0.606
<i>Linear Trend</i>				<i>p=0.383</i>				<i>p=0.220</i>				<i>p=0.730</i>
<b>With Painting</b>												
Combination 0	15.4	10/65	1.00 (reference)		13.4	9/67	1.00 (reference)		23.5	16/68	1.00 (reference)	
Combination 1	24.6	44/179	1.97 (0.89, 4.36)	0.094	15.9	29/183	1.24 (0.54, 2.83)	0.614	34.6	64/185	1.81 (0.94, 3.49)	0.075
Combination 2	43.8	7/16	5.39 (1.44, 20.25)	0.013	43.8	7/16	5.35 (1.46, 19.68)	0.012	66.7	12/18	7.22 (2.25, 23.22)	0.001
<i>Linear Trend</i>				<i>p=0.013</i>				<i>p=0.048</i>				<i>p=0.002</i>
<b>Difference in bedding effect by room painting</b>				<i>p = 0.095</i>				<i>p = 0.290</i>				<i>p = 0.039</i>
				<i>Likelihood ratio test</i>				<i>Likelihood ratio test</i>				<i>Likelihood ratio test</i>

\*Adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.

**Table 7.7 Potentiation of composite bedding effects on wheeze by absence of bedroom carpet in the Infant cohort study with 1995 follow-up**

Bedding combinations by environmental factors	Recent wheeze			Night Wheeze			Asthma ever					
	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value
<b>Without Carpet</b>												
Combination 0	13.3	2/15	1.00 (reference)		14.3	2/14	1.00 (reference)		33.3	5/15	1.00 (reference)	
Combination 1	30.4	14/46	2.51 (0.47, 13.55)	0.284	21.7	10/46	1.50 (0.30, 8.33)	0.645	41.7	20/48	1.61 (0.42, 6.19)	0.487
Combination 2	58.3	5/12	8.13 (1.14, 56.20)	0.037	58.3	7/12	8.53 (1.15, 59.82)	0.036	53.9	7/13	2.40 (0.46, 12.48)	0.298
Linear Trend				<i>p</i> =0.032				<i>p</i> =0.023				<i>p</i> =0.298
<b>With Carpet</b>												
Combination 0	24.7	46/186	1.00 (reference)		17.0	32/188	1.00 (reference)		29.6	58/196	1.00 (reference)	
Combination 1	25.5	112/440	1.01 (0.67, 1.51)	0.966	17.4	78/449	1.00 (0.63, 1.58)	0.984	31.7	146/461	1.10 (0.76, 1.60)	0.621
Combination 2	40.7	22/54	1.82 (0.94, 3.53)	0.075	32.1	17/53	2.00 (0.98, 4.05)	0.058	43.9	25/57	1.72 (0.92, 3.23)	0.090
Linear Trend				<i>p</i> =0.200				<i>p</i> =0.176				<i>p</i> =0.157
<b>Difference in bedding effect by room carpet</b>				<i>p</i> = 0.003				<i>p</i> = 0.002				<i>p</i> = 0.001
				Likelihood ratio test				Likelihood ratio test				Likelihood ratio test

\*Adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.

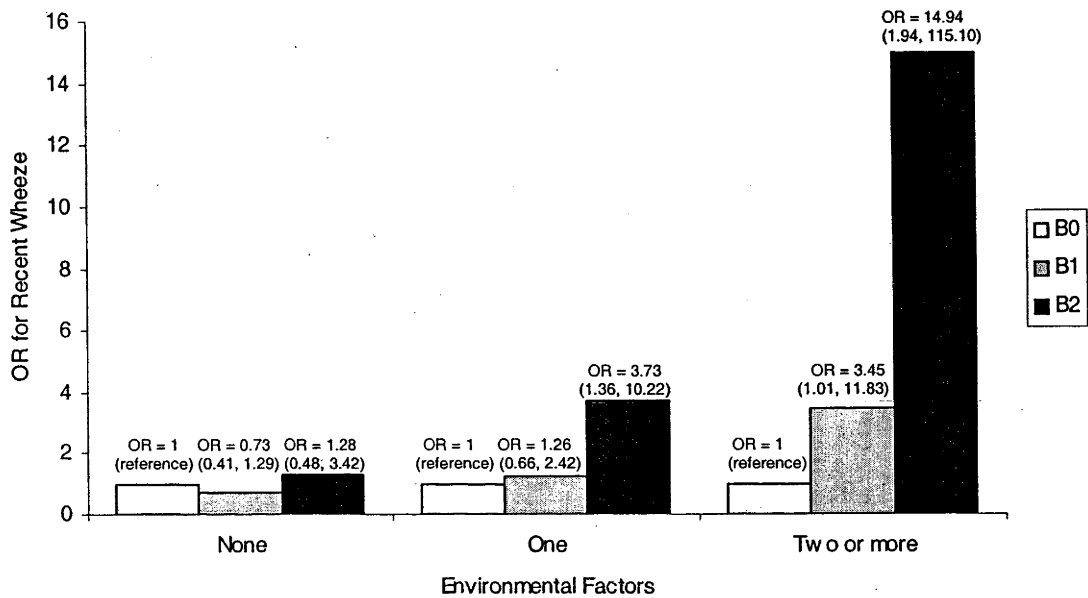
#### ***7.4.3.4 Risk potentiation of composite bedding in the presence of environmental tobacco smoke or home gas appliance use***

The use of home gas appliances was not found to potentiate the bedding effect on wheeze for either B<sub>1</sub> or B<sub>2</sub> (Likelihood ratio test,  $p=0.124$ ). Exposure to environmental tobacco smoke was also not found to potentiate the bedding effect (Likelihood ratio test,  $p=0.285$ ). As the increase in risk per bedding classification was not altered if there was either smoking or gas appliance use in the home environment, both these exposure variables were then considered as potential confounders in the process of determining the final models.

#### ***7.4.3.5 Risk potentiation of composite bedding in the presence of one or more environmental factors***

The effect modification patterns reported above for bedroom heating, recent bedroom painting and the absence of carpet, each remained following further adjustment for the other two environmental factors, either individually or together, plus the confounders listed at the bottom of Table 7.4. Thus, bedroom heating, recent bedroom painting and the absence of carpet appeared to potentiate the risk of the composite bedding classification on wheeze independently of these confounders and each other. Next, I considered concomitant infant exposure to one or more of these environmental factors. Figure 7.3 shows when any two or more of these environmental bedding-wheeze enhancers were present the B<sub>1</sub>-wheeze association was increased (OR 3.45; 95% CI 1.01, 11.83). The B<sub>2</sub>-wheeze association was even stronger (OR 14.94; 95% CI 1.94, 115.1). The difference for potentiation of the bedding classification B<sub>2</sub>-wheeze effect by environmental factor number was significant ( $p=0.012$ ) (see Figure 7.3).

Figure 7.3 Relationship between the number of environmental factors (bedroom heating, recent bedroom painting, absence of bedroom carpet) and potentiation of composite bedding- wheeze effect by bedding combination\* B<sub>0</sub>, B<sub>1</sub> and B<sub>2</sub> in the Infant cohorts with 1995 follow-up

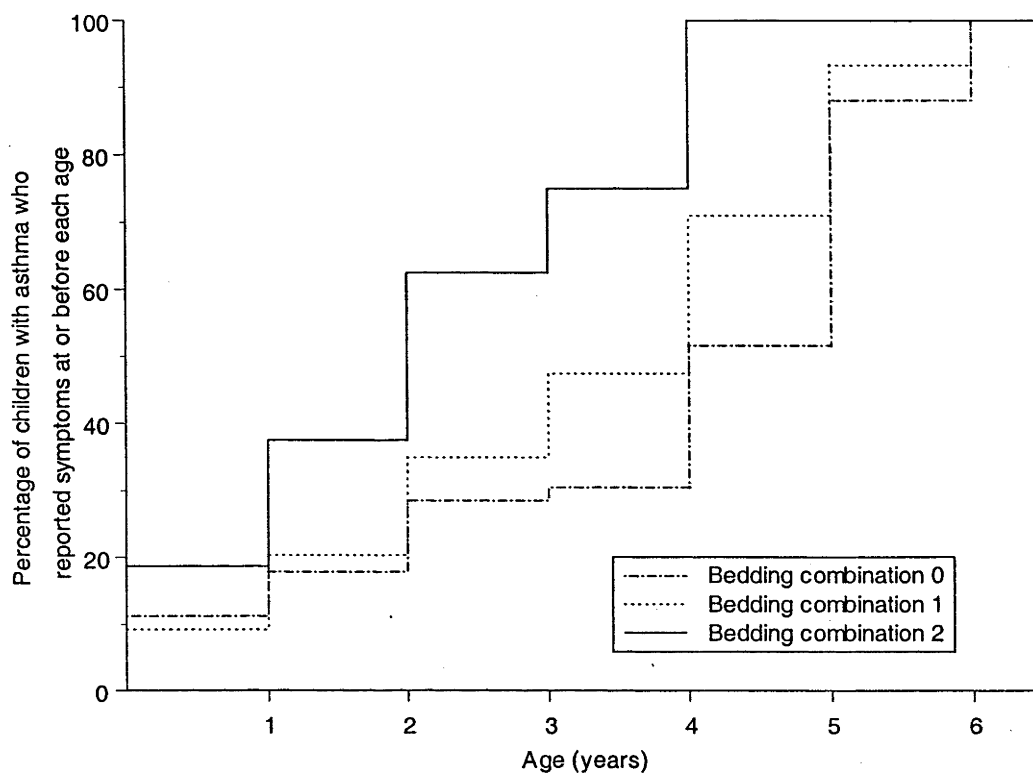


\*The reference group is B<sub>0</sub>. The difference in effect for potentiation of the bedding combination B<sub>1</sub>-wheeze effect, from none to two or more of the environmental factors is p=0.017. The difference in effect for potentiation of the bedding combination B<sub>2</sub>-wheeze effect, from none to two or more of the environmental factors is p=0.012.

#### **7.4.4 Composite bedding and age of onset of asthma**

Overall, there was a shift to earlier onset of asthma symptoms with an increase in the amount of infant composite bedding items (Log-rank test,  $p=0.002$ ) (see Figure 7.4). Among infants with childhood asthma, increasing the number of high HDM allergen-rich bedding items was associated with an increased risk of subsequent earlier onset of asthma symptoms by age 7 years compared with infants without these bedding items (see Table 7.8). Infants with bedding combinations 0, 1 and 2 had a mean age of onset of 3.7, 3.2 and 2.1 years respectively. The adjusted Hazard Ratio for bedding combinations 0, 1 and 2 were 1.00 (reference); 1.20; (95% CI 0.89, 1.61); and, 1.73 (95% CI 1.10, 2.73) respectively. Thus, an earlier onset of asthma symptoms was associated with children who as infants had the highest HDM allergen-rich composite bedding, after adjustment for at-birth family history of asthma, male sex, mother smoking during infancy, and foam mattress use in infancy.

Figure 7.4 Age of onset of wheezy breathing\* by composite bedding use at 1 month of age in the Infant cohort study with 1995 follow-up



\*Log-rank test for equality of survivor functions,  $p = 0.002$ .

**Table 7.8 Age of onset of reported symptoms for children with asthma in the Infant cohort study with 1995 follow-up**

	Age on or before children with asthma report symptoms							Total no. of children with asthma at age 7 years
	0 year	1 year	2 years	3 years	4 years	5 years	6 years	
<b>Bedding Combination 0</b>								
No. children with symptoms	17	10	16	3	32	55	18	151
Percent (%)	11.3	6.6	10.6	2.0	21.2	36.4	11.9	
<b>Bedding Combination 1</b>								
No. children with symptoms	33	40	52	45	84	80	24	358
Percent (%)	9.2	11.2	14.5	12.6	23.5	22.4	6.7	
<b>Bedding Combination 2</b>								
No. children with symptoms	9	9	12	6	12	0	0	48
Percent (%)	18.8	18.8	25.0	12.5	25.0	0	0	



#### **7.4.5 Role of home environmental factors on composite bedding and age of onset of asthma**

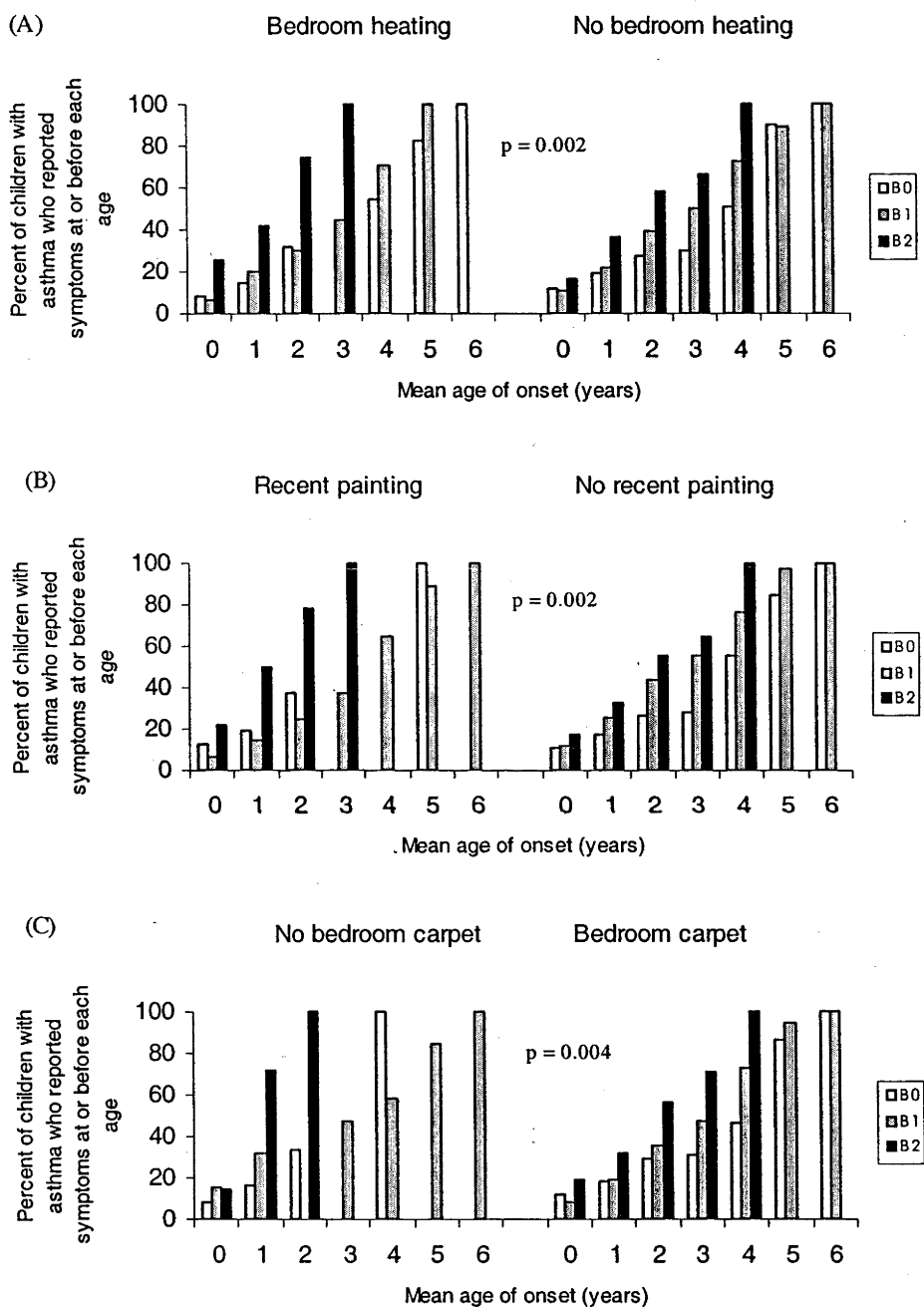
Figure 7.5 shows that the presence of environmental factors identified as bedding-wheeze enhancers in infancy (bedroom heating, recent bedroom painting, and absence of bedroom carpet), also potentiated the shift by the bedding combinations to an earlier age of onset of asthma. Infants sleeping in a heated bedroom had an earlier onset of asthma than infants with bedrooms not heated (Stratified logrank test,  $p=0.002$ ). With heated bedroom, infants with bedding combinations 0, 1 and 2 had a mean age of onset for asthma of 3.8, 3.3 and 1.6 years respectively, and 3.7, 3.2 and 2.2 years respectively for infants with no bedroom heating.

This potentiation of shift to earlier age of onset of asthma by bedding combinations was also found for infants sleeping in a recently painted bedroom compared with infants in a non-painted room (Stratified logrank test,  $p=0.002$ ). For infants in a recently painted bedroom, with bedding combinations 0, 1 and 2 the mean age of onset for asthma was 3.6, 3.6 and 1.5 years respectively, compared with 3.8, 2.9 and 2.3 years respectively for infants sleeping in a bedroom that had not been recently painted.

The absence of carpet in an infant's bedroom was associated with an earlier onset of wheeze for the bedding combinations than if the infant's bedroom was carpeted (Stratified logrank test,  $p=0.004$ ). If the infant's bedroom was un-carpeted, the mean age for asthma onset for bedding combinations 0, 1 and 2 was 3.1, 3.3 and 1.1 years respectively, whereas for infants with a carpeted bedroom it was 3.8, 3.2 and 2.2 years respectively.

The environmental factors, bedroom heating, recent bedroom painting or absence of bedroom carpet, as individual factors did not influence the age of onset of asthma.

Figure 7.5 Mean age of onset of asthma or wheezy breathing by bedding combinations and environmental factors in the Infant cohort study with 1995 follow-up



(A) The p value is for the difference between mean age of onset of asthma when infants' bedroom heated versus non-heated bedroom; (B) The p value is for the difference between mean age of onset of asthma when infants' bedroom recently painted versus non-painted bedroom; and, (C) The p value is for the difference between mean age of onset of asthma when infants' bedroom not carpeted versus infants' bedroom carpeted.

#### **7.4.6 Summary of findings from the Infant cohort study with 1995 follow-up**

Composite infant bedding was associated with subsequent recent wheeze. This composite bedding effect was further enhanced by the home environmental factors of bedroom heating, recent bedroom painting and the absence of bedroom carpet. When two or more of these home environmental bedding-wheeze enhancers were present, a dose-response was evident. Among infants with childhood asthma, composite bedding was associated with subsequent earlier onset of asthma, an effect which was again potentiated by indoor environmental factors.

### **7.5 RESULTS: THE 1997 CARHS**

#### **7.5.1. Characteristics of the study population**

The characteristics of the study population are shown in Table 7.9. Infant bedding data for all bedding combinations was available on 408 children. The percentage of infants exposed to each composite bedding classification was 32.8%, 62.3% and 4.9% for B<sub>0</sub>, B<sub>1</sub> and B<sub>2</sub> respectively. The majority of infant's bedrooms were carpeted (89.9%) and had also been recently painted within the previous 12 months (67.9%) whereas less infants were exposed to bedroom heating (30.5%).

**Table 7.9 Characteristics of the study population in the 1997 CARHS**

	%	n/total N*
Mean age (years)	8.7 (standard deviation=0.6)	
<b>Respiratory symptoms</b>		
Recent wheeze over past year	30.8	153/497
Night wheeze over past year	20.7	101/487
Asthma ever	37.8	188/497
HDM sensitization*	23.3	116/498
Lung function tests undertaken	99.2	495/499
<b>Infant bedding</b>		
Synthetic pillowcase use at 1 month age	8.7	40/458
Synthetic quilt use at 1 month age	51.1	210/411
Cocoon use at 1 month age	1.2	5/411
Sheepskin use at 1 month age	23.2	107/461
<i>Six-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or cocoon, or sheepskin	32.8	134/408
Combination 1: Sheepskin only	12.0	49/408
Combination 2: 1 synthetic item	39.0	159/408
Combination 3: Sheepskin and 1 synthetic item	11.3	46/408
Combination 4: 2 or more synthetic items	3.7	15/408
Combination 5: 2 synthetic items and sheepskin	1.2	5/408
<i>Three-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or cocoon, or sheepskin	32.8	134/408
Combination 1: 1 Synthetic and/or 1 sheepskin item	62.3	254/408
Combination 2: 2 or more synthetic items	4.9	20/408
<b>Environment</b>		
Heating in infant's bedroom	30.5	140/459
Carpet in infant's bedroom	89.9	408/454
Infant's bedroom painted within previous 12 months	67.9	311/458
Any gas appliance use in infant's house	3.9	18/457
Infant exposed to tobacco smoke in house	64.7	295/456

\*Any skin prick reaction of greater than or equal to 3mm to mite allergens *D. pteronyssinus* or *D. farinae*.

## 7.5.2 Risk of HDM sensitization associated with increasing numbers of bedding items in infancy

No association was found between infants exposed to B<sub>1</sub> and B<sub>2</sub> and subsequent HDM sensitization when compared with children who had none of these bedding items in infancy (see Table 7.10). The absence of any association remained when SPT positivity was taken as equal or greater than a 2 mm HDM allergen wheal diameter.

**Table 7.10 Prospective association between infant composite bedding combinations and HDM sensitization in childhood in the 1997 CARHS**

Bedding combinations	% Children with infant bedding combination with HDM sensitization*		Unadjusted odds ratio		
	%	n/total N	Odds ratio	95% CI	p value
Combination 0	32.6	31/95	1.00 (reference)		
Combination 1	63.2	60/95	1.03	0.63, 1.69	0.898
Combination 2	4.2	4/95	0.83	0.26, 2.67	0.755
<i>Linear Trend</i>					<i>p=0.933</i>

\*Any skin prick reaction of greater than or equal to 3mm to mite allergens *D. pteronyssinus* or *D. farinae*.

## 7.5.3 Risk of childhood wheeze associated with increasing numbers of bedding items in infancy

Infants exposed to B<sub>2</sub> showed a non-significant increase in risk of asthma ever at age 9 years when compared with children who had none of these bedding items in infancy (Test for linear trend,  $p=0.072$ ). This trend was less evident for recent wheeze and night wheeze (see Table 7.11).

**Table 7.11 Prospective association between Infant composite bedding combinations and childhood wheeze in the 1997 CARHS**

	% Children with infant bedding combination with wheeze		Unadjusted odds ratio		Adjusted odds ratio*	
	%	n/total N	Odds Ratio	95% CI	Odds Ratio	95% CI
<b>Recent wheeze</b>						
Combination 0	26.9	36/134	1.00 (reference)		1.00 (reference)	
Combination 1	29.3	74/253	1.13	0.70, 1.80	1.22	0.76, 1.97
Combination 2	30.0	6/20	1.17	0.42, 3.27	1.07	0.37, 3.05
<i>Linear Trend</i>						<i>p = 0.528</i>
<b>Night wheeze</b>						
Combination 0	17.1	22/129	1.00 (reference)		1.00 (reference)	
Combination 1	18.4	46/250	1.10	0.63, 1.92	1.24	0.70, 2.19
Combination 2	25.0	5/20	1.62	0.53, 4.93	1.67	0.53, 5.29
<i>Linear Trend</i>						<i>p = 0.328</i>
<b>Asthma ever</b>						
Combination 0	31.8	42/132	1.00 (reference)		1.00 (reference)	
Combination 1	37.8	96/254	1.30	0.83, 2.03	1.45	0.92, 2.29
Combination 2	50.0	10/20	2.14	0.83, 5.54	1.91	0.72, 5.07
<i>Linear Trend</i>						<i>p = 0.072</i>

\*Adjusted for male sex, at-birth family history of asthma, foam mattress use in infancy, exposure as infant to maternal cigarette smoking. Further adjustment for cohort entry criteria did not alter the results.

#### **7.5.4 The effect of composite bedding classification in infancy and changes in lung function**

Composite bedding was not associated with FEV<sub>1</sub> or FVC measures in childhood. The mean difference in the FEV<sub>1</sub>/FVC ratio among children exposed to B<sub>1</sub> or B<sub>2</sub> in infancy was not significantly different from children who had not been exposed to these bedding items in infancy after adjustment for other determinants of lung function as shown in Table 7.12 and Table 7.13. The adjusted mean difference in the FEV<sub>1</sub>/FVC ratio among children exposed to composite bedding category B<sub>2</sub> in infancy was reduced -1.8% (95% CI -5.0, 1.4). As a measure of airways obstruction (196, 504), this reduction for children exposed to B<sub>2</sub> in infancy was slightly greater than the reduction of the FEV<sub>1</sub>/FVC ratio for children with recent wheeze, (-1.8% vs -1.1 % respectively). The adjusted difference in mean FEV<sub>1</sub>/FVC ratio for children with frequent wheeze (>12 episodes) was more substantial, that is, -3.8 % (95% CI -7.1, -0.57). Even though small, this margin of difference may be important as a measure of airways obstruction (196, 504) in those children exposed to B<sub>2</sub>. However, the sub-set, limited by those children with the three bedding categories, has small numbers across the strata, making it difficult to examine fully and possibly reducing the relative importance of these findings.

#### **7.5.5 Bedding and home environmental factors**

The very small numbers in some of the strata of each composite bedding classification and individual environmental factors did not allow investigation of any possible associations between these variables in the 1997 CARHS.

**Table 7.12 Unadjusted differences in mean spirometric values between children with different composite bedding classification in infancy, recent wheeze, frequent wheeze and night wheeze in the 1997 CARHS**

	Unadjusted difference in mean FEV <sub>1</sub> (mL) with 95% CI between children with and without the bedding combinations	p value	Unadjusted difference in mean FVC (mL) with 95% CI between children with and without the bedding combinations	p value	Unadjusted difference in mean FEV <sub>1</sub> /FVC (%) with 95% CI between children with and without the bedding combinations	p value
B <sub>0</sub>	1 (reference)		1 (reference)		1 (reference)	
B <sub>1</sub>	-2.3 (-8.3, 3.7)	0.449	-2.0 (-9.2, 5.3)	0.590	0.41 (-1.8, 1.0)	0.576
B <sub>2</sub>	8.8 (-4.6, 22.2)	0.199	12.7 (-3.5, 29.0)	0.123	-1.5 (-4.7, 1.7)	0.347

\*All estimates adjusted for child height (cm), child age (years), child sex, season of lung function (3-month periods) and technician.

**Table 7.13 Adjusted differences in mean spirometric values between children with different composite bedding classification in infancy, recent wheeze, frequent wheeze and night wheeze in the 1997 CARHS**

	Adjusted* difference in mean FEV <sub>1</sub> (mL) with 95% CI between children with and without the bedding combinations	p value	Adjusted* difference in mean FVC (mL) with 95% CI between children with and without the bedding combinations	p value	Adjusted* difference in mean FEV <sub>1</sub> /FVC (%) with 95% CI between children with and without the bedding combinations	p-value
B <sub>0</sub>	1 (reference)		1 (reference)		1 (reference)	
B <sub>1</sub>	-3.0 (-7.1, 1.2)	0.161	-2.7 (-7.9, 2.5)	0.309	-0.4 (-1.8, 1.0)	0.583
B <sub>2</sub>	4.5 (-4.8, 13.9)	0.344	8.3 (-3.3, 19.9)	0.161	-1.8 (-5.0, 1.4)	0.269

\*All estimates adjusted for child height (cm), child age (years), child sex, season of lung function (3-month periods) and technician.



## **7.6 RESULTS: THE 1995 CHILDHOOD ASTHMA SURVEY**

### **7.6.1. Characteristics of the study population**

The characteristics of the study population are shown in Table 7.14. Data for all bedding combinations was available on 6,265 children. The percentage of children exposed to each composite bedding classification was: B<sub>0</sub> 5.6%; B<sub>1</sub> 55.3%; and B<sub>2</sub> 39.1%. The majority of children's bedrooms were carpeted (93.4%).

### **7.6.2 Risk of childhood wheeze associated with increasing numbers of bedding items in childhood**

Children currently exposed to B<sub>2</sub> versus B<sub>0</sub> had an increased likelihood of wheeze (aOR 1.44; 95% CI 1.07, 1.92). There was a dose-response relationship between the current exposure to increasing number of bedding items and the risk of recent wheeze (Test for linear trend,  $p < 0.001$ ) This trend for a higher number of bedding items and increasing risk of recent wheeze was also found for asthma ever (Test for linear trend,  $p < 0.001$ ) and night wheeze (Test for linear trend,  $p = 0.001$ ). These results are shown in Table 7.15.

### **7.6.3 Bedding and home environmental factors**

Children who currently slept with bedding combination B<sub>2</sub> had a more than 3-fold risk of recent wheeze if their bedroom floor was un-carpeted (aOR 3.87; 95% CI 1.26, 11.87) when compared to children with B<sub>0</sub> who were also sleeping in un-carpeted bedrooms. The potentiation of composite bedding effect on recent wheeze was significant when bedroom carpet was absent in a child's bedroom compared with the presence of carpet (Likelihood ratio test,  $p = 0.001$ ). However, the slightly stronger composite bedding effects for both asthma ever and night wheeze found in uncarpeted compared to carpeted rooms were not statistically significant. For children with the same bedding combination B<sub>2</sub>, the presence of bedroom carpet did not significantly increase their risk of recent wheeze. These results are shown in Table 7.16. As the increase in risk per bedding category was not modified by either smoking or gas appliance use in the home

environment, both these exposure variables were considered as potential confounders in the final models.

**Table 7.14 Characteristics of the study population in the 1995 Childhood Asthma Survey**

	%	n/total N*
Mean age (years)	6.9 (standard deviation=0.3)	
Male sex	50.5	3220/6378
<b>Respiratory symptoms</b>		
Recent wheeze over past year	22.9	1400/6107
Night wheeze over past year	14.4	889/6172
Asthma ever	27.1	1710/6307
<b>Child bedding</b>		
Synthetic pillowcase use at age 7 years	90.1	5709/6340
Synthetic quilt use at age 7 years	41.6	2649/6364
Sheepskin use at age 7 years	21.1	1331/6307
<i>Six-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or sheepskin	5.6	350/6265
Combination 1: Sheepskin only	1.9	119/6265
Combination 2: 1 synthetic item	41.2	2582/6265
Combination 3: Sheepskin and 1 synthetic item	12.2	766/6265
Combination 4: 2 or more synthetic items	32.0	2007/6265
Combination 5: 2 synthetic items and sheepskin	7.0	441/6265
<i>Three-level composite bedding classification</i>		
Combination 0: No synthetic quilt, pillow or sheepskin	5.6	350/6265
Combination 1: 1 synthetic and/or 1 sheepskin item	55.3	3467/6265
Combination 2: 2 or more synthetic items	39.1	2448/6265
<b>Environment</b>		
Carpet in child's bedroom	93.4	5952/6370
Home gas appliance use during childhood	9.1	581/6361
Child exposed to indoor tobacco smoke	41.7	2632/6320

**Table 7.15 Association between Child Composite Bedding Classification and Childhood Wheeze in the 1995 Childhood Asthma Survey**

Bedding combinations by respiratory symptoms	% Children with child bedding combination with wheeze		Unadjusted odds ratio			Adjusted odds ratio*		
	n/ total N		Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
<b>Recent wheeze</b>								
Combination 0	67/332	20.2	1.00 (reference)			1.00 (reference)		
Combination 1	679/3324	20.4	1.02	0.77, 1.34	0.915	1.02	0.76, 1.36	0.903
Combination 2	627/2344	26.6	1.44	1.09, 1.92	0.011	1.44	1.07, 1.92	0.015
<i>Linear Trend</i>					<i>p = 0.000</i>			<i>p &lt; 0.001</i>
<b>Night wheeze</b>								
Combination 0	41/334	12.3	1.00 (reference)			1.00 (reference)		
Combination 1	437/2927	14.9	1.07	0.76, 1.50	0.710	1.08	0.76, 1.53	0.6760
Combination 2	394/2371	16.6	1.42	1.01, 2.01	0.044	1.41	0.99, 2.01	0.056
<i>Linear Trend</i>					<i>p = 0.000</i>			<i>p &lt; 0.001</i>
<b>Asthma ever</b>								
Combination 0	72/342	21.1	1.00 (reference)			1.00 (reference)		
Combination 1	836/3431	24.4	1.21	0.92, 1.58	0.172	1.19	0.90, 1.57	0.223
Combination 2	756/2423	31.2	1.70	1.29, 2.24	0.000	1.64	1.24, 2.17	0.000
<i>Linear Trend</i>					<i>p = 0.000</i>			<i>p &lt; 0.001</i>

\*Adjusted for male sex, child exposure to active smoking and household resident number at 7 years of age.

Table 7.16 Potentiation of composite bedding effects on wheeze by home environmental factors in the 1995 Childhood Asthma Survey

Bedding combinations by environmental factors	Recent wheeze			Night Wheeze			Asthma ever					
	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value	%	n/total N	Adjusted Odds ratio* (95% CI)	p value
<b>Without Carpet</b>												
Combination 0	13.8	4/29	1.00 (reference)		16.1	5/31	1.00 (reference)		27.6	8/29	1.00 (reference)	
Combination 1	25.4	53/209	2.12 (0.70, 6.48)	0.186	16.4	34/208	0.98 (0.34, 2.77)	0.963	32.7	69/211	1.35 (0.55, 3.28)	0.513
Combination 2	38.7	58/150	3.87 (1.26, 11.87)	0.018	24.0	37/154	1.51 (0.53, 4.28)	0.441	39.4	61/155	1.70 (0.69, 4.19)	0.246
<i>Linear Trend</i>				<i>p=0.001</i>				<i>p=0.141</i>				<i>p=0.167</i>
<b>With carpet</b>												
Combination 0	20.9	63/302	1.00 (reference)		11.9	36/302	1.00 (reference)		20.5	64/312	1.00 (reference)	
Combination 1	20.1	624/3110	0.96 (0.71, 1.29)	0.789	12.7	401/3151	1.11 (0.76, 1.61)	0.598	23.8	766/3215	1.20 (0.89, 1.60)	0.227
Combination 2	25.9	569/2194	1.33 (0.98, 1.79)	0.067	16.1	357/2217	1.43 (0.98, 2.08)	0.064	30.6	695/2268	1.66 (1.24, 2.23)	0.001
<i>Linear Trend</i>				<i>p=0&lt;001</i>				<i>p=0.001</i>				<i>p=0.000</i>
<b>Difference in bedding effect by room carpet</b>												
				<i>Likelihood ratio test</i>				<i>Likelihood ratio test</i>				<i>Likelihood ratio test</i>
				<i>p=0.001</i>				<i>p=0.016</i>				<i>p=0.001</i>

\*Adjusted for male sex, child exposure to active smoking and household resident number.

## 7.7 DISCUSSION

### 7.7.1 Overview of results

#### ***7.7.1.1 The Infant cohort study with 1995 follow-up and the 1997 CARHS***

This is the first report to investigate composite infant bedding and subsequent wheeze taking into consideration modification by the home environment. Wheeze risk in childhood at age 7 years increased linearly with increasing numbers of potentially high HDM allergen-rich bedding items at one month of age, with a two-fold overall increase between the highest compared to lowest bedding classification. This composite bedding effect was further modified by the indoor environmental factors of bedroom heating, recent bedroom painting and absence of bedroom carpet. When two or more of these environmental factors were present the bedding-wheeze effect was markedly exacerbated with increasing composite bedding in infancy (OR 14.94; 95% CI 1.94, 115.1 for B<sub>2</sub> versus B<sub>0</sub>). The findings in this study, of a dose-response for the number of synthetic items and frequent wheeze ( $p=0.004$ ), or earlier age of onset among children with asthma ( $p=0.03$ ), indicates the importance of now considering bedding items not in isolation but part of a composite bedding environment. For children aged 9 years, there was also a linear increase in wheeze risk, for asthma ever and night wheeze, with increasing number of composite bedding items, but this was not statistically significant, possibly reflecting the inadequate statistical power due to small sample size.

The strengths and potential weaknesses of these prospective studies have been discussed earlier (see Section 4.7 and Section 5.7). An additional strength of this particular study was the use of a composite bedding classification and the interaction with home environmental factors that has allowed for a more realistic assessment of the actual infant bedding environment. It is recognized, however, that bedding items may change over time, so the one measure of use in this study may not be a reliable measure regarding the long term use, for example of sheepskin over the first five years of a child's life. In addition, no data was available on the biological mechanisms underlying the findings in these studies.

### **7.7.1.2 The 1995 Childhood Asthma Survey**

The 1995 Childhood Asthma Survey cross-sectional data also showed a linear increase in the risk of recent wheeze with increasing numbers of the selected bedding items. The strengths and potential weaknesses of this cross-sectional study have been discussed in Section 6.5. Here, these results support an earlier report using the same study population where current synthetic pillow and quilt use was strongly associated with frequent wheeze (aRR 5.2; 95% CI 1.3, 20.6) (13). In addition, children with wheeze may have removed their sheepskins as an allergy-reducing measure. This would tend to work against the patterns found here, but these patterns have been found despite the preferential removal of any HDM-loaded bedding items. The composite bedding effect on recent wheeze found here was also further modified by the indoor home environmental factor of the absence of carpet in the child's bedroom.

### **7.7.2 Reported findings from the Infant cohort study with 1995 follow-up that support causality**

The issue of internal validity for the prospective study population has been discussed in detail in Chapter 5. Specifically for this Chapter, the research nurse validation of baby's bedroom heating and floor covering has minimized measurement error for these environmental factors. Any misclassification of the other dichotomous exposures, both bedding type and environmental factors, if present, would likely be non-differential and distort the results toward the null value. Also, past literature supports the proposal that the bedding items in this study are likely to reflect high HDM exposure (9, 14, 479, 535) (see Section 8.2.2.1). Again, the prospective associations have remained after adjustment for a large number of possible confounding factors. This study has demonstrated several criteria indicative of a causal relationship (330) between composite bedding and wheeze: consistency in the bedding-wheeze effect and the findings from other studies (see Section 5.1), a high strength of association with an OR greater than 14 which remained after adjusting for confounding factors, and a marked dose-response effect for wheeze (see Table 2). Furthermore, the prospective measurement of infant bedding before asthma development and the earlier shift in age of onset of asthma with the use of bedding combination B<sub>2</sub>, establishes the causal feature of temporality. In addition, the environment-enhancers not only increased the magnitude of the bedding-wheeze associations but also shifted to earlier age of asthma onset. The specificity of an association as it relates to the bedding-wheeze effect has

been discussed in Section 6.5.2. I will now discuss another criterion of causality, biological plausibility. A diagrammatic model of the possible biological mechanisms underlying the bedding-wheeze effects is presented in Figure 7.6.

### ***7.7.2.1 Possible biological mechanisms for the bedding-wheeze effects***

The three-level composite bedding classification used in this study is based on the distribution of bedding exposures to the HDM allergen-rich synthetic pillows, synthetic quilts, cocoons or sheepskin (see Section 8.2.2.2). Thus, if these findings are causal, one possible mechanism might be that the use of synthetic or sheepskin bedding items results in increased HDM allergen exposure (9, 14, 479, 535) in early childhood, increasing the risk of atopic disease by placing a higher allergen load near the infant's airway compared with either fewer or none of these items (13). These results are also consistent with past work. In this Tasmanian study sensitization to HDM is increased in children exposed to sheepskin (548) (see Chapter 4) or to synthetic bedding (as compared to those using feather bedding) in infancy (196). In addition, although carpet was associated with higher floor dust Der p1 levels than the infant's bed (2.25 versus 0.91 µg per gm), carpet was not associated with subsequent asthma (aRR 0.92; 95% CI 0.70, 1.21) (245)) in a small sub-study within the TIHS (444). As of April 2004, seven cross-sectional studies and two prospective studies have reported associations between synthetic bedding and wheeze (see Section 5.1). The results from these previous studies prompted speculation that the increase in the use of non-feather (synthetic) pillows contributed to the increasing exposure to HDMs (198), which in turn has been partly responsible for the increase in childhood wheezing (198).

With the exception of a small sub-study (444), HDM allergen levels are not available in these Tasmanian studies. However, a single allergen measure of, for example, bedroom carpet (178), which may not have consistent patterns of allergen distribution (609), would not have encompassed the bedding and home environmental determinants leading to personal allergen exposure studied here. There is great variation of Der p 1 levels between areas within a room, and no consistent pattern of distribution of mite allergen within carpeted rooms has been found (610, 611). A prospective association between infant bedroom floor HDM levels and asthma has been found in only one (170) of three studies (178, 209). Moreover, the concept of a putative role for proximity to the airways of HDM allergen-rich bedding items is further reinforced by the findings reported in Chapter 6 which show that the adverse effect of synthetic quilts on wheeze

varies by sleeping position (612). Thus, exposure models that take into account the multiple determinants of personal allergen exposure are required. The inhalational HDM allergen dose will reflect HDM allergen from multiple sources. Clearly, prospective allergen measurement of only one component of this complex system is not likely to adequately reflect the infant's inhalational HDM allergen dose over time in early life. The composite bedding model was based on HDM allergen loading, but it is also recognized that other possible biological mechanisms include the release of VOCs from synthetic materials (see Section 4.7.2) and/or the role of endotoxins in the synthetic bedding (see Section 5.7.5).

### ***7.7.2.2 Possible biological mechanisms for the bedding-wheeze effects and home environment interactions***

Induction of asthmatic symptoms are influenced by various environmental adjuvant factors (613, 614). For atopic infants, the presence of other environmental exposures, in addition to aeroallergens, has been hypothesized to be synergistic and increase the risk of asthma. A recent study reported that the animal (pet) sensitization-wheeze association in children during their first two years of life was significantly modified by exposure to an increasing number of home environmental factors, with a multiplicative interaction in the presence of three risk environmental factors (Test for trend,  $p < 0.001$ ) (615).

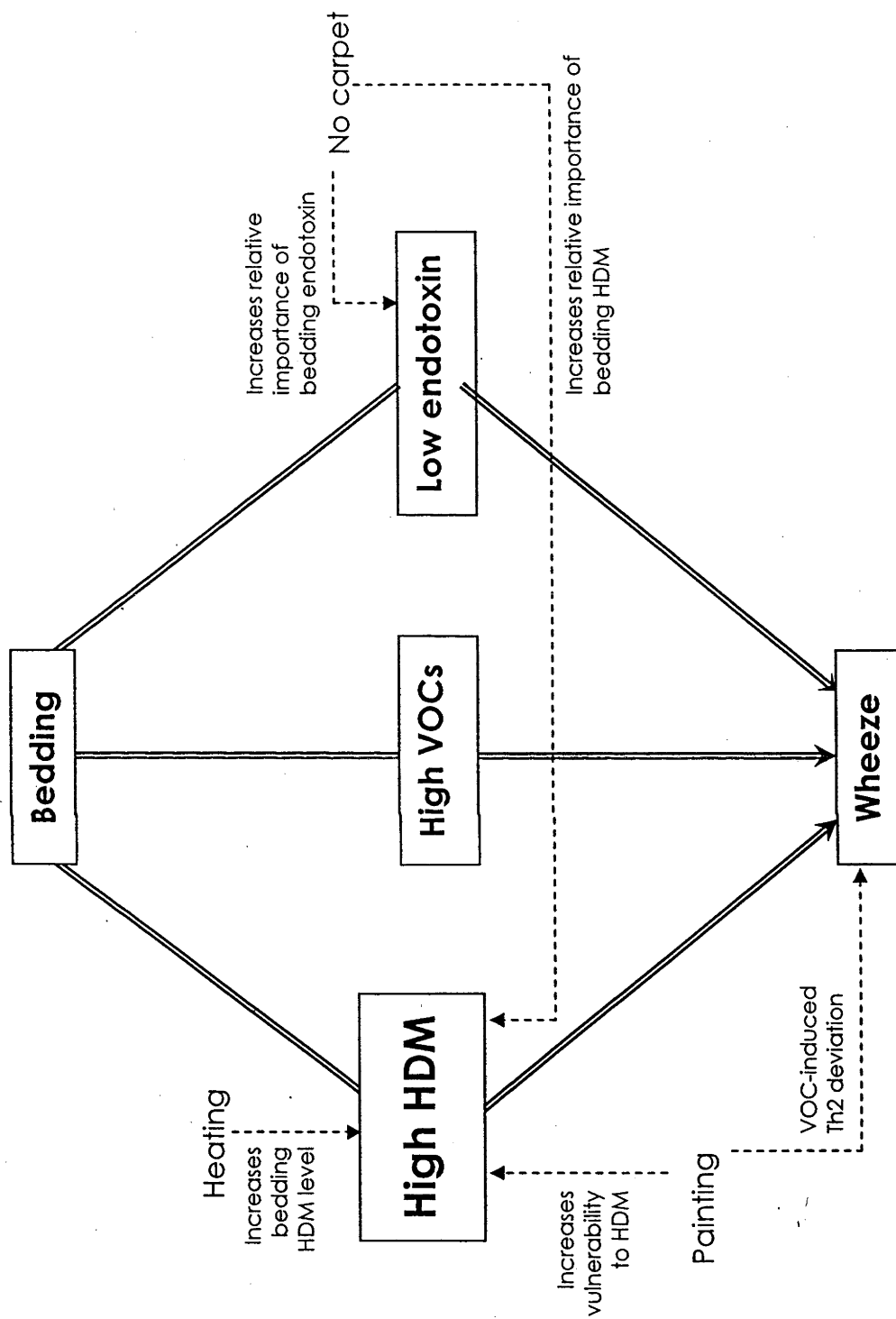
Synergy is the causal counterpart of statistical interaction (616), and, in this study I have reported that the potentiation of the composite bedding-wheeze effect is greatest in the presence of two or more of the environmental factors, bedroom heating, recent painting or absence of carpet. Possible synergistic mechanisms could include increased HDM exposure, increased allergen sensitization, increased organic compound-induced inflammation in vulnerable early life airways, or reduced exposure to endotoxin. The potentiation of the composite bedding on wheeze by room heating may be due to an enrichment of the allergen content of bedding and is consistent with previous studies that reported room heating increased HDM load in bedding (481, 582, 583). Many residential characteristics are interrelated such as temperature, age and structure of the house, central heating, type of carpets and bedding, which are, in turn, also related to other residential characteristics, potentially influencing the HDM allergen levels (579). Thus, differing room conditions may impact directly on the bedding microclimate and enhance HDM proliferation and levels. A warm, humid bedroom may not operate independently of bedding HDM allergen levels to increase asthma risk.



The potentiation of the HDM allergen-rich bedding effect on wheeze by recent painting operates possibly through a different mechanism that may influence an infant's vulnerability to HDM allergen. Pollutant-allergen interactions within the home environment may be important (617). Exposure to certain air pollutants has been shown to enhance the airway response to inhaled allergens in susceptible individuals (237) (see Section 4.7.2). Recently painted walls release VOCs (618, 619) and their presence in the infant's bedroom may enhance sensitization to HDM by airway inflammation resulting in increased permeability and enhanced allergen presentation to the immune system (492, 519), and / or by VOC-induced Th2 deviation (496). Other birth cohort studies in addition to this Tasmanian study, have also found an exposure-response relationship between recent home redecoration, including wall painting, and an increase risk of bronchial obstruction (618, 620) or asthma (621, 622).

The potentiating effect of having no carpet raises the possibility that carpet exposure in infancy is the source of a protective influence. The promoting effect of no carpet did not operate independently of composite bedding exposure. A reason for the apparent bedding-potential effect of no carpet may be that the absence of bedroom carpet as a habitat for HDM (609), has increased the relative importance of the bedding as a HDM allergen reservoir (510). One further possibility to be considered is that in infancy the bedroom carpet is a significant reservoir of endotoxin (334, 623, 624). And, endotoxin exposure at a critical time in infancy has been postulated to be protective for the development of atopic asthma (625) (see Section 2.3.6). Bedroom carpets contain significantly more endotoxin than bedding (624) and thus may be a major reservoir for infantile endotoxin exposure. In addition, measures associated with carpet cleaning such as vacuuming (626) and steam cleaning (623) may significantly increase airborne levels of carpet contaminants, and the re-use of vacuum dust collection bags, possibly because of the dispersal of dust back into the room during dust disposal, also significantly increases bedroom endotoxin levels (623). As synthetic bedding may contain less endotoxin as compared to other bedding (549), this could be counterbalanced by increased levels in the bedroom carpet.

Figure 7.6 Diagrammatic model of the possible biological mechanisms underlying the bedding-wheeze effects and home environment interactions



## 7.8 CONCLUSION

In conclusion, composite HDM allergen-rich bedding exposure as an infant at one month of age predicts subsequent childhood wheeze, particularly if exacerbating home environmental factors are present. Asthma epidemiology has been hampered by problems in exposure and disease classification and the absence of detailed bedding information in a prospective infant cohort. In this study, improvements in defining exposure by composite bedding combinations has revealed stronger associations than previously demonstrated for most home environmental factors. This study has demonstrated that the sleeping environment should not be based on a single bedding item. Composite bedding arrangements in infancy have been shown to increase the risk of subsequent wheeze. Furthermore, my results indicate that the home environment appears to modify the bedding effect on subsequent asthma development. There may be interaction of more than one environmental factor. Few studies have compared the increase in asthma prevalence over time with changes in the identified potential risk factors for asthma and atopy development (see Section 2.6). However, Butland et al., 1997 (136), reported that home environmental risk factors appeared to explain 52% of the increase in the population prevalence odds of wheeze. Bedding items, specifically the type of pillow, was one home environmental factor for which trends in exposure were conducive to an increase in prevalence. The results in this Chapter support the findings of that study where there is not just one, but various, home environmental factors impacting on the level of child asthma.

Furthermore, the inter-relation of environmental factors is important. Mhrshahi et al., 2002 (481), reported that when only the significant factors associated with HDM allergen level (such as synthetic quilts) were absent from the bed, the mean Der p 1 allergen concentration in the bed was reduced from 14.30  $\mu\text{g/g}$  to 8.55  $\mu\text{g/g}$  (95% CI 6.54,11.16). However, analysis of houses with characteristics shown in univariate and other studies to be related to lower HDM levels, had an even lower level of bed HDM allergen (Der p 1 of 3.19  $\mu\text{g/g}$  (95% CI 1.21, 8.39) (481).

Infants spend a significant proportion of their time in bed with consequent opportunity for prolonged exposure to adverse environmental influences. Bedding is a readily modifiable environmental factor but these results suggest that greater attention and further study should also be given to other environmental factors relating to the bedding environment that may potentiate any adverse bedding effect. These findings indicate that a greater public health effort to promote optimal infant sleeping environments for primary prevention of asthma is required. RCTs of infant

bedding interventions which target not only the components of, but also, the combined sleep environment to reduce childhood wheeze are now required.

## **7.9 POST-SCRIPT**

The findings here further emphasize the likely important role of the infant sleeping environment on asthma development. Chapter 8 discusses the key findings of this thesis, the relevance of these findings to current knowledge and the implications for future research.

# Key findings and implications for public health policy and future research directions

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## 8.0 INTRODUCTION

The aim of this thesis was to extend knowledge on home environmental risk factors for HDM sensitization and child asthma, focusing on infant and child bedding and the bedding environment. The key findings of this thesis emphasize the likely dominant role of the infant sleeping environment on both asthma development and the provocation of symptoms. Most importantly, Chapter 7 shows that composite bedding, not single bedding items, may more validly reflect the true bedding environment and its relationship to allergic sensitization and adverse respiratory associations. In addition, the bedding and home environment interactions were found to influence the relationships between bedding items and respiratory health.

The level of evidence provided by the results reported in this thesis for the two prospective Tasmanian studies can be considered as Type III-2 and future studies, such as RCTs, are needed to provide a higher level of evidence (627). There were limitations from using the Tasmanian studies, and these have been discussed in detail in the preceding Chapters. Notwithstanding, there remains a strong effect with the identified associations. The infant cohort, TIHS, was a study designed, not for asthma, but to explore SIDS. However, the study is unique, providing a wealth of information regarding an infant's early home and bedding environment. The TIHS cohort was restricted to Tasmania and thus is not representative of the general infant population of Australia, yet the study base fulfils the criteria that would support the generalization of the findings of this birth cohort (550). The number of children participating in the prospective asthma studies was not large: limiting, at times, the exposure to individual bedding items and environmental factors, and impacting on the ability to identify consistency in the results between each study. The identification of these limitations serves to inform future studies. And, ideally, future studies, designed to specifically examine the role of bedding in child asthma, will be of RCT design.

## **8.1 KEY FINDINGS OF THIS THESIS AND THEIR IMPLICATIONS**

### **8.1.1 Underbedding, mattress and bed type**

This thesis reports the first prospective association between the use of sheepskin or the use of plastic mattress covers in infancy with an increased risk of HDM sensitization in childhood. The adverse association of bedding items with HDM sensitization and/or wheeze may be influenced by the HDM-loading of the individual item. Furthermore, this adverse association may also be influenced by the material composition of the bedding item, such that HDM or endotoxin loading in bedding items may not be the only biological mechanisms accounting for the associations. The emission of VOCs from individual bedding items may provide another plausible biological mechanism.

#### ***8.1.1.1 Sheepskin***

It is well recognized that infant sheepskins harbour high levels of HDM, indicating likelihood of a high infant exposure to HDM allergen when in the bed. The prospective association between sheepskin use and subsequent HDM sensitization, is consistent with this concept that sheepskins have high HDM. Moreover, these results support current recommendations that the use of sheepskins as infant bedding in atopic families is inappropriate. A novel finding in this thesis was that exposure to sheepskin in infancy tended to be positively associated with HDM sensitization even among the sub-group of those with no at-birth family history of asthma. This finding supports earlier reports that many children who develop atopic diseases during the first years of life come from families without an atopic heredity (628, 629).

#### ***8.1.1.2 Plastic mattress covers***

The novel finding of an association between plastic mattress cover use and HDM sensitization adds to the evidence that greater attention and further study should be given to other potentially adverse environmental factors, such as VOCs, related to the bedding environment. Plastic mattress covers have previously been considered a priori to protect from sensitization to HDM. This has not been proven and the findings in this thesis are also inconsistent with this assumption. Moreover, there is conflicting evidence regarding the efficacy of using mattress covers in the prevention of asthma symptoms despite a reduction in HDM levels (488). The

influence of VOCs is one explanation that may also be considered in attempting to explain these findings and there is some support from other work to make this suggestion worthy of consideration (496). In addition, there is also a body of work to support the proposition that organic or other components affecting infant air quality may induce sensitization to allergens (504). Previous studies have measured HDM and endotoxin levels in bedding; it would now be appropriate for future studies to consider other potential factors, such as the emission of chemical compounds from bedding materials, that may initiate and/or trigger asthma in those individuals exposed to plastic mattress covers.

### ***8.1.1.3 Implications of the sheepskin and plastic mattress cover associations: the current public health recommendations for bedding and asthma***

These findings, described above, have implications for the current public health recommendations regarding sheepskin use in infancy. The reported associations suggest that further consideration of the current preventive measures for infants at high-risk of atopic disease and sheepskin use, now be given to the whole population. That is, future guidelines may consider that all infants, and not only those infants at high-risk of acquiring asthma, should avoid the use of sheepskins in infancy if laundering techniques are unable to maintain low mite populations (479).

In addition, plastic (PVC) or vinyl mattress covers, commonly used to prevent bedwetting, may also form part of a HDM reduction program by acting as an occlusive cover to the underlying mattress. Plastic mattress covers, however, but should not be considered beneficial for infants at high-risk of atopic disease without a careful evaluation of other potential adverse health effects that may arise from the barrier method that is being used to reduce HDM bedding levels.

### ***8.1.1.4 Bunk beds and electric blanket***

In Chapter 4, those children sleeping in the bottom bunk-bed were found to have an increased risk of frequent wheeze compared with children sleeping in the top bunk-bed. Also, in this same study population, a positive association was found between the current use of electric blanket and wheeze. As these associations have been found in a cross-sectional study issues related to

measurement bias, disease-related changes in behaviour and bedding, and confounding may have contributed to the observed association. However, there are no previous reports of an association between the current use of electric blanket and wheeze. The proposed role, presented in this thesis, of HDMs contributing to the increased association of frequent wheeze and the use of electric blankets or sleeping on a bottom bunk-bed is speculative. At this time, there are no recommendations regarding the use of electric blankets for children at risk of, or suffering from, atopic diseases. Thus, these findings suggest new areas which might be the subject of further consideration and study, for example, further studies to explore the associations between electric blanket and bunk-bed use and HDM sensitization and wheeze.

#### ***8.1.1.5 Allergen-specific determinants of atopy***

Close proximity of a bedding item to the infant's airways may play an important role in the reported associations and is supported by the finding in Chapter 4 of the absence of interaction when both sheepskin and plastic mattress cover were used together. It may be appropriate for future work to consider allergen-specific outcomes when searching for determinants of atopy as the exposure effect, from sheepskin or plastic mattress cover use, was acting principally on inhalant allergens present in the bedding environment. This was demonstrated by the lack of any association between an infant's exposure to these types of underbedding and outdoor aeroallergens such as rye grass.

#### ***8.1.1.6 The use of frequent wheeze as marker of allergen-induced airway disease and disease misclassification***

There is strong evidence that children with asthma who are also sensitized to HDM, are more likely to have severe or frequent asthma (Sections 6.3.2.1 and 2.2.1.6). The findings in this thesis provide further support to this concept and suggest consideration of asthma phenotypes in the assessment of allergen-induced airway disease through the use of wheeze frequency as an outcome measure. The positive associations between either sleeping in the bottom bunk-bed or current use of an electric blanket, compared to children who were not exposed to these bedding items, were stronger for children with frequent wheeze in the past year. These findings may be related to HDM sensitization. The reporting of the frequencies of wheeze episodes as outcome measures should reduce the level of disease misclassification for atopic asthma by identifying



sub-groups of children with more frequent episodes of wheeze in the past year that are more likely to reflect allergen-induced airway disease rather than airway disturbance due to viral infection or other non-atopic factors.

## **8.1.2 Synthetic bedding exposure, sleep position and increased risk of asthma**

### ***8.1.2.1 Infant cocoons***

A prospective association of predominantly synthetic cocoon use in infancy with an increased risk of wheeze at age 7 years has been reported in this thesis. Cocoon use in infancy was also associated with an increased wheeze frequency. Furthermore, these results are consistent with, and support, the growing evidence that synthetic bedding materials are associated with increased childhood wheeze (Section 5.1). Cocoons are an easily modifiable environmental factor that is currently used in child care. The association between infant cocoon use and childhood wheeze may be causal in nature, but further work is required to confirm these results, particularly as the number of children using cocoons was small, thus the role of chance must be considered.

### ***8.1.2.2 Synthetic quilts and sleep position***

In Chapter 6, the interaction between quilt use and sleep position on respiratory function was assessed among seven year old children. There was an adverse effect associated with synthetic quilt use on frequent wheeze and post-exercise lung function among children who slept supine but not among children who did not sleep supine. The interaction is consistent with an adverse effect of synthetic quilt use that is mediated by close proximity. These results are also consistent with two recent birth cohorts (12, 13) reporting an association between synthetic material and frequent wheeze. Selection bias due to bedding choice by parents whose children are at higher risk of asthma has been one possible explanation for these findings (12, 13), however, the findings in Chapter 6 are unlikely to reflect selection bias. Moreover, these findings have added support to the causal inference between synthetic bedding and wheeze by predicting specificity of association as the adverse effect of synthetic quilts was most evident in children who would be more likely to sleep face-up near the quilt.

### **8.1.3 Composite bedding and environmental interactions**

The reported findings of this thesis are the first to investigate composite infant bedding and subsequent wheeze taking into consideration modification by the home environment, utilizing a new conceptual approach. Wheeze risk in childhood at age 7 years increased linearly with increasing numbers of potentially high HDM allergen-rich bedding items at one month of age. This composite bedding effect was further potentiated by the indoor environmental factors of bedroom heating, recent bedroom painting and absence of bedroom carpet. When two or more of these environmental factors were present the bedding-wheeze effect was markedly exacerbated with increasing composite bedding in infancy. The findings in this thesis, of a dose-response for the number of bedding items and frequent wheeze, or earlier age of onset among children with asthma, indicates the importance of considering bedding items not in isolation but as part of a composite bedding environment.

## **8.2 FUTURE RESEARCH IN CHILD ASTHMA: A FOCUS ON BEDDING**

This thesis raises issues pertaining to bedding and the sleep environment that will contribute to the further evaluation and identification of factors involved in both child asthma development and symptom exacerbation. For infants at high-risk of developing asthma and for children with the disease, the bed may be considered the most important site of allergen exposure because of the high level of mite allergen exposure experienced during sleep (473, 475), the proximity of the subject to the source, the high proportion of indoor time spent at this one site (14, 15), and the large amounts of dust present in the bed (14).

It has been argued that there is strong evidence for allergen exposure as an important factor in the aetiology of asthma and in determining the severity of the disease. Existing data and the findings from this thesis support the role of allergen avoidance as a component of both asthma prevention and management strategies (630). The findings from this thesis also suggest that other factors in the bedding environment may be operating to potentiate the effect of HDM-allergen exposure in a susceptible individual. Multiple components, not single items, and their relationship to the proximal sleeping microenvironment, may all play a role in child asthma.

### **8.2.1 Personal allergen measures**

Personal allergen measures during sleep should take into account bedding, proximity and ideally, individual inhaled dose. To date, there is poor understanding of what constitutes the true level of personal allergen exposure (630). Current indices used to measure HDM allergen level in dust reservoirs vary spatially (611) and temporally (578) and, as allergens are taken up by inhalation, dust mite allergen concentrations in reservoir dust cannot directly reflect personal exposure (631). There is a key role for direct measures of inhaled allergens to avoid the misclassification of inhalational exposure that occurs when proxy measures such as the floor are used to indicate bedding exposure levels. Airborne allergens during sleep have been shown to be generated from used (HDM-loaded) bedding and not from the floor (473). And, moreover, measurement of mattress mite levels at a particular moment does not necessarily reflect the dynamics of exposure during sleep, as movement will disturb HDMs in the individual bedding items, such as quilts. Furthermore, Chapter 6 indicates the importance of proximity to bedding items.

I had the opportunity to assess the feasibility of using a new technology, the intra nasal air sampler, to measure the amount of personal HDM allergen inhaled associated with different sleeping positions and proximity of bedding items <sup>2</sup>. The intra nasal air sampler provides a measure of directly inspired allergen-bearing particles (507). Future research studies should also consider HDM allergen levels in bedding, in addition to the bedroom floor, as well as the proximity of the HDM reservoir to the airways. The intra nasal air sampler offers the potential to compare the personal mite aeroallergen exposure of children using beds fitted with pillows and duvets made from differing materials such as synthetic or feather. Quantitative measures of personal inhaled allergen exposure will assist in the understanding of additional factors that may be involved in the bedding environment.

### **8.2.2 Bedding changes over time**

Bedding changes over time should be considered as a possible contributing factor to temporal changes in asthma prevalence. It is, therefore, appropriate to consider recent reports of either a decline (3, 4, 150-152) or a plateauing (5, 154-156) of child asthma prevalence in the context of the findings in this thesis. Evidence is not readily available indicating a temporal change in

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<sup>2</sup> The nasal air samplers were provided for the feasibility study by Inhalix, Institute of Respiratory Medicine, University of Sydney, Sydney, Australia.

factors, both environment and genetic influences, previously considered responsible for the increase in the burden of asthma. Some authors have suggested that the lack of a further increase in asthma prevalence is a result of the environmental factors that promote or trigger asthma, having reached their maximum effect on a susceptible genetic background (152, 154). Whereas others have cited as possible factors, the increase in the number of nursery places since 1996 in Britain (156) or the increased attendance at DCCs (3). Two Australian studies have recently reported a decrease in the prevalence of child asthma (3, 4). Robertson et al., 2003, reported a 26% reduction in current wheeze prevalence from 1993 to 2002 in Melbourne schoolchildren (3). Whereas, Toelle et al., 2004 (4), found the prevalence of recent wheeze decreased significantly (-4.9%; 95% CI -9.1%, -0.7%) between 1992 and 2002 in schoolchildren from Belmont, Australia.

The studies discussed in Chapter 2 (see Section 2.1.3) indicate that these reported decreases in child asthma prevalence are, however, likely to reflect disease changes, not changes in diagnostic criteria. Moreover, a child's bedroom environment may have changed over that period. In addition, epidemiological associations between the home environment and asthma may be underestimated by the greater tendency of cases and their families to avoid potential causes of asthma in the home. Strachan & Carey, 1995 (197), in a population based case-control study in 1991 in Sheffield UK found that the bedroom environmental factors, including bedding pillows and quilts, of 25% of teenagers with troublesome asthma had been altered because of the child's allergy or asthma (197).

Thus, the results of this thesis support the case that the role of a change in infant bedding and the bedroom environment to these childhood asthma trends should be considered in future research directions. This is particularly important in view of changes in infant bedding during the 1990's, the same time period for the reported decrease in asthma prevalence, principally as a result of campaigns conducted to reduce the risk of SIDS (632-634). Hiley & Morley, 1994, reviewed the change in duvet (quilt) use at one year (634) and two years (633) after the UK's Department of Health's 1991 "Back to Sleep" campaign in three East Anglian health districts. One year after the campaign, mothers having their first baby were less likely to use a duvet than were mothers with other children (for infants three months of age: 34% versus 66%,  $p < 0.001$ ). Compared with 1992, quilts or duvets were used less frequently two years after the campaign (for infants three months of age: rate difference -8; 95% CI -1, -13). Dwyer et al., 1995 (632), compared the prevalence of infant, parental and environmental risk factors before and after the 1991 Australian "Reducing the Risks of Cot Death" campaign in the TIHS. Infant use of sheepskins was found to be less in the

18-month period after the intervention (aOR 0.79; 95% CI 0.70, 0.90 for prevalence after versus before the campaign). The ISAAC Phase 3 (146) may offer the opportunity to compare prevalence changes in asthma with bedding changes in the period from ISAAC Phase 1 to ISAAC Phase 3.

### **8.2.3 Composite bedding measurements**

Composite bedding, not single bedding items, as an exposure measure may more validly reflect the true bedding environment and its relationship to allergic sensitization and adverse respiratory associations. Bedding and home environmental interactions should be considered when exploring relationships between bedding items and respiratory health. The role of bedding manipulation, including the sleep environment, in primary prevention of atopy and wheeze may not yet have been fully assessed. Future studies addressing the concepts raised in this thesis could prove worthwhile in regards to prevention activities and are needed to determine the relevance of these findings. Identification of modifiable factors contributing to the burden of asthmatic disease would have considerable public health benefit. Many environmental factors have been proposed as risk factors for the development of childhood asthma and atopy, but the relevant causes are as yet not fully determined. More information that may be provided through appropriate RCTs is required about the relative contribution of individual sites to personal exposure in order to target prevention and intervention strategies. Thus, multifaceted approaches are necessary to determine the combinations of factors which influence HDM allergen exposure.

## **8.3 CONCLUSION**

In conclusion, this thesis has contributed to the current knowledge regarding the possible aetiology of child asthma with a focus on the home and bedding environment. It has presented new findings in regards to a composite bedding effect. Moreover, the contribution of this thesis to public health is evidenced by three published papers, one paper provisionally accepted for publication, and two further papers in progress (including a Review of bedding and asthma). Further research is required in both the identification of risk factors and also the understanding of the underlying mechanisms through which the identified risk factors are responsible for child asthma

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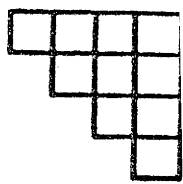
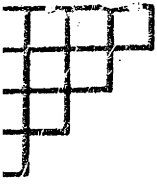
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Appendix 1

**1995 Childhood Asthma Survey Questionnaire.**

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### How To Answer The Questionnaire About Your Child Who Turns Seven In 1995

Please read the information letter first. Please make sure that all questions have an answer. In most cases, unless otherwise indicated, you are asked to answer by putting a tick (✓) in the appropriate box; (e.g. if you want to answer 'yes', mark Yes  No )

If you wish to add more information please write in the space provided at the end of the questionnaire. Thank you for participating in childhood asthma research.

(PLEASE PRINT ALL NAMES IN BLOCK LETTERS)

Child's name \_\_\_\_\_  
 \_\_\_\_\_  
 (Surname) (Given names)

Child's full name as registered at birth \_\_\_\_\_  
 \_\_\_\_\_  
 (Surname) (Given names)  
*(If the same as above, please write 'as above').*

Current Address \_\_\_\_\_  
 \_\_\_\_\_ P/C \_\_\_\_\_

Mother's name \_\_\_\_\_  
 \_\_\_\_\_  
 (Surname) (Given name)

Mother's name when the child was born *(if the same as above please write 'as above').* \_\_\_\_\_  
 \_\_\_\_\_  
 (Surname) (Given name)

Date questionnaire filled out ... / ... / ...

**BIRTH AND OTHER DETAILS**

Mother's Date of Birth ... / ... / ...

Child's date of birth ... / ... / ...

Sex Boy  Girl

School \_\_\_\_\_

Where was this child born?  
 Tasmania   
 Other Australian State   
 Other Country *(Please specify)* \_\_\_\_\_

6. Place/hospital of birth?

Queen Alexandra Division, RHH, Hobart .....   
 Queen Victoria Hospital, Launceston .....   
 Calvary Hospital, Hobart .....   
 NW Regional Hospital, Burnie .....   
 Mersey Women's Division, Devonport .....   
 Other Hospital *(Please specify below)* \_\_\_\_\_   
 Other circumstances *(Please specify below)* \_\_\_\_\_

7. Was this child premature? *(i.e., more than 3 wks early).*  
 Yes  No

8. Complete child's birthweight, if known  
 \_\_\_\_\_ lbs. \_\_\_\_\_ oz. OR \_\_\_\_\_ gms

9. Is this child from:-  
 A single birth .....   
 First of a twin birth .....   
 Second of a twin birth .....   
 Triplet birth .....

10. Do you recall this child taking part in the Tasmanian Infant Health Survey conducted by the Menzies Centre when he/she was a baby? *(You may remember a sister visited your home with a thermometer).*  
 Yes  No

11. What are the ages of the brothers or sisters of this child? *(List ages from eldest down eg. 11, 9, 9, 3)*  
 \_\_\_\_\_

### CHILDHOOD ILLNESS

12. Has he/she ever had eczema in the creases (bends) or elbows, wrists, or knees?  
 Yes  No

13. Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?  
*(NB. Please regard "asthma" and "wheezy breathing" as being much the same thing for the purposes of this questionnaire.)*  
 Yes  No

1. At what age did these attacks begin? \_\_\_\_\_ Years  
Not applicable
5. Does he/she get attacks of "hay fever" (that is, sneezing, running or blocked nose, sometimes with itchy eyes or nose)?  
Yes  No
6. Has your child had wheezing or whistling in the chest in the last 12 months?  
Yes  No
7. How many attacks of wheezing has your child had in the last 12 months?  
None .....   
1 to 3 .....   
4 to 12 .....   
More than 12 .....
8. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?  
Never woken with wheezing .....   
Less than one night per week .....   
One or more nights per week .....
9. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?  
Yes  No
10. Has your child ever had asthma?  
Yes  No
11. In the last 12 months, has your child's chest sounded wheezy during or after exercise?  
Yes  No
12. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?  
Yes  No
13. Since birth has this child attended hospital for any reason?  
a. (If yes tick all applicable boxes) Yes  No
- b. In Southern Tasmania (002) .....
- c. In Northern Tasmania (003) .....
- d. In North Western Tasmania (004) .....
- e. Outside Tasmania (Please specify) .....
- Since birth has this child attended hospital for:  
a. Asthma Yes  No
- b. Other breathing problems Yes  No
- (Please specify) \_\_\_\_\_
- Has your child ever taken any medicine for asthma?  
(Medicine includes inhalers, liquids, tablets, nebulisers).  
Yes  No

26. In the last 12 months how often on average has your child taken asthma medicine?  
Not at all .....   
Less than once a month .....   
More than once a month .....   
Every day .....
27. In the last 12 months has your child taken any of the following medicines for asthma?  
Ventolin, Bricanyl, Berofec .....   
Intal .....   
Becotide, Becloforte, Pulmicort .....   
None of the above .....
28. Did this child attend regular child care\* with more than two other children at the following ages:-  
Less than 1 year of age Yes  No   
1 year of age Yes  No   
2 years of age Yes  No   
3 years of age Yes  No   
4 years of age Yes  No
- (\* please consider regular child care as being at least once a week for 3 hours or more)
29. Has child had any of the following?  
(please tick applicable box/boxes)
- Bronchitis .....   
Cough lasting for more than 3 weeks .....   
Pneumonia .....   
Pleurisy .....   
Frequent ear infections (more than 2/year) .....   
None of the above .....

## FAMILY HISTORY

30. Do any of the child's brothers or sisters, parents or grandparents, have any history of the following?  
(please tick applicable box/boxes)
- Febrile-convulsions .....   
Asthma .....   
Heart disease, dying before age of 60 years .....   
Epilepsy or fits .....   
Diabetes (requiring insulin injections) .....   
Diabetes (not requiring insulin injections, often called 'late onset' or 'sugar' diabetes) .....   
Eczema .....   
Hayfever .....   
None of the above illnesses .....
31. Please indicate your relationship to the child:
- Mother       Father       Step-parent/adopted parent/guardian
- Other (please state) \_\_\_\_\_

**CHILD'S PARENTS**

32. Has child's natural mother ever had asthma or attacks of wheezing like asthma?  
 Yes  No   
 Medical details of mother unknown.....

33. Has she ever suffered from "hay fever"  
 Yes  No   
 Medical details of mother unknown.....

34. Please indicate the highest level of school education the child's mother has completed:  
 Primary school (eg. left before end of year 10) .....   
 High school completed to end of year 10 .....   
 Completed secondary education to end yr. 12 ...   
 University, TAFE or other institution .....   
 Unknown .....

35. Which one of the following best describes the mother's current employment status?  
 Unemployed .....  0  
 Home duties .....  1  
 Employed part-time .....  2  
 Employed full-time .....  3  
 Student .....  4  
 Sole parent pension .....  5  
 Other (please state) .....

36. The mother's current occupation is (please print):  
 .....

37. Has child's natural father ever had asthma or attacks of wheezing like asthma?  
 Yes  No   
 Medical details of father unknown .....

38. Has he ever suffered from "hay fever"  
 Yes  No   
 Medical details of father unknown.....

39. Please indicate the highest level of school education completed by the child's father:  
 Primary school (eg. left before end of year 10) .....   
 High school completed to end of year 10 .....   
 Completed secondary education to end yr. 12 ...   
 University, TAFE or other institution .....   
 Unknown .....

40. Which of the following best describes the father's current employment status?  
 Unemployed .....  0  
 Home duties .....  1  
 Employed part-time .....  2  
 Employed full-time .....  3  
 Student .....  4  
 Permanently unable to work or ill .....  5  
 Other (please state) .....

41. The father's current occupation is (please print):  
 \_\_\_\_\_

**SMOKING**

42. How many cigarettes does child's mother smoke per day?  
 Nil .....   
 1 - 10/day .....   
 11 - 20/day .....   
 21 - 40/day .....   
 41+/day .....

43. How often does child's mother smoke in the same room as the child?  
 Usually .....   
 Sometimes .....   
 Never .....

44. How many other adults excluding child's mother smoke in the house?  
 \_\_\_\_\_ Other

45. How many cigarettes do other adults (excluding mother) your household smoke, in total, per day?  
 Nil .....   
 1 - 10/day .....   
 11 - 20/day .....   
 21 - 40/day .....   
 41+/day .....   
 Don't know .....

46. How often do other adults (excluding mother) smoke in same room as the child?  
 Usually .....   
 Sometimes .....   
 Never .....

**INFANT & CHILD FEEDING**

47. Was your child breastfed?  
 Yes  No

48. Age of child when breastfeeding ceased? (completed months).  
 \_\_\_\_\_ Month  
 Not applicable.....

49. At what age were solids introduced?  
 \_\_\_\_\_ Month

50. How often does your child eat fish?  
 Never .....   
 Once a week or less .....   
 More than once a week .....

Which of the following fats does your child usually have on bread or toast:

- Butter .....
- Canola, soy, olive margarine .....
- Other margarines (eg. sunflower, safflower, mixed vegetable) .....
- None of the above .....

Has your family had a cat for a pet during this child's life?

Yes  No

(please tick all the ages of your child when a cat was a pet)

- 0-6 mths of age
- 6-12 mths of age
- 1yr of age
- 2yrs of age
- 3yrs of age
- 4yrs of age
- 5yrs of age
- 6yrs of age
- 7yrs of age

### HOME ENVIRONMENT

What is your home made from?

- Weatherboard .....
- Brick veneer .....
- Double brick .....
- Other (please specify) .....

What main type of floor does your house have? (tick one box).

- Wooden .....
- Concrete slab on ground .....
- Raised concrete slab .....
- Other (please specify) .....

Do you have wall to wall carpet or large rugs (occupying more than half the floor area in total) in your living room?

Yes  No

What is the main heating used in your living room?

(Tick one box)

- No heating .....
- Open fire .....
- Wood heater (freestanding or in fireplace) .....
- Oil heater with fan .....
- Oil heater without fan .....
- Gas heater with flue (chimney) .....
- Gas heater without flue .....
- Kerosene heater .....
- Off-peak electricity .....
- Electric radiators or fan heaters .....
- Electric Central heating .....
- Gas Central heating .....
- Other (please specify) .....

57. What power source do you use for cooking? (Tick one box)

- Electricity .....
- Gas .....
- Wood stove .....
- Other (please specify) .....

58. How many rooms does your house have?

(Excluding bathroom and toilet)

\_\_\_\_\_ Rooms

59. How many people live in your home?

\_\_\_\_\_ People

60. Have you noticed mould inside your house?

(Excluding bathroom)

Yes

61. What is the floor covering in the child's bedroom?

(Tick one box).

- Wood .....
- Lino .....
- Concrete .....
- Carpet .....
- Tiles .....
- Other (Please specify) .....

62. Is there also a rug or rugs on the floor of your child's room which occupy more than half the floor area?

Yes  No

63. At night, is/are window(s) in room where child sleeps:- (Tick one box).

- Partly open in cold weather only .....
- Partly open in warm weather only .....
- Partly open all year round .....
- Closed all year round .....

64. What type of bed does your child use?

- Child's small bed .....
- Single bed .....
- Double bed .....
- Top bunk .....
- Bottom bunk .....
- Other (Please specify) .....

65. Is child's bed -

- On the floor .....
- Supported by legs/frame .....

66. What type of mattress is now on child's bed?

- Foam .....
- Innerspring .....
- Other (Please specify) .....

67. In the last month have you used the following products - (tick all applicable boxes)

	In the home	In child's bedroom
Airfreshener spray	<input type="checkbox"/>	<input type="checkbox"/>
Insect killing strips	<input type="checkbox"/>	<input type="checkbox"/>
Insect killing spray	<input type="checkbox"/>	<input type="checkbox"/>

68. Which of the following are between the child and the mattress? (Tick all applicable boxes).

- No covering .....
- Cotton covered quilted mattress protectors ...
- Plastic/PVC .....
- Wool fleece with hide/material backing .....
- Electric Blanket .....
- Allergy cover (eg. 'Allersearch') .....
- Other (Please specify) .....

69. What type of pillow does your child have?

- No pillow .....
- Foam/Sponge/Tontine/Polyester/Dacron ...
- Rubber .....
- Feather .....
- Material .....
- Other (please specify) .....

70. Which of the following is usually over your child during sleep? (Tick all applicable boxes).

- Sheet(s) .....
- Feather doona/duvet/quilt(s) .....
- Dacron/polyester doona/duvet/quilt(s) .....
- Woollen doona(s) .....
- Woollen blanket(s) .....
- Cotton blanket(s) .....
- Synthetic blanket(s) (eg. acrylic) .....
- Other covering(s) (Please specify) .....

71. What position does child usually sleep in?

- On side .....
- On stomach, face down .....
- On stomach, face to the side .....
- On back, face up .....
- On back face to the side .....
- Child doesn't have usual sleeping position ...
- Not known .....
- Other (Please specify) .....

Comments:

I have read and understand the information letter. I agree that information on my child from this survey, from the Tasmanian Infant Health Survey (if applicable) and from my child's hospital of birth may be used for the purpose of asthma research. I agree that research data gathered for the study may be published provided that my child cannot be identified as a subject.

PLEASE SIGN HERE

Signature of parent/guardian

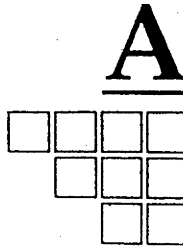
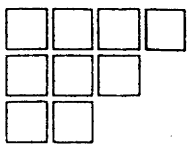
This is the end of the questionnaire.

☺ Thank You for your time.

Appendix 2

**1997 Childhood Allergy & Respiratory Health Study  
Questionnaire.**

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## How To Answer The Questionnaire About Your Child

Please read the information letter first. Please make sure that all questions have an answer. In most cases, unless otherwise indicated, you are asked to answer by putting a tick (✓) in the appropriate box; (e.g. if you want to answer 'yes', mark Yes  No )

If you wish to add more information please write in the space provided at the end of the questionnaire.  
Thank you for participating in childhood asthma research

(PLEASE PRINT ALL NAMES IN BLOCK LETTERS)

Child's name \_\_\_\_\_  
(Surname) (Given names)

Child's full name as registered at birth  
(If the same as above, please write 'as above').  
\_\_\_\_\_  
(Surname) (Given names)

Current Address \_\_\_\_\_  
\_\_\_\_\_ P/C \_\_\_\_\_

Mother's name \_\_\_\_\_  
(Surname) (Given name)

Mother's name when the child was born (if the same as above please write 'as above').  
\_\_\_\_\_  
(Surname)  
(Given name)

Date questionnaire filled out ... / ... / ...

### BIRTH AND OTHER DETAILS

- Mother's Date of Birth ... / ... / ...
- Child's date of birth ... / ... / ...
- Sex Boy  Girl
- School \_\_\_\_\_
- Where was this child born?  
Tasmania   
Other Australian State   
Other Country (Please specify) \_\_\_\_\_

### 6. Place/hospital of birth?

- Queen Alexandra Division, RHH, Hobart .....  
 Queen Victoria Hospital, Launceston .....  
 Calvary Hospital, Hobart .....  
 NW Regional Hospital, Burnie .....  
 Mersey Women's Division, Devonport .....  
 Other Hospital (Please specify below) \_\_\_\_\_  
 Other circumstances (Please specify below) \_\_\_\_\_

### 7. Was this child premature? (i.e. more than 3 wks early). Yes No

### 8. Complete child's birthweight, if known

\_\_\_\_\_ lbs. \_\_\_\_\_ oz. OR \_\_\_\_\_ g

### 9. Is this child from:-

- A single birth .....  
 First of a twin birth .....  
 Second of a twin birth .....  
 Triplet birth .....

### 10. Do you recall this child taking part in the Tasmanian Infant Health Survey conducted by the Menzies Centre when he/she was a baby? (You may remember a sister visited your home with a thermometer. Yes No

### 11. What are the ages of the brothers or sisters of the child? (List ages from eldest down eg. 11, 9, 9, 3)

### CHILDHOOD ILLNESS

- Has he/she ever had eczema in the creases (bend of elbows, wrists, or knees)?  
Yes  No
- Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?  
(NB. Please regard 'asthma' and 'wheezy breathing' as being much the same thing for this question; we do not ask you to try to tell the difference)  
Yes  No





**CHILD'S PARENTS**

32. Has child's natural mother ever had asthma or attacks of wheezing like asthma?  
 Yes  No   
 Medical details of mother unknown.....

33. Has she ever suffered from "hay fever"  
 Yes  No   
 Medical details of mother unknown.....

34. Please indicate the highest level of school education the child's mother has completed:  
 Primary school (eg. left before end of year 10) .....   
 High school completed to end of year 10 .....   
 Completed secondary education to end yr. 12 ...   
 University, TAFE or other institution .....   
 Unknown .....

Which one of the following best describes the mother's current employment status?  
 Unemployed   
 Home duties   
 Employed part-time   
 Employed full-time   
 Student   
 Sole parent pension   
 Other (please state)

36. The mother's current occupation is (please print):  
 \_\_\_\_\_

37. Has child's natural father ever had asthma or attacks of wheezing like asthma?  
 Yes  No   
 Medical details of father unknown.....

38. Has he ever suffered from "hay fever"  
 Yes  No   
 Medical details of father unknown.....

39. Please indicate the highest level of school education completed by the child's father:  
 Primary school (eg. left before end of year 10) .....   
 High school completed to end of year 10 .....   
 Completed secondary education to end yr. 12 ...   
 University, TAFE or other institution .....   
 Unknown .....

40. Which of the following best describes the father's current employment status?  
 Unemployed .....   
 Home duties .....   
 Employed part-time .....   
 Employed full-time .....   
 Student .....   
 Permanently unable to work or ill .....   
 Other (please state) .....

41. The father's current occupation is (please print):  
 \_\_\_\_\_

**SMOKING**

42. How many cigarettes does child's mother smoke per day?  
 Nil .....   
 1 - 10/day .....   
 11 - 20/day .....   
 21 - 40/day .....   
 41+ /day .....

43. How often does child's mother smoke in the same room as the child?  
 Usually .....   
 Sometimes .....   
 Never .....

44. How many other adults excluding child's mother smoke in the house?  
 \_\_\_\_\_ Other

45. How many cigarettes do other adults (excluding mother) in your household smoke, in total, per day  
 Nil .....   
 1 - 10/day .....   
 11 - 20/day .....   
 21 - 40/day .....   
 41+ /day .....   
 Don't know .....

46. How often do other adults (excluding mother) smoke in the same room as the child?  
 Usually .....   
 Sometimes .....   
 Never .....

**INFANT & CHILD FEEDING**

47. Was your child breastfed?  
 Yes  No

48. Age of child when breastfeeding ceased?  
 (completed months). \_\_\_\_\_ Mont  
 Not applicable.....

49. At what age were solids introduced?  
 \_\_\_\_\_ Mont

50. How often does your child eat fish?  
 Never .....   
 Once a week or less .....   
 More than once a week .....

51. Which of the following fats does your child usually have on bread or toast:
- Butter .....
- Canola, soy, olive margarine .....
- Other margarines (eg. sunflower, safflower, mixed vegetable) .....
- None of the above .....
52. Has your family had a cat for a pet during this child's life?
- Yes  No
- (please tick all the ages of your child when a cat was a pet)
- |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                          |
| 0-6 mths                 | 6-12 mths                | 1yr                      | 2yrs                     | 3yrs                     |                          |
| of age                   | of age                   | of age                   | of age                   | of age                   |                          |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4yrs                     | 5yrs                     | 6yrs                     | 7yrs                     | 8 yrs                    | 9 yrs                    |
| of age                   | of age                   | of age                   | of age                   | of age                   | of age                   |

### HOME ENVIRONMENT

53. What is your home made from?
- Weatherboard .....
- Brick veneer .....
- Double brick .....
- Other (please specify) \_\_\_\_\_
54. What main type of floor does your house have? (tick one box).
- Wooden .....
- Concrete slab on ground .....
- Raised concrete slab .....
- Other (please specify) \_\_\_\_\_
55. Do you have wall to wall carpet or large rugs (occupying more than half the floor area in total) in your living room?
- Yes  No
56. What is the main heating used in your living room? (Tick one box)
- No heating .....
- Open fire .....
- Wood heater (freestanding • or in fireplace) .....
- Oil heater with fan .....
- Oil heater without fan .....
- Gas heater with flue (chimney) .....
- Gas heater without flue .....
- Kerosene heater .....
- Off-peak electricity .....
- Electric radiators or fan heaters .....
- Electric Central heating .....
- Gas Central heating .....
- Other (please specify) \_\_\_\_\_

57. What power source do you use for cooking? (Tick one box)
- Electricity .....
- Gas .....
- Wood stove .....
- Other (please specify) \_\_\_\_\_
58. How many rooms does your house have? (Excluding bathroom and toilet)
- \_\_\_\_\_ Rooms
59. How many people live in your home?
- \_\_\_\_\_ People
60. Have you noticed mould inside your house? (Excluding bathroom)
- Yes  No
61. What is the floor covering in the child's bedroom? (Tick one box).
- Wood .....
- Lino .....
- Concrete .....
- Carpet .....
- Tiles .....
- Other (Please specify) \_\_\_\_\_
62. Is there also a rug or rugs on the floor of your child's room which occupy more than half the floor area?
- Yes  No
63. At night, is/are window(s) in room where child sleeps:- (Tick one box).
- Partly open in cold weather only .....
- Partly open in warm weather only .....
- Partly open all year round .....
- Closed all year round .....
64. What type of bed does your child use?
- Child's small bed .....
- Single bed .....
- Double bed .....
- Top bunk .....
- Bottom bunk .....
- Other (Please specify) \_\_\_\_\_
65. Is child's bed -
- On the floor .....
- Supported by legs/frame .....
66. What type of mattress is now on child's bed?
- Foam .....
- Innerspring .....
- Other (Please specify) \_\_\_\_\_



Comments:

.....

.....

.....

I have read and understand the information letter. I agree that information on my child from this survey, from the Tasmanian Infant Health Survey (if applicable) and from my child's hospital of birth may be used for the purpose of asthma and allergy research. I agree that research data gathered for the study may be published provided that my child cannot be identified as a subject.

PLEASE SIGN HERE .....  
Signature of parent/guardian

I would like a copy of my child's allergy results to be sent to:

- our address
- our family doctor

Dr. \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
SUBURB \_\_\_\_\_ PC \_\_\_\_\_

This is the end of this questionnaire.  
Thank You for your time.

Appendix 3

**Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. An association between plastic mattress covers and sheepskin underbedding use in infancy and house dust mite sensitization in childhood: a prospective study. Clin Exp Allergy 2003; 33(4):483-9.**

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## An association between plastic mattress covers and sheepskin underbedding use in infancy and house dust mite sensitization in childhood: a prospective study

L. F. Trevillian\*, A.-L. Ponsonby\*†, T. Dwyer†, L. L.-Y. Lim\*, A. Kemp§, J. Cochran† and A. Carmichael‡

\*National Centre for Epidemiology and Population Health, The Australian National University, Canberra, †Menzies Centre for Population Health, University of Tasmania, Hobart, §Department of Immunology, Royal Children's Hospital, University of Melbourne, Melbourne and ‡Department of Paediatrics and Child Health, University of Tasmania, Hobart, Australia

### Summary

**Background** Higher house dust mite (HDM) allergen exposure during infancy has been associated with increased HDM sensitization. Infant bedding has been associated with the accumulation of varying levels of HDM. Prospective data on the relationship between infant bedding and the development of HDM sensitization has not been previously examined.

**Objectives** To determine if particular types of bedding used in infancy are associated with increased risk of house dust mite sensitization in childhood.

**Methods** A population-based sample ( $n=498$ ) of children born in 1988 or 1989, and who were resident in Northern Tasmania in 1997, participated in this study. These children were part of a birth cohort study (1988–95), the Tasmanian Infant Health Survey. Data on infant underbedding and mattresses was available on 460 and 457 children, respectively. The main outcome measure was HDM sensitization defined as a skin prick test (SPT) reaction of 3 mm or more to the allergens of *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*.

**Results** The use of either sheepskin underbedding or plastic mattress covers in infancy was associated with an increased risk of sensitization to HDM allergens at age 8 years. The adjusted risk ratio (RR) for sensitization to HDM with sheepskin in infancy was 2.27 (95% CI: 1.14, 4.55),  $P=0.020$ . The adjusted RR for sensitization to HDM with the use of plastic mattress covers in infancy was 2.06 (95% CI: 1.22, 3.51),  $P=0.007$ . The use of a foam mattress in infancy was not related to subsequent HDM sensitization.

**Conclusion** Infant's bedding plays a role in the development of HDM sensitization in childhood. Intervention studies to examine mite allergen levels and the role of underbedding on the development of HDM sensitization are required.

**Keywords** aeroallergen sensitization, house dust mite, infant bedding, mattress covers, prospective cohort, volatile organic compounds

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### Introduction

Inhalant allergen sensitization is an important determinant of childhood asthma [1–3]. Early infancy has been identified as a critical period for primary sensitization [4, 5] to indoor inhalant allergens such as house dust mite (HDM). The bedding environment during infancy may play an important role in increasing an infant's likelihood of HDM sensitization [3, 6]. Infants spend prolonged periods in bed with close proximity to bedding items, enhanced further by their sleep position. Moreover, mattress and bedding are two of the main reservoirs of HDM [7, 8] and also a potential source of pulmonary irritants in the form of volatile organic compounds [9, 10].

Both prospective [5, 11, 12] and cross-sectional [2, 13, 14] studies have now shown a dose–response relationship between the level of exposure to HDM allergens and allergic sensitization. In a cohort of 1314 newborns followed for 3 years, Wahn and co-workers [5], using mixed floor dust from the child's bedroom, parent's bedroom and living room, found that in homes with low ( $\leq 25$ th percentile) dust concentrations, the risk of sensitization to HDM for these children was substantially lower, 1.6% compared to 6.5%, with domestic exposure to the HDM allergen than if dust concentrations were above the 75th percentile. A similar result, with increasing HDM sensitization occurring at increasing HDM levels to the infant's bedroom and living room dust, was reported during the first 5 years of life from a smaller study in Sweden [11]. An earlier study examined the incidence of sensitization to *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) in 1812 children with a mean initial age of 7.3 years over a two-year period [12]. It identified an increased risk for initial sensitization for increasing levels of Der p 1 in the child's mattress dust.

Correspondence: L. F. Trevillian, National Centre for Epidemiology and Population Health, The Australian National University, Canberra ACT 0200, Australia. E-mail: leigh.trevillian@anu.edu.au

Prospective data, however, on infant underbedding and subsequent HDM sensitization are not available. This is likely to be an important area because different bedding items differ with regard to HDM allergen levels. For example infant sheepskins, because of their frequent use, dampness, and warmth, can contain very high populations of mites [6, 15]. In addition, mattress type has been the determinant for differing Der p 1 levels in some studies, with higher allergen levels found on innerspring and kapok compared with foam rubber mattresses [16]. Kapok is a natural cotton-like fibre which surrounds the seeds of the kapok tree. Both sheepskins and mattresses have been shown to accumulate allergen rapidly [17, 18], whereas, mattress covers have been shown to be effective in reducing the amount of house dust mite allergen [19, 20]. Secondly, several cross-sectional studies have shown that later sensitization to mites is strongly associated with HDM mattress level in childhood [13, 14, 21]. An effect of bedding type on allergen sensitization may not only be due to allergen levels [22]. Waterproof infant cot mattress covers release volatile organic compounds (VOC) that can be associated with airway inflammation (either atopic or non-atopic) in humans [9, 23] and animals [10], and the promotion of sensitization to allergens [24].

In this report we examine the relationship between types of underbedding (sheepskins and plastic mattress covers), and mattress type used in infancy and the subsequent development of HDM sensitization in childhood.

## Methods

### *The Tasmanian Infant Health Survey (TIHS)*

The TIHS was a cohort study of infants born from 1988 to 1995 in Tasmania, Australia. This study operated from hospitals, where approximately 93% of births in Tasmania occurred. Infants born were scored to assess the risk of sudden infant death syndrome (SIDS) using a perinatal score model based on maternal age, birth weight, gender, breastfeeding, season of birth and duration of second stage of labour [25]. Infants exceeding a scoring cut-off were eligible for inclusion together with all multiple births. The eligibility criteria and study methods are discussed in more detail elsewhere [26]. Data were obtained on three occasions. The first interview was conducted in hospital on the fourth day of the infant's life. A home interview was conducted during the fifth postnatal week, and a telephone interview at approximately 10 weeks postnatally. At the home interview, data were collected on a number of parental, infant, environmental and childcare factors. Data were collected on the type of underbedding used, including under-sheet, mattress coverings and mattress types. Use of sheepskin as underbedding at time of interview or intention to use sheepskin in cold weather was recorded in order to avoid the effect of current season when questioned. Responses of plastic to the type of mattress lining used were classified as having plastic mattress covers. In addition, the usual sleeping position of the infant was also recorded.

### *The 1997 Childhood Allergy and Respiratory Health Study (CARHS)*

In 1997, a follow-up study of TIHS participants born in 1988 or 1989 was conducted in Northern Tasmania through school

records. Eligible children and their parents were invited to attend the Launceston General Hospital for a parental interview and child assessment. The parental questionnaire included childhood questions on asthma, wheeze, hayfever and eczema from the International Study of Asthma and Allergy in Childhood (ISAAC) [27] and also questions on the home environment and other factors. Skin prick test (SPT) was used to assess the cutaneous reaction to exposure to the allergens of house dust mites *D. pteronyssinus* and *Dermatophagoides farinae* (*D. farinae*), cat, dog, alternaria, ryegrass, cow's milk, egg, and peanut (Hollister-Stier purified allergen extracts supplied by Bayer, Sydney, Australia) and positive (histamine 10 mg/mL and 1 mg/mL) and negative (glycerine) controls. Weal size was determined at 15 min. To examine the influence of bedding on HDM sensitization we examined weal sizes of both greater than and equal to 2 mm. In addition, we further examined any relationship using a weal size of greater than or equal to 3 mm [28]. Children with a positive SPT were classified as atopic. Children with a positive SPT to either *D. pteronyssinus* or *D. farinae* were classified as sensitized to house dust mite [28].

### *Statistical methods*

The main bedding exposure variables of interest were the use in infancy of sheepskin underbedding, plastic mattress cover and foam mattress. Sheepskin is a common form of underbedding for infants in Australia and comprises the animal hide with the natural wool fibres attached. Infants are typically placed directly on the sheepskin. A plastic mattress cover is used mostly as a mattress protector from wetting. All three variables were dichotomous for exposure or no exposure to the bedding variable. The dichotomous outcome variable was HDM sensitization which refers to a positive skin test to either *D. pteronyssinus* or *D. farinae*.

The Cox proportional hazard model [29] was applied as the main method of analysis. The risk ratio (RR) was used as the measure of effect to report any risk associations, firstly for exposure to outcome associations without any potential confounders, and secondly, for the multivariate analysis that included potential confounders. 'Time to event' was defined as the period in days from birth to the date of assessment. Children not HDM sensitized at the time of follow-up assessment were considered censored.

To identify potential confounders, we examined the association between a large number of factors and HDM sensitization (Table 1). We further examined how these factors related to the bedding exposures of interest. We examined more than 80 potential confounders to see how they each related separately to use of the individual exposure variables and HDM sensitization. Several factors, early introduction of solid food, home gas heating and private health insurance at birth, are associated with sensitization to HDM and have been previously reported [30]. Moreover, we have previously shown in this population that feather bedding is inversely associated with HDM sensitization [31].

A proportional hazards model was then constructed as follows. For each exposure, potential confounders [32] were added to the model as covariates if the variables were associated with HDM sensitization in the exposure to outcome analysis, or were reported to be related to HDM sensitization or asthma in the literature. We examined the confounding effect of these



**Table 1.** Unadjusted risk ratio for infant underbedding, mattress and potential predictors of HDM sensitization\*

	HDM sensitization	
	Unadjusted RR (95% CI)	P-value
<b>Exposure variables</b>		
<b>Underbedding</b>		
Neither sheepskin nor plastic cover	1.00 (reference)	–
Only sheepskin	2.12 (1.12, 4.04)	0.022
Only plastic mattress cover	1.96 (1.18, 3.25)	0.009
Both sheepskin and plastic cover	2.97 (1.51, 5.86)	0.022
<b>Mattress type</b>		
No foam mattress	1.00 (reference)	–
Foam mattress	1.01 (0.69, 1.48)	0.945
<b>Potential confounding infant variables</b>		
<b>Maternal factors</b>		
Mother smoking during pregnancy	0.89 (0.62, 1.30)	0.566
Teenage motherhood	0.75 (0.43, 1.32)	0.323
Family history of asthma	1.30 (0.90, 1.89)	0.168
<b>Infant factors</b>		
Infant only child	0.29(0.07, 1.19)	0.087
Infant first born	0.78 (0.54, 1.14)	0.203
Low birth weight	1.15 (0.73, 1.82)	0.550
Infant bottle fed at one month	1.03 (0.69, 1.54)	0.883
Solid food introduced by phone interview at 10 weeks	1.26 (0.85, 1.85)	0.247
Infant exclusively breastfed by phone interview at 10 weeks	0.74 (0.48, 1.15)	0.183
<b>Infant sleep position</b>		
Usual sleep position in infancy: supine	1.00 (reference)	–
Usual sleep position in infancy: prone	1.33 (0.47, 3.73)	0.591
Usual sleep position in infancy: side	1.33 (0.48, 3.71)	0.582
<b>Household factors</b>		
Private health insurance at birth	1.86 (1.29, 2.70)	0.001
Home gas appliance use	1.83 (0.89, 3.77)	0.101
No-one smoking in same room as infant	1.18 (0.80, 1.72)	0.402
More than six residents in household at birth	1.23 (0.76, 2.00)	0.404
Cat as pet during infancy	1.42 (0.97, 2.08)	0.069
<b>Bedroom factors</b>		
Use of foam pillow at one month age	0.62 (0.27, 1.41)	0.251
Infant sleeping in bedroom alone	0.75 (0.50, 1.13)	0.176
Carpet in infant's bedroom	1.13 (0.59, 2.17)	0.716
Humidity in infant's bedroom > 75%	1.44 (0.70, 2.98)	0.321
Window in infant's bedroom open at night	1.06 (0.70, 1.60)	0.774
Use of feather quilt as child	0.65 (0.45, 0.95)	0.025

\*Skin prick reaction of greater than or equal to 3 mm to either mite allergen, *D. pteronyssinus* or *D. farinae*.

factors on each exposure–disease association using change-in estimate methods [33]. Those factors that altered the point estimate for the exposure–HDM association by 10% or more were included. To confirm that the final confounder sets used were the most appropriate, we then added in the remaining variables in Table 1 as individual factors into the final model. None of these factors substantially altered the adjusted risk ratios reported in Table 2. Family history was defined as asthma in any of the infant's siblings, parents or grandparents. A positive family history at birth may result from shared bedding practices within the family [34], thus the possible contribution of family history of asthma to the association between bedding and HDM sensitization was explored. The proximity of bedding to the infant's airway may be affected by sleep position. Thus, the infant's usual sleep position and its association with subsequent HDM sensitization were also examined.

The aetiologic fraction of HDM sensitization in childhood attributable to either plastic mattress cover or sheepskin use in infancy we calculated as  $p(aRR-1)/aRR$ , where  $p$  = the proportion of children with either plastic mattress cover or sheepskin use in infancy among those with the outcome of HDM sensitization and  $aRR$  = the relative risk estimate for either plastic mattress cover or sheepskin use and HDM sensitization, after adjustment for the confounders listed in Table 2 [32]. We conducted the analysis using STATA 7 [35].

## Results

In Northern Tasmania in 1997, 499 (84%) of the 596 children identified as participants in the 1988–89 TIHS at birth agreed to participate in the CARHS study. The mean age at follow-up

**Table 2.** The prospective association between sheepskin, plastic mattress cover, foam mattress use in infancy and child sensitization to house dust mite

Underbedding	% HDM sensitized* among exposed	Adjusted** RR (95% CI) for underbedding vs. none	P-value
Neither sheepskin nor plastic cover	15.8% (22/139)	1.00 (reference)	–
Only plastic mattress cover	25.6% (55/215)	2.06 (1.22, 3.51)	0.007
Only sheepskin	25.4% (17/67)	2.27 (1.14, 4.55)	0.020
Both sheepskin and plastic cover	35.9% (14/39)	2.25 (1.05, 4.83)	0.038
No foam mattress	23.2% (51/220)	1.00 (reference)	–
Foam mattress	23.6% (56/237)	1.09 (0.72, 1.67)	0.676

\*Skin prick reaction of greater than or equal to 3 mm to either mite allergen, *D. pteronyssinus* or *D. farinae*. \*\* The risk ratio has been adjusted for parent's with private health insurance at time of child's birth, at-birth family history of asthma, being an only child, whether child was exclusively breastfed by 10 weeks of age, home gas heater use in infancy, and use of a feather quilt as a child.

was 8.7 (standard deviation = 0.6) years. SPT data were available on 498. One autistic child did not undergo the SPT. Data on use of underbedding was available on 460, and for mattresses on 457 children. The characteristics of the study sample are shown in Table 3. Overall, 31.5% of the children were sensitized to at least one HDM species.

Plastic mattress covers (55%, 254/460) were used more commonly than sheepskin underbedding (23%, 106/460) in early infancy. Other types of mattress covers used included cotton, wool or synthetic. The use of foam mattresses (52%, 237/457) was also common. Non-foam mattresses were predominantly ti-tree (40%) or other (8%). Ti-tree is native to Australasia and the bark is used for mattress filling. The time-period of use for each particular bedding item was not available.

In Table 1, the unadjusted RR showed that use of sheepskin only, without a plastic mattress cover, in infancy was significantly associated with sensitization to HDM in childhood (unadjusted RR 2.12 (1.12, 4.04)  $P = 0.022$ ). The use of only plastic mattress covers was associated with a significant increase in the risk ratio of HDM sensitization (unadjusted RR 1.96 (1.18, 3.25)  $P = 0.009$ ). The use of both a sheepskin and a plastic mattress cover remained significantly associated with HDM sensitization (unadjusted RR 2.97 (1.51, 5.86)  $P = 0.022$ ). Foam mattress use in infancy was not significantly more likely to be associated with HDM sensitization in childhood (unadjusted RR 1.01 (0.69, 1.48)  $P = 0.945$ ).

An at-birth family history of asthma was not significantly associated with subsequent HDM sensitization (unadjusted RR 1.30 (0.90, 1.89)). HDM sensitization was significantly associated with childhood asthma, but there was no relation between the use of either sheepskin or plastic mattress covers in infancy and childhood asthma. Individual adjustment for the factors, listed in Table 1, considered as potential predictors of subsequent HDM sensitization did not alter the point estimate for the exposure–HDM association by 10% or more.

Table 2 reports the association between underbedding and mattress type and HDM sensitization after adjustment for confounders using a weal size of 3 mm as SPT positivity. The adjusted risk ratios for subsequent HDM sensitization remained significant when the different bedding combinations of sheepskin use and/or plastic mattress cover use were compared against a reference variable of neither sheepskin nor plastic mattress cover use. The use of a plastic mattress cover in infancy alone was significantly associated with subsequent HDM sensitization (Table 2). Similarly, the use of sheepskin alone was significantly related to HDM sensitization in

**Table 3.** Characteristics of the study sample

Categorical measures	%	n/total n
<i>D. pteronyssinus</i> sensitization*	22.5	112/498
<i>D. farinae</i> sensitization*	11.9	59/498
HDM sensitization*	23.3	116/498
Ryegrass sensitization**	17.1	85/498
Other indoor aeroallergen sensitization***	7.0	35/498
Cat sensitization	2.8	14/498
Alternaria sensitization	4.0	20/498
Dog sensitization	0.2	1/498
Underbedding		
Neither sheepskin nor plastic cover use	30.2	139/460
Only sheepskin use in infancy	14.6	67/460
Only plastic mattress cover	46.7	215/460
Both sheepskin and plastic cover	8.5	39/460
Mattress type		
No foam mattress	48.1	220/457
Foam mattress	51.9	237/457

\*Any skin prick reaction of greater than or equal to 3 mm to mite allergen, *D. pteronyssinus* or *D. farinae*. \*\*Any skin prick reaction of greater than or equal to 3 mm to ryegrass. \*\*\*Any skin prick reaction of greater than or equal to 3 mm to alternaria, cat or dog.

childhood (Table 2). There was very little additional effect with exposure to both sheepskin and plastic mattress cover in infancy. Both sheepskin use and plastic mattress cover use in combination were significantly associated with HDM sensitization (Table 2). The population attributable fractions for HDM sensitization associated with sheepskin or plastic mattress cover use in infancy, if causal, were as follows: 8.8% for sheepskin; and 26.2% for plastic mattress cover. The use of a foam mattress in infancy was not prospectively associated with an increased risk of sensitization to HDM. The results in Table 2 were not altered when the SPT cut-off was 2 mm.

Among children exposed only to plastic mattress covers in infancy, there was no significant association with childhood sensitization to the other primarily indoor aeroallergens, cat (unadjusted RR 0.60 (0.18, 1.97)) or alternaria (unadjusted RR 1.46 (0.55, 3.90)). Moreover, there was no association with exposure to sheepskin and/or plastic mattress cover as an infant and subsequent ryegrass sensitization. A childhood history of asthma or hayfever was significantly associated with HDM sensitization. Hayfever in childhood was also significantly associated with use in infancy of sheepskin alone (adjusted RR 2.26

(1.19, 4.32)  $P = 0.013$ ). The use of plastic mattress covers alone in infancy was associated with hayfever in childhood (adjusted RR 1.78 (1.09, 2.90)  $P = 0.022$ ).

Further adjustment for at-birth family history of asthma did not alter the results in Table 2. There was no evidence that parents of infants with an at-birth family history of asthma were selectively avoiding sheepskins (37.1% use vs. 37.0% non-use,  $P = 0.953$ ) as part of a bed allergen reduction strategy, nor were they selectively using a plastic mattress cover (38.8% use vs. 34.8% non-use,  $P = 0.376$ ). Exposures to sheepskin (unadjusted RR 2.12 (0.94, 4.80)) or plastic mattress cover (unadjusted RR 1.89 (1.01, 3.55)) tended to be positively associated with HDM sensitization even among the subgroup of those with no at-birth family history of asthma. The positive association with either sheepskin use or plastic mattress cover use in infancy and subsequent HDM sensitization remained significant after adjustment for the child's history of eczema, hayfever and asthma, and also the family history of asthma in 1997.

We found that usual infant sleep position was not significantly associated with HDM sensitization. The association between sheepskin and HDM sensitization or plastic cover and HDM sensitization did not vary by whether child slept prone or not. Similar patterns to Table 2 were also found using *D. pteronyssinus* or *D. farinae* as individual species-specific outcomes.

## Discussion

In this birth cohort, the use of sheepskin or the use of plastic mattress covers in infancy were associated with an increased risk of HDM sensitization in childhood. The lack of an association with ryegrass sensitization is consistent with an exposure effect acting principally on inhaled allergens present in the bedding environment. No association was found between either foam mattress use or infant sleep position and HDM sensitization.

The strengths of this study include prospective infant bedding measures, the ability to examine many potential confounders and the availability of a biological parameter to HDM sensitization among the child sample. The study sample was not representative of all live births in the geographical area, it consisted of infants born at higher risk of SIDS [26]. However, none of the cohort entry criteria predicted HDM sensitization. After controlling for the factors listed in Table 2, additional individual adjustment for any scoring system components did not alter the results. The results are not likely to be influenced by differential follow-up as the proportion of TIHS children followed up from infancy did not differ by the type of bedding to which they were exposed. In addition, we were able to control for other bedding variables that are associated with underbedding plus a large number of potential confounding factors operating in either infancy or childhood. There was a good follow-up rate and the children in this study should not differ from other children to any large extent with regard to the development of allergic sensitization. Furthermore, there was no recall bias as the exposure was measured prospectively and was independent of disease awareness. At the time of assessment for HDM sensitization, the nurse was also unaware of the infant bedding status.

Personal exposure measures to HDM allergen levels were not available. Furthermore, there is uncertainty concerning the most appropriate measures of personal exposure thus, further studies which measure (i) inhaled HDM dose [36], (ii) HDM allergen levels both on the mattress surface [13] and in the bedding [2], and (iii) bedding composition arrangements during early infancy, are needed to assess to what extent the positive association between sheepskin and HDM sensitization is mediated by higher exposure to inhaled HDM allergens.

Confounding, including that due to family history of asthma, could not explain the identified associations. In fact, the risk ratio increased after adjustment for significant confounders, showing the importance of being able to take these into account. Previous work indicates that underbedding may increase the risk of HDM sensitization by allergen loading and/or a potentiation of bedding allergenicity [34]. Infant sheepskins may harbour very high levels of mites and potentially serve as an important source of exposure for infants. Moreover, it has been shown that the high levels of airborne HDM allergens experienced during sleep are generated from the bedding and not from the floor [37].

The increased risk of sensitization to HDM in those children exposed to plastic mattress covers in infancy demonstrated in this study is unexpected as previous studies have shown mattress covers to be effective in reducing the amount of house dust mite allergen in the bed [38, 39]. Occlusive bedding covers are advocated as an important avoidance measure to mite allergens [19, 20]. Far fewer mites have been collected from cot mattresses which were either vinyl topped or covered with a plastic coverslip than were collected from a cot mattress with a cotton top alone [15]. Yet, despite allergen levels being dramatically reduced in the weeks after the introduction of such covers [38], long-term effectiveness is unknown. A meta-analysis [40] found that bedding changes aimed at reducing exposure to allergens from house dust mites seem to be ineffective, even among the subgroup on whom effective allergen reduction was documented. This could be because, even though beneficial in relation to HDM allergen reduction, there may be other adverse effects from the barrier method used. The finding that exposure to plastic mattress covers is not associated with other indoor allergen sensitization does not mean that HDM loading is the only mechanism. Plastic mattress covers release VOC which in animal models produce airway inflammation and airflow limitation after a brief 1-h exposure [10]. Furthermore the presence of these compounds in the bedroom has been associated with Th2 deviation and increased allergen sensitization in children [24]. This could specifically affect house dust mites. One possibility is that VOC and HDM interaction at the bedding site is greater than at other locations. Sleeping infants whose airway is in close proximity to the covers may be exposed to high concentrations of these compounds for considerable periods of time [10]. Sensitization to inhaled allergens such as house dust mite could thus be enhanced either by airway inflammation resulting in increased airway permeability and enhanced allergen presentation to the immune system [9, 10, 41–44], by volatile organic compound induced Th2 deviation [24, 45, 46] or a combination of both.

In conclusion, this study has shown that an infant's underbedding in the form of sheepskins and the use of plastic mattress covers are associated with the development of HDM sensitization in childhood. Infants spend a significant proportion of their

time in bed with consequent opportunity for prolonged exposure to adverse environmental influences. Furthermore bedding is a readily modifiable environmental factor. Sheepskins are commonly used in infant bedding in New Zealand and Australia. Although they may have a more restricted use world-wide, due to their high content of HDM allergen [15, 17], they indicate a likelihood of a high infant exposure to HDM allergen when in the bed. Plastic mattress covers are used throughout the world as part of infant bedding. Our results support current recommendations [47] that the use of sheepskins as infant bedding in atopic families is inappropriate because they are responsible for significantly greater exposures to HDM allergens and also suggest that greater attention and further study should be given to other potentially adverse environmental factors related to the bedding environment such as VOC.

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Appendix 4

**Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, Carmichael A. A prospective association between cocoon use in infancy and childhood asthma. Paediatric and Perinatal Epidemiology 2004; July 18(4):281-289.**

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# A prospective association between cocoon use in infancy and childhood asthma

L. F. Trevillian<sup>a</sup>, A. L. Ponsonby<sup>a,b</sup>, T. Dwyer<sup>b</sup>, L. L. Y. Lim<sup>a</sup>, A. Kemp<sup>d</sup>, J. Cochrane<sup>b</sup> and A. Carmichael<sup>c</sup>

<sup>a</sup>National Centre for Epidemiology and Population Health, The Australian National University, Canberra, <sup>b</sup>Menzies Centre for Population Health and <sup>c</sup>Department of Paediatrics and Child Health, University of Tasmania, Hobart, and <sup>d</sup>Department of Allergy, Immunology and Infectious Diseases, The Children's Hospital, Westmead and Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia

## Summary

### Correspondence:

Dr Leigh F. Trevillian,  
National Centre for  
Epidemiology and Population  
Health, The Australian  
National University, Canberra  
ACT 0200, Australia. E-mail:  
leigh.trevillian@anu.edu.au

There is increasing evidence for a role for bedding items in the development of asthma. The use of some forms of synthetic bedding, such as foam mattresses and pillows, is associated with a significantly increased risk of childhood wheeze. Our aim was to examine prospectively whether the use of synthetic cocoon/baby nests in infancy is associated with the subsequent development of wheeze in childhood. Data collected in 1988 as part of the Tasmanian Infant Health Survey were linked to the cross-sectional Childhood Asthma Survey conducted in 1995 in Tasmania, Australia.

We were able to match 863 records out of the 1111 in the 1988 survey. Information including parental, child-care, and the infant's sleeping environment was collected at home interview in 1988 when the infant was 1 month of age. Data including sleep environment and asthma symptoms were available for each child at age 7 years. A generalised linear model was used to calculate the adjusted relative risk (RR) estimates for symptoms of wheeze and infant cocoon use. For children who were placed in a cocoon in infancy, there was an increased risk of recent wheeze (adjusted RR = 4.33 [95% CI 2.08, 9.02]) and night wheeze (adjusted RR = 3.35 [95% CI 1.52, 7.39]) at age 7 years.

In view of the increasing prevalence of childhood asthma, the identification of potentially modifiable environmental factors which might operate in infancy is of importance. The present findings implicate infant bedding choice as a significant factor and further studies on the infant sleeping environment are indicated.

## Introduction

Bedding items, and more specifically their material composition, are gaining recognition for their possible role in childhood asthma. The use of synthetic bedding (foam mattresses, pillows, blankets) is associated with a significantly increased risk of childhood wheeze in children from varying world environments.<sup>1-4</sup>

Indoor environmental factors, notably inhalant allergens such as house dust mite (HDM), are well recognised as contributing to childhood asthma.<sup>5,6</sup> Bedding is a major source of HDM<sup>7,8</sup> and HDM levels have been shown to vary within different composite bedding materials. Significantly higher levels of dust mite allergens<sup>9-11</sup> are found in synthetic bedding than in feather bedding. *Dermatophagoides pteronyssinus* (Der

p) allergen levels (recorded as geometric means) have been found to be 5-8 times greater in synthetic pillows than in feather pillows.<sup>10,12</sup>

In addition to mattresses, pillows and doonas or quilts, there are other infant synthetic bedding items such as cocoons/baby nests that might influence asthma development or symptoms. Cocoons are similar to a padded sleeping bag with a hood that comes close to the sides of the baby's head, fully encasing the infant, leaving only the face exposed (Fig. 1). While lying within the cocoon, the infant is then placed on a flat surface or in the cot or pram. A pillow is usually not used in conjunction with a cocoon nor, unless it is exceptionally cold, would it be necessary to place an additional covering on top of an infant lying within a

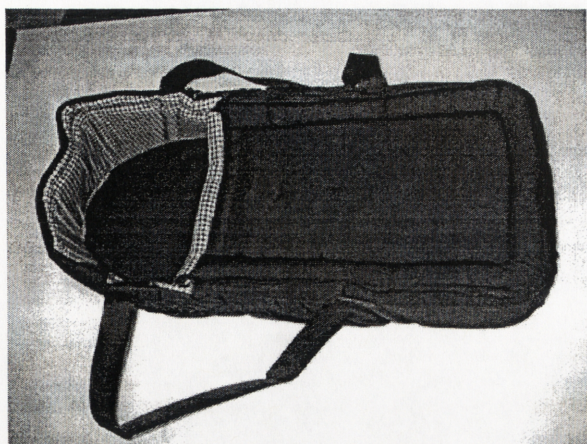


Figure 1. Infant cocoon.

cocoon. If attached, straps allow the cocoon to be hand carried or tied against the mother's chest. Infants placed in cocoons or baby nests may spend prolonged periods of time with their airways in closer proximity to the cocoon material than if placed on a pillow and/or covered with a quilt, potentially increasing any adverse effect on health mediated by close proximity. There is currently no specific advice with regard to asthma prevention and the use of cocoons containing synthetic materials in infancy.

In this prospective study, we examine the relationship between the use of cocoons/baby nests in infancy and the subsequent development of wheeze in childhood.

## Methods

### *The Tasmanian Infant Health Survey (TIHS)*

The TIHS was a cohort study of infants born over an 8-year period 1988–95 in Tasmania, Australia. This study operated from hospitals where approximately 93% of births in Tasmania occurred. Newborn infants were scored to assess the risk of sudden infant death syndrome (SIDS) using perinatal entry criteria based on maternal age, birthweight, gender, breast feeding, season of birth and duration of second stage of labour.<sup>13</sup> Infants exceeding a scoring cut-off were eligible for inclusion together with all multiple births. The eligibility criteria and study methods are discussed in more detail elsewhere.<sup>14</sup> From 1988 to 1995, a total of 9826 (89%) of eligible infants participated in hospital and home interviews.

Data were obtained on three occasions. The first interview was conducted in hospital on the fourth day of the infant's life. A home interview was conducted during the fifth postnatal week, and a telephone interview at approximately 10 weeks postnatally. At the home interview, data were collected on a number of parental, infant, environmental and child-care factors. Data were collected on the infant's sleeping environment, including type of pillow, mattress coverings, mattress types and bed. Use of a cocoon at time of interview or intention to use a cocoon in cold weather was recorded, thereby avoiding the effect of current season when interviewed. In 1994, further details regarding cocoons and sleeping bags were collected. At least 84% of cocoons were noted to be either quilted or padded by the research nurse at the 1 month home interview. In addition, infant cocoons manufactured and sold in Southern Tasmania during the study period most commonly comprised outer coverings of cotton or polycotton with a polyester (synthetic) filling.

### *The 1995 Childhood Asthma Survey*

In 1995, a cross-sectional survey was conducted on all children who turned 7 years of age in Tasmania. This survey included 863 (78%) of the 1111 children who were born in 1988 and participated in the TIHS home interview. Children were identified through primary schools, home learning and distance education organisations. Data included sleeping environment and asthma symptoms, using questions from the International Study of Asthma and Allergies in Childhood.<sup>15</sup> The child's age (in completed years) at onset of wheezy breathing or asthma was obtained. We linked the 1995 asthma data of the 863 children for whom a home interview had occurred at 1 month of age in 1988 as part of the TIHS (Fig. 2).

### *Definitions*

*Recent wheeze* refers to one or more wheeze episodes over the past 12 months. *Nocturnal wheeze* is defined as the child's sleep being disturbed one or more nights per week in the past 12 months due to wheezing. In accordance with ISAAC terminology, a *history of asthma* refers to a positive response to the question, 'Has your child ever had asthma?'<sup>15</sup> A *family history of asthma* was defined as asthma in any of the infant's siblings, parents or grandparents.



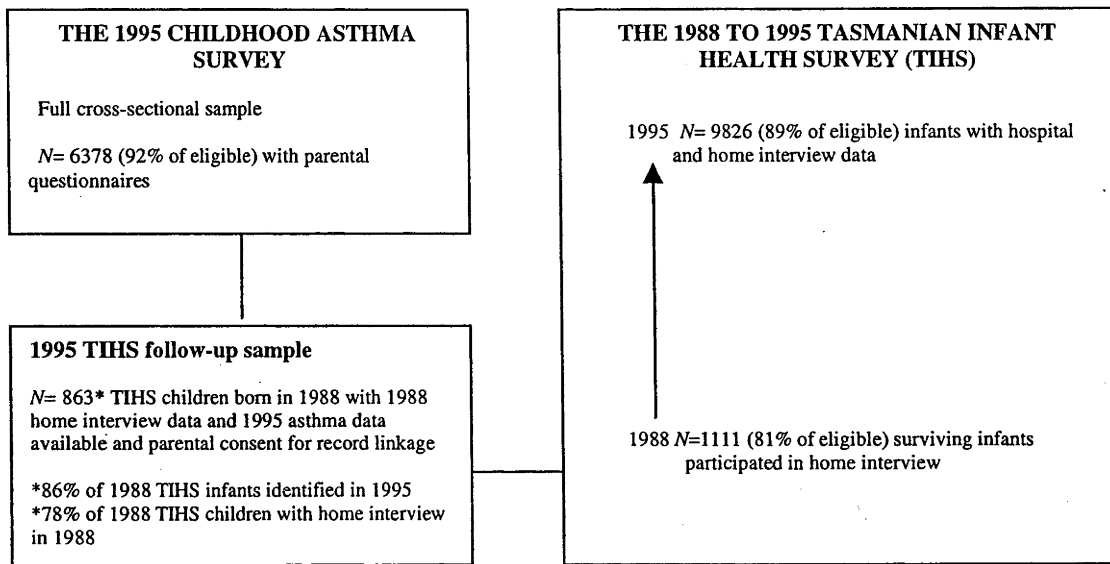


Figure 2. The relation between the Tasmanian Infant Health Survey and the 1995 Childhood Asthma Survey.

### Statistical methods

The bedding exposure variable of interest was cocoon use in infancy and was dichotomous for exposure or no exposure. The dichotomous outcome variables were the child's recent wheeze, night wheeze or asthma ever. A generalised linear model with a log link function and binomial error structure was used to control simultaneously for multiple confounders and to obtain confidence intervals for relative risk (RR) estimates.<sup>16</sup>

To identify potential confounders, we examined the association between a large number of factors and childhood wheeze (Table 1). We further examined how these factors related to cocoon bedding. We examined more than 40 confounders to see how they each related separately to cocoon use and wheeze. A generalised linear model was then constructed as follows. Each potential confounder<sup>17</sup> was individually added to the model as a covariate if the variable was associated with wheeze in the exposure to outcome analysis, or had been reported to be related to asthma in the literature. We examined the confounding effect of these factors on the exposure-disease association using change-in-estimate methods.<sup>18</sup> Those factors that altered the point estimate for the exposure-wheeze association by 10% or more were included in the final model. In addition, we then added in the remaining variables in Table 1 as individual factors into the final model. None of these factors altered the adjusted risk ratios reported in

Table 2 and were not retained in the final confounder set.

Pearson chi-square test was used to explore further the possible associations between the explanatory variables. Logistic regression was not used because in asthma epidemiological studies, where the proportion of the children with the disease is large, odds ratios will not approximate RRs well.<sup>19</sup> We assessed the relation between infant cocoon use and age of onset of asthma symptoms using discrete proportional hazard modelling.<sup>20</sup> The aetiological fraction of asthma in childhood attributable to cocoon use in infancy we calculated as  $p(aRR - 1)/aRR$ , where  $p$  denotes the proportion of children with cocoon use in infancy among those with the outcome of asthma and  $aRR$  equals the RR estimate for cocoon use and asthma, after adjustment for the confounders listed in Table 2. We conducted the analysis using statistical software, STATA 7.0.<sup>21</sup>

### Results

The 863 subjects (78%) of the TIHS cohort who had a home interview agreed to participate. In 1995 their mean age was 6.9 years (standard deviation = 0.6). Data were available for recent wheeze, night wheeze and asthma ever on 823, 834 and 863 children, respectively. Data on use of cocoon in infancy was available on 802 children. The prevalences of asthma ever and recent wheeze were high, 32.4% (280/863) and 27.0%

Table 1. Identification of potential confounders: unadjusted relative risk (RR) for infant cocoon use and childhood wheeze

	Recent wheeze in 1995 Unadjusted RR [95% CI]	P-value	Cocoon use in infancy Unadjusted RR [95% CI]	P-value
<b>Exposure variables</b>				
Cocoon	2.00 [1.29, 3.12]	0.002	–	
<b>Potential confounding variables</b>				
<i>Parental factors</i>				
Mother smoked during pregnancy	1.41 [1.12, 1.77]	0.003	2.33 [0.89, 6.07]	0.083
Teenage motherhood <sup>a</sup>	1.19 [0.90, 1.56]	0.225	0.86 [0.26, 2.93]	0.814
Family history of asthma at child's birth	1.50 [1.20, 1.88]	<0.001	1.31 [0.53, 3.22]	0.557
Family history of asthma in 1995	2.27 [1.72, 2.99]	<0.001	3.55 [1.03, 12.26]	0.045
Low maternal education at child's birth	1.13 [0.63, 2.03]	0.678	0.66 [0.14, 3.16]	0.602
Low paternal education at child's birth	1.24 [1.04, 1.93]	0.023	0.77 [0.27, 2.18]	0.618
Maternal postnatal smoking at 1 month	1.38 [1.10, 1.73]	0.006	2.66 [1.02, 6.92]	0.037
Maternal smoking at child age 7	1.45 [1.15, 1.81]	0.001	4.42 [1.45, 13.44]	0.004
Duration of second stage labour (5, 15 vs. 0, 5 min) <sup>a</sup>	1.09 [0.85, 1.39]	0.497	2.15 [0.88, 5.22]	0.084
Duration of second stage labour (CS vs. 0, 5 min) <sup>a</sup>	1.00 [0.75, 1.34]	0.989	0.25 [0.03, 1.84]	0.136
Season of birth (May–Jun vs. Mar–Apr) <sup>a</sup>	1.12 [0.88, 1.43]	0.344	0.62 [0.21, 1.86]	0.393
Season of birth (Aug–Feb vs. Mar–Apr) <sup>a</sup>	1.02 [0.81, 1.28]	0.854	2.80 [1.07, 7.29]	0.028
<i>Infant factors</i>				
Male sex <sup>a</sup>	1.42 [1.08, 1.88]	0.010	0.90 [0.35, 2.33]	0.825
Infant first born	1.06 [0.85, 1.33]	0.604	0.50 [0.18, 1.37]	0.166
Low birthweight <sup>a</sup>	0.99 [0.75, 1.30]	0.916	0.64 [0.19, 2.17]	0.467
Intention to bottle feed at birth <sup>a</sup>	1.26 [1.01, 1.58]	0.045	1.79 [0.73, 4.40]	0.199
Multiple births <sup>a</sup>	0.89 [0.62, 1.27]	0.504	0.77 [0.18, 3.30]	0.726
Prematurity	1.06 [0.80, 1.41]	0.673	0.53 [0.12, 2.27]	0.382
Solid food introduced, by phone interview at 10 weeks	1.30 [1.04, 1.72]	0.024	1.36 [0.56, 3.31]	0.494
Infant exclusively breast fed, by phone interview at 10 weeks	0.67 [0.49, 0.92]	0.009	0.18 [0.02, 1.36]	0.060
<i>Childhood factors</i>				
History of eczema	1.75 [1.39, 2.20]	<0.001	1.76 [0.68, 4.56]	0.240
History of hay fever	2.87 [2.34, 3.52]	<0.001	2.03 [0.79, 5.26]	0.137
History of bronchitis	2.58 [2.08, 3.21]	<0.001	1.46 [0.55, 3.89]	0.452
History of pneumonia	1.87 [1.40, 2.50]	<0.001	–	
Child's fish consumption vs. none	0.76 [0.57, 1.02]	0.082	0.75 [0.22, 2.54]	0.642
No siblings in 1995	1.68 [1.18, 2.38]	0.009	–	
<i>Household factors</i>				
Private health insurance at birth	0.71 [0.55, 0.91]	0.005	0.90 [0.36, 2.27]	0.827
Home gas appliance use in infancy	1.25 [0.73, 2.16]	0.439	1.79 [0.25, 12.89]	0.559
No-one smoking in same room as infant	0.72 [0.56, 0.93]	0.009	0.60 [0.22, 1.65]	0.317
More than six residents in household at birth	0.90 [0.65, 1.26]	0.549	0.68 [0.16, 2.90]	0.599
Cat as pet during infancy	1.09 [0.86, 1.37]	0.491	0.53 [0.18, 1.59]	0.249
Paternal full-time employment at child age 7	0.91 [0.72, 1.15]	0.446	0.77 [0.31, 1.93]	0.573
<i>Bedroom factors – infant</i>				
Use of foam pillow at age 1 month	1.27 [0.92, 1.75]	0.159	2.19 [0.74, 6.44]	0.149
Infant sleeping in bedroom alone	0.84 [0.65, 1.09]	0.180	0.44 [0.13, 1.49]	0.171
Carpet in infant's bedroom	0.89 [0.62, 1.28]	0.535	0.30 [0.11, 0.80]	0.013
Humidity in infant's bedroom >75%	1.22 [0.79, 1.88]	0.389	0.87 [0.12, 6.35]	0.888
Window in infant's bedroom open at night	1.05 [0.83, 1.32]	0.690	1.26 [0.52, 3.05]	0.616
Sheepskin underbedding	0.99 [0.78, 1.27]	0.962	0.12 [0.02, 0.91]	0.014
Plastic mattress liner	0.99 [0.79, 1.25]	0.933	0.88 [0.35, 2.22]	0.792
Foam mattress as infant	1.05 [0.83, 1.33]	0.705	1.58 [0.58, 4.35]	0.367

Table 1. Continued

	Recent wheeze in 1995		Cocoon use in infancy	
	Unadjusted RR [95% CI]	P-value	Unadjusted RR [95% CI]	P-value
Use of feather quilt	0.74 [0.21, 2.57]	0.619	–	
Use of synthetic quilt	1.05 [0.84, 1.33]	0.654	0.19 [0.06, 0.65]	0.003
Use of feather pillow	0.94 [0.35, 2.51]	0.894	3.98 [0.58, 27.28]	0.141
Use of synthetic pillow	1.29 [0.97, 1.72]	0.086	1.51 [0.51, 4.48]	0.455
Use of air freshener in infant's bedroom	1.52 [1.04, 2.22]	0.047	4.25 [1.47, 12.30]	0.005
<i>Bedroom factors – child</i>				
Sleeping on bottom bunk as child	1.11 [0.81, 1.52]	0.509	–	
Use of feather quilt	0.85 [0.68, 1.07]	0.166	0.51 [0.20, 1.33]	0.158
Use of synthetic quilt	1.29 [1.03, 1.61]	0.027	3.06 [1.18, 7.97]	0.016
Use of feather pillow	0.86 [0.53, 1.38]	0.516	0.70 [0.09, 5.14]	0.722
Use of synthetic pillow	1.04 [0.71, 1.54]	0.825	0.58 [0.17, 1.95]	0.375
Carpet in child's bedroom	0.93 [0.58, 1.49]	0.755	0.49 [0.12, 2.06]	0.322

\*The cohort entry scoring system was based on a composite score derived from these factors.<sup>13</sup> Multiple births were automatically included.

(222/823), respectively. The prevalence of night wheeze was 19.2% (160/843) and cocoon use in infancy 2.4% (19/802).

Table 1 shows that cocoon use in infancy was associated with recent wheeze in childhood (RR = 2.00 [95% CI 1.29, 3.12]). The use of a cocoon in infancy was associated with both night wheeze (RR = 2.27 [95% CI 1.31, 3.93]) and history of asthma ever (RR = 1.63 [95% CI 1.05, 2.53]) in childhood.

To identify potential confounders, we examined how each factor related separately to the use of cocoon in infancy and also to recent wheeze. The infant factors of most relevance are summarised in Table 1. Potential confounders included: small sibling size,<sup>22</sup> infant and child exposure to tobacco smoke<sup>23</sup> and home gas heating,<sup>23</sup> infant synthetic pillow use,<sup>24</sup> sheepskin use and

season of birth. An at-birth family history of asthma was not significantly associated with cocoon use in infancy; however, it was related to subsequent development of recent wheeze (RR = 1.50 [95% CI 1.20, 1.88]). Both childhood and infant exposure to maternal smoking were associated with wheeze. In fact, 88% of mothers who smoked when their infant was 1 month of age, were still smoking when their child was aged 7 years. The association between infant and childhood maternal tobacco smoke exposure was highly significant ( $P = 0.0001$ ).

The association between cocoon use and recent wheeze remained after adjustment for the perinatal entry criteria as either individual factors or as a set. Adjustment for mattress type and mattress cover type, including sheepskin or plastic mattress cover, had lit-

Table 2. The association between cocoon use in infancy and asthma symptoms in childhood

Respiratory symptom in 1995	n	Cocoon use in infancy	%	RR [95% CI] for cocoon use and respiratory symptom	P-value	aRR [95% CI] for cocoon use and respiratory symptom	P-value
No wheeze	559	9	1.6	1.00 [Reference]		1.00 [Reference]	
Recent wheeze	196	10	5.1	2.00 [1.29, 3.12]	0.002	4.33 [2.08, 9.02]	<0.001 <sup>a</sup>
No night wheeze	626	11	1.8	1.00 [Reference]		1.00 [Reference]	
Night wheeze	148	8	5.4	2.27 [1.31, 3.93]	0.003	3.35 [1.52, 7.39]	0.003 <sup>b</sup>
No asthma ever	539	9	1.7	1.00 [Reference]		1.00 [Reference]	
Asthma ever	262	10	3.8	1.63 [1.05, 2.53]	0.029	2.56 [1.33, 4.92]	0.005 <sup>c</sup>

<sup>a,b,c</sup>Adjusted for family history of asthma at birth, home gas appliance use in infancy, synthetic quilt use in infancy, synthetic pillow use in infancy, maternal education at birth, maternal smoking at infant 1 month age, no other siblings in 1995. CI, confidence interval.

the effect but additional adjustment for synthetic quilt or pillow use in infancy further increased the association between cocoon use and childhood wheeze (adjusted RR [aRR] = 4.33 [95% CI 2.08, 9.02]) (Table 2). Similarly, the association remained significant between the use of cocoon in infancy and night wheeze (aRR = 3.35 [95% CI 1.52, 7.39]), and with a history of asthma (aRR = 2.56 [95% CI 1.33, 4.92]) (Table 2). The population attributable fraction for recent wheeze in childhood associated with cocoon use in infancy was 4.3%.

We examined the association with family and childhood history of atopic disease. Further adjustment for at-birth family history of asthma did not alter the results in Table 2, and the positive association with cocoon use in infancy and recent wheeze remained significant after adjustment for the child's history of eczema and asthma, and also the family history of asthma in 1995. These positive associations persisted after adjustment for the factors listed in Table 2 and individual adjustment for over 40 possible confounders including those listed above. The parents of infants with an at-birth family history of asthma were not selectively using cocoons (42.1% use vs. 35.6% non-use,  $P = 0.56$ ). Exposure to cocoon was positively associated with recent wheeze (RR = 2.56 [95% CI 1.45, 4.51]  $P = 0.001$ ) even among children without an at-birth family history of asthma. The use of cocoon in infancy did not relate to age of onset of wheeze (aRR = 0.83 [95% CI 0.30, 2.31]) overall nor to wheeze frequency subgroups of moderate (4–12) or frequent (>12) episodes of wheeze.

## Discussion

In this birth cohort, the use of cocoon/baby nests in infancy was associated with an increased risk of recent wheeze and nocturnal wheeze in childhood. Close proximity to the airways combined with the infant's prolonged exposure to the cocoon material may have contributed to this finding. The prospective association remained after adjustment for other synthetic bedding items in infancy. Our findings indicate that atopic children were not preferentially using or avoiding the use of cocoons as evidenced by the lack of association with eczema and rhinitis in infancy and an at-birth family history of asthma. The adverse role of synthetic bedding on asthma has been demonstrated in previous studies; however, currently there is no evidence with

regard to the use of cocoons containing synthetic materials in infancy.

The strengths of this study include the availability of prospective infant data, a high participation rate and the ability to control for multiple confounders, including bedding variables and other potential confounding factors operating in either infancy or childhood. The study sample was not representative of all live births in the geographical area; it consisted of infants born at higher risk of SIDS.<sup>14</sup> The eligibility criteria were well defined and the potential effects of the entry scoring system components were taken into account in the multivariate analyses. After controlling for the factors listed in Table 2, further adjustment for these perinatal entry criteria did not alter the results. Thus the TIHS cohort entry criteria are unlikely to affect the generalisability of these results. The children in this study should not differ from other children to any large extent with regard to the biological development of asthma.

As the exposure was measured prospectively and was independent of disease awareness, there was no recall bias. At the time of assessment for wheeze, the nurse was also unaware of the infant bedding status. The results are not likely to be influenced by differential follow-up as the proportion of TIHS children followed up from infancy did not differ by whether they used a cocoon or not. Cocoons manufactured and sold during the study period most commonly comprised synthetic materials. However some infants may have been exposed to cocoons made of natural materials. This could lead to misclassification of the dichotomous exposure. This misclassification would be likely to be non-differential<sup>17</sup> and therefore, if present, it would reduce the study's ability to detect the effect of cocoon use on wheeze.

Confounding, including that due to infant or child exposure to maternal smoking or family history of asthma, could not explain the identified associations. We included only one variable for maternal smoking, when infant was aged 1 month, as a potential confounder in the final model due to the high collinearity between this variable and the variable for maternal smoking when child was aged 7 years. Limitations of this study included the use of a parental questionnaire and the absence of a biological or physician assessment of asthma. The ISAAC questionnaire, however, is considered a valid instrument for the determination of current asthma symptoms in the past 12 months; the report of 'wheeze' over the past 12 months has a sen-

sitivity of 0.85 and a specificity of 0.81 for the physician diagnosis of asthma in childhood.<sup>25</sup> The prospective findings in this study were, however, based on a small number of exposed children and further studies are required to confirm these findings. It is important to note that no study to date has shown a lower wheeze prevalence with exposure to synthetic bedding.<sup>1-4</sup> Moreover, we have previously reported<sup>24</sup> that the association between synthetic upper bedding and frequent wheeze in childhood displayed the features of high strength of association, temporality, dose-response and consistency.<sup>17</sup>

Cocoons provide an intimate and prolonged relationship between the cocoon material and the infant's breathing zone. Thus one possibility for the effect noted in this study is that exposure to dust mite allergen in synthetic cocoons could contribute to the increased development of wheeze in children. Bedding items may be particularly relevant to the development or triggering of asthma symptoms due to their proximity to the airway and their prolonged periods of exposure in addition to bedding allergen levels. Air sampling has identified that the bed is a major site of exposure to HDM allergens with airborne HDM allergen levels shown to be 10-fold higher during sleep than in the living room during the day.<sup>26</sup> Exposure to HDM allergen is a factor in triggering attacks of asthma in asthmatic subjects,<sup>27</sup> with a clear dose-response relation demonstrated between levels of Der p 1 in the home and current asthma symptoms.<sup>28,29</sup>

Two population-based case-control studies<sup>30</sup> investigated the association between childhood wheeze in schoolchildren 7-8 years of age and changes in the home environment between 1978 and 1991 in Croydon, London. The study found that of the potential indoor environmental risk factors examined, the increasing use of non-feather pillows (from 44% in 1978 to 67% in 1991) explained greater than half of the 20% increase in the population prevalence odds of current wheeze (OR = 1.20 [95% CI 1.04, 1.39]). The use of non-feather pillows was positively associated with childhood wheeze (OR = 1.54 [95% CI 1.13, 2.10]). A case-control study of children in Sheffield, UK,<sup>31</sup> found that pillows with synthetic fillings were a risk factor for severe childhood asthma (OR = 2.78 [95% CI 1.89, 4.17]), after the exclusion of asthmatic subjects whose bedding had been changed because of their disease. These results prompted speculation that the increase in the use of non-feather pillows contributed to the increasing exposure to HDMs, which in turn could

have been partly responsible for the increase in childhood wheezing.<sup>32</sup> In a cross-sectional study of children in Canberra, Australia, synthetic quilt use was associated with asthma (AOR = 1.67 [95% CI 1.05, 2.65]) and recent wheeze (AOR = 2.11 [95% CI 1.33, 3.34]) among SPT-positive to aeroallergens, including Der p, children but not SPT-negative children.<sup>33</sup>

These results support the view that if the adverse respiratory effect of synthetic bedding such as cocoons, is mediated by the previously documented higher HDM allergens found in synthetic bedding,<sup>10-12</sup> this adverse effect would be more evident among children who were sensitised to aeroallergens rather than non-sensitised children.

Other mechanisms, related to bedding items, may be contributing to childhood wheezing. An increased risk of asthma related to the indoor emissions of volatile organic compounds (VOCs) has been demonstrated in children and adults,<sup>34-36</sup> and VOCs released in low concentrations close to the breathing zone might increase mucosal permeability to inhaled allergens<sup>31</sup> or promote sensitisation to HDM within the household environment similar to that which has been observed for indoor gas heating<sup>37</sup> or other infant bedding materials.<sup>38</sup> Exposure to house dust endotoxin may protect against the development of atopy by enhancing Th1 responses.<sup>39</sup> A study<sup>40</sup> of 61 infants with a high risk for developing asthma in Colorado, USA, showed that allergen sensitised infants had significantly lower house dust endotoxin levels than non-sensitised infants. However recent reports<sup>41</sup> that endotoxin levels were not significantly different between synthetic and feather pillows makes this a less likely mechanism of action. The exposure to the bedding environment may be further increased as the infant is often transported from the bed to other locations while still remaining within the cocoon. In addition, with the close proximity of the synthetic cocoon material to the infant's airway it is likely that exposure to bedding-related factors such as allergens, VOCs or endotoxins occurs in a continuous low dose fashion.

In conclusion, this study adds to the increasing evidence for a role for bedding items in the development of childhood asthma. Our findings suggest that synthetic cocoon use in infancy is associated with an increased subsequent risk of child asthma. However, the number of children exposed to cocoons in this cohort study was small and further studies are now required to confirm these findings. The contribution of infant bedding to the increasing problem of childhood

asthma must be more clearly determined in view of the implications of bedding modification for both primary and secondary preventative measures for childhood asthma.

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Appendix 5

**Ponsonby AL, Dwyer T, Trevillian L, Kemp A, Cochrane J, Couper D, Carmichael A. The bedding environment, sleep position, and frequent wheeze in childhood. *Pediatrics* 2004; May 113(5):1216-22.**

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## The Bedding Environment, Sleep Position, and Frequent Wheeze in Childhood

Anne-Louise Ponsonby, PhD, FAFPHM\*†; Terence Dwyer, PhD, FAFPHM‡; Leigh Trevillian, MPH\*;  
Andrew Kemp, PhD, FRACP§; Jennifer Cochrane, BA‡; David Couper, PhD||; and  
Allan Carmichael, MD, FRACP¶

**ABSTRACT.** *Objective.* Synthetic quilt use has been associated with increased childhood wheeze in previous studies. Our aim was to examine whether the adverse effect of synthetic quilt use on frequent wheeze differed by usual sleep position.

*Design, Setting, and Participants.* A population-based cross-sectional study of 6378 (92% of those eligible) 7-year-olds in Tasmania, Australia, was conducted in 1995. Exercise-challenge lung function was obtained on a subset of 414 children from randomly selected schools.

*Exposure Measures.* Child bedding including pillow and overbedding composition and usual sleep position by parental questionnaire.

*Outcome Measures.* Frequent wheeze (>12 wheeze episodes over the past year), using the International Study of Asthma and Allergies in Childhood parental questionnaire, and baseline and postexercise forced expiratory volume in 1 second lung-function measures.

*Results.* Frequent wheeze ( $n = 117$ ) was positively associated with synthetic quilts, synthetic pillows, electric blankets, and sleeping in a bottom bunk bed but did not vary by sleep position. In a nested case-control analysis, the association between synthetic quilt use and frequent wheeze differed by sleep position. Among children who slept supine, synthetic (versus feather) quilt use was associated with frequent wheeze (adjusted odds ratio: 2.37 [1.08, 5.23]). However, among nonsupine sleepers, overlying synthetic quilt use was not associated with frequent wheeze (adjusted odds ratio: 1.06 [0.60, 1.88]). This difference in quilt effect by sleep position was highly significant. Similarly, synthetic quilt use was associated with lower postexercise forced expiratory volume in 1 second measures among supine but not nonsupine sleeping children.

*Conclusion.* An increasing focus on the bedding environment immediately adjacent to the nose and mouth is required for respiratory disorders provoked by bedding, such as child asthma characterized by frequent wheeze. *Pediatrics* 2004;113:1216–1222; bedding, sleep position, interaction, asthma, wheeze.

ABBREVIATIONS. IIDM, house dust mite; Der p, *Dermatophagoides pteronyssinus*; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; OR, odds ratio.

Bedding can trigger child wheeze, particularly wheeze caused by house dust mite (HDM)-related airway obstruction. Bedding HDM (such as *Dermatophagoides pteronyssinus* [Der p]) levels predict respiratory symptoms and lung function.<sup>1,2</sup> Mattresses and underbedding are significant HDM allergen reservoirs.<sup>3,4</sup> It is less recognized that upperbedding such as quilts also can be a source of HDM exposure during sleep. A 10-fold reduction of airborne IIDM allergen near the face during sleep was obtained by replacing used overlying quilts with new quilts.<sup>5</sup> Recently, synthetic quilts have been shown to have a markedly higher Der p content than feather quilts<sup>6</sup>; the ratio (synthetic/feather) of the geometric mean for Der p ( $\mu\text{g}/\text{m}^2$ ) was 15.45 (95% confidence interval [CI]: 4.28–55.8).<sup>6</sup> Higher HDM allergen levels have been found also in synthetic as compared with feather pillows.<sup>7,8</sup> The higher allergen loading near a child's airway has been proposed as one possible explanation<sup>7,8</sup> for the numerous cross-sectional<sup>9–11</sup> and prospective associations<sup>12,13</sup> between synthetic bedding and childhood wheeze. However, the association may reflect selection bias associated with the preferential choice of synthetic bedding for children at risk of later allergic asthma.<sup>11</sup> Although randomized, controlled trials are constrained by the ethics of applying potentially deleterious synthetic bedding to children with severe wheeze, additional confirmatory evidence is needed from observational studies.

One novel approach to assess the role of bedding in asthma could be to look at the interaction between bedding and different sleep positions with regard to child wheeze. Specifically, if it could be demonstrated that synthetic quilt use, for example, conferred a different risk if a child slept in a different sleep position, then the case for synthetic quilt use being causally related to asthma would be strengthened. If the adverse effect was mediated through some mechanism that involved the bedding being in close proximity to the airway, one would postulate that the association between overlying synthetic quilt use and adverse respiratory outcomes would be observed specifically among children sleeping supine,

From the \*National Centre for Epidemiology and Population Health, Australian National University, Canberra ACT, Australia; †Menzies Centre for Population Health and ‡Department of Paediatrics and Child Health, University of Tasmania, Tasmania, Australia; §Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina; and ¶Department of Immunology, Royal Children's Hospital, University of Melbourne, Melbourne, Australia.

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Address correspondence to Anne-Louise Ponsonby, PhD, FAFPHM, National Centre for Epidemiology and Population Health, Mills Rd, Australian National University, Canberra ACT 0200, Australia. E-mail: anne-louise.ponsonby@anu.edu.au

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during which the face would be closer to overlying bedding.

In the Tasmanian Asthma Survey, synthetic bedding was strongly associated with frequent wheeze.<sup>13</sup> The aim of this report is to examine whether the association between synthetic quilt use and frequent wheeze is significantly stronger among children who slept supine compared with children who slept non-supine.

## METHODS

### The 1995 Tasmanian Asthma Survey

We conducted a cross-sectional survey on all children who turned 7 years old in Tasmania, Australia, identified through primary schools and home-learning and distance-education organizations. By December 31, 1995, questionnaires had been completed for 92% (6378 of 6911) of eligible children.<sup>13</sup> The questionnaire included questions from the International Study of Asthma and Allergies in Childhood.<sup>14</sup> Previous validation work has shown that the report of wheeze over the past 12 months has a sensitivity of 0.81 and a specificity of 0.85 for the physician diagnosis of asthma in childhood.<sup>15</sup>

Sleep position was classified as supine if the parents reported that the child usually slept on the back in response to the question: "What position does your child usually sleep in?" Children usually sleeping on their sides or stomachs were termed nonsupine sleepers. Synthetic pillows were those reported as foam/sponge/tontine/polyester/Dacron. Quilts, doonas, or duvets of Dacron, polyester, or other synthetic composition were classed as synthetic quilts. Overlying bedding was categorized into 3 categories: any synthetic quilt, feather quilt, and other bedding (ie, neither feather nor synthetic quilt). Sheepskin was any wool fleece underbedding with either hide or material backing.

In addition, we conducted full exercise-challenge lung-function testing on 414 children at 23 randomly selected schools in Southern Tasmania; the method is described in detail elsewhere.<sup>16</sup> It included baseline and postexercise spirometric measures of forced expiratory volume in 1 second (FEV<sub>1</sub>), the latter after 6 minutes of free running.<sup>16</sup> These studies were approved by the University of Tasmania Ethics Committee (Human Experimentation), and parents provided informed, written consent.

### Outcome Measurement

Disease misclassification within the broad spectrum of asthma has been a large problem in asthma epidemiology. For this bedding study, we were interested in identifying children who would

be more likely to have HDM-triggered airway disease rather than those with asthma caused by other mechanisms. We chose to compare children with frequent wheeze (>12 episodes in the past year compared with children with no wheeze) for the following reasons: 1) children with asthma who are also sensitized to HDM are more likely to have severe or frequent asthma<sup>17</sup>; 2) feather pillow and quilt use has been inversely associated with severe wheeze<sup>18</sup>; and 3) in our setting, we have reported previously that HDM-sensitized children are much more likely ( $P < .0001$ ) to have frequent wheeze than nonsensitized children in our setting (prevalence ratio 19.6 [95% CI: 6.9, 55.6]).<sup>19</sup> In addition, we examined postexercise FEV<sub>1</sub>, a lung measure previously observed to be lower in children with recent wheeze or asthma.<sup>16</sup>

### Statistical Methods

First, univariate odds ratios (ORs) were calculated by using logistic regression.<sup>20</sup> The reference group chosen for upperbedding was feather quilts, because this bedding type has 1) lower HDM levels<sup>2,8</sup> and 2) has been associated previously with reduced wheeze, compared with synthetic quilts.<sup>10</sup> We examined the interaction between quilt type and sleep position by comparing synthetic and feather quilts. Most children (88.1%) slept under these 2 overbedding types (Table 1). For sleep position, children who slept supine were compared with nonsupine children, and children with no usual sleep position were excluded. The Breslow-Day test was used to examine differences in the association between synthetic versus feather quilt use and severe wheeze by sleep-position strata.<sup>21</sup> We then conducted a nested case-control study among the children who were reported to have a usual sleep position. Each child with frequent wheeze matched to control children with no wheeze over the past year. Each index child was matched to the nearest controls by date of birth who had the same status as the index child with regard to 4 characteristics: gender, foam mattress or not, electric blanket or not, and sheepskin or not. Thus, in the matched analysis, each matched set was standardized with regard to underbedding except for pillow type. Feather pillows and allergen-occlusive mattress covers were too uncommon to allow adequate matching and thus were considered as additional confounders in the matched analyses. In total, 117 children with frequent wheeze were matched to 1162 controls, with up to 10 controls per case. More than 80% of controls were born within a month of the index case. Conditional logistic regression models then were used to examine the relation between quilt use, sleep position, and reported respiratory outcomes, with control for confounders.<sup>20</sup> The difference in the quilt-wheeze associations by sleep position was examined by the log likelihood ratio test for the reduction in deviance associated with the addition of an interaction term into the logistic model.<sup>22</sup> Thus, the interaction is based on a multiplicative model. Any interactions observed would be

TABLE 1. Distribution of Sleeping Environment Characteristics and Respiratory Wheeze in the 1995 Cross-Sectional Study

Characteristic	Total, n	n	% With Variable
Usual sleep position	6355		
Supine (on back) sleep position		2431	38.3
Nonsupine (on side or tummy)		3048	48.0
No usual sleep position or other		876	13.8
Overbedding	6345		
Any synthetic quilt use		2649	41.7
Feather quilt use		2941	46.4
Other overbedding		755	11.9
Pillow	6340		
Any synthetic pillow		5709	90.0
Feather pillow		231	3.6
Other pillow		400	6.3
Sheepskin underbedding	6307	1331	21.1
Electric blanket	6307	1347	21.4
Allergen-occlusive mattress cover	6307	54	0.9
Foam mattress	6363	2038	32.0
Bed type	6354		
Bottom bunk bed		686	10.8
Wheeze frequency over the past year	6107		
None (0 episodes)		4707	77.1
Moderate (1-12 episodes)		1264	20.7
Frequent (>12 episodes)		136	2.2

present also in an additive model, but negative or absent findings cannot be taken to mean that additive interactions are not present.<sup>23</sup> The lung-function sample was relatively small, and thus synthetic quilt use was examined as a dichotomous exposure to maximize the sample size for analysis. Multiple linear regression models were used to examine FEV<sub>1</sub> as a continuous outcome, with adjustment for relevant confounders.<sup>24</sup>

## RESULTS

### General Features

The mean age of the participants was 6.9 years (SD: 0.3), and 50.5% were male. Synthetic pillow or quilt use was common (Table 1). Feather quilt use was also common, but feather pillow use was not. Most parents were able to report a usual child sleep position, with 86% of children with frequent wheeze (117 of 136) or no wheeze (4048 of 4707) reported to have a usual position. More than one third of the children slept supine (Table 1). Among nonsupine children, the side position ( $n = 2564$ ) was much more common than the prone sleep position ( $n = 484$ ). Although many children had recent wheeze (23%), only 2% ( $n = 136$ ) of the children were reported to have had frequent wheeze with >12 episodes in the last year (Table 1).

### Sleeping Environment and Other Characteristics Associated With Frequent Wheeze or Sleep Position

Frequent wheeze was positively associated with the use of a synthetic quilt, synthetic pillow, or electric blanket and sleeping in a bottom bunk (Table 2). A supine sleep position was associated with electric blanket or foam mattress use but not with frequent wheeze, rhinitis, or eczema (Table 2). Asthma medication type and use over the past year did not relate to sleep position. In Australia in 1997, bedding advice to children with asthma included the use of an

allergen-occlusive mattress cover and sheepskin avoidance.<sup>25</sup> Consistent with this, children with frequent wheeze were more likely (OR: 18.39;  $P < .0001$ ) to sleep on allergen-occlusive covers but less likely (OR: 0.54;  $P = .02$ ) to sleep on a sheepskin.

### The Relation Between Overbedding Composition and Frequent Wheeze by Usual Sleep Position

First, we examined the association between quilt use and severe wheeze after stratification by sleep position (Table 2). Among supine sleepers, synthetic (versus feather) quilt use was associated with frequent wheeze (OR: 3.75 [95% CI: 1.78, 8.63]). However, this apparent adverse effect was not evident among nonsupine children (OR: 1.12 [95% CI: 0.65, 1.93]). The difference in synthetic quilt effect by sleep position was significant (test for interaction:  $P = .007$ ). There was no difference in the association between allergen-occlusive cover use or sheepskin use and recent wheeze by sleep position.

Second, we examined the data, taking possible confounding factors into account. We examined the nested case-control sample in which each child with frequent wheeze was matched to controls without wheeze with regard to age, gender, foam mattress use, electric blanket use, and sheepskin use. Again, synthetic compared with feather quilt use was associated ( $P = .02$ ) with severe wheeze among supine sleepers (OR: 2.54 [95% CI: 1.18, 5.48]), but this association was absent for children sleeping on their sides or prone (OR: 1.09 [95% CI: 0.62, 1.92]; test for interaction:  $P = .005$ ). Additional adjustment for synthetic pillow use provided matched ORs of 2.37 (95% CI: 1.08, 5.23) and 1.06 (95% CI: 0.60, 1.88), respectively (test for interaction:  $P = .005$ ). Among nonsupine children, the effect of synthetic versus feather

TABLE 2. The Association Between Sleeping Environment, Child Characteristics, and Frequent Wheeze or Supine Sleep Position in the Tasmanian Asthma Survey

Characteristic (Reference Group)	OR (95% CI) for Frequent Wheeze	OR (95% CI) for Supine Sleep Position
Sleeping environment		
Usual supine position (usual side or prone)	0.90 (0.61, 1.33)	...
Synthetic quilt (feather quilt)	1.74 (1.20, 2.51)	1.03 (0.92, 1.16)
Other overbedding (feather quilt)	1.37 (0.78, 2.39)	0.92 (0.77, 1.10)
Synthetic pillow (feather pillow)	3.24 (1.03, 10.24)	0.98 (0.78, 1.23)
Other pillow (feather pillow)	2.59 (0.57, 11.73)	1.26 (0.88, 1.81)
Sheepskin underbedding (no sheepskin)	0.54 (0.33, 0.90)	1.06 (0.93, 1.20)
Electric blanket (no electric blanket)	1.56 (1.07, 2.29)	1.17 (1.02, 1.33)
Foam mattress (no foam mattress)	1.35 (0.95, 1.92)	1.21 (1.08, 1.36)
Bottom bunk bed (other type of bed)	1.76 (1.08, 2.88)	0.96 (0.81, 1.15)
Overbedding by sleep position		
Among supine sleepers, synthetic (feather) quilt	3.75 (1.78, 8.63)*	—
Among nonsupine sleepers, synthetic (feather) quilt	1.12 (0.65, 1.93)*	—
Among supine sleepers, other overbedding (feather) quilt	2.76 (0.89, 7.90)†	—
Among nonsupine sleepers, other overbedding (feather) quilt	0.99 (0.39, 2.21)†	—
Child characteristics		
Male sex	1.31 (0.93, 1.85)	1.07 (0.96, 1.20)
Premature (<37 wk gestation) birth	2.19 (1.31, 3.64)	0.86 (0.70, 1.06)
Breastfed in infancy	0.61 (0.41, 0.92)	0.93 (0.81, 1.06)
No siblings	1.31 (0.66, 2.62)	0.95 (0.75, 1.21)
Family history of asthma	5.43 (3.50, 8.41)	1.03 (0.92, 1.15)
Eczema	3.69 (2.60, 5.23)	1.12 (0.98, 1.28)
Hay fever	9.05 (6.37, 12.86)	1.11 (0.97, 1.27)

\* Difference in effect by sleep position;  $P = .007$ .

† Difference in effect by sleep position;  $P = .10$ .

## DISCUSSION

An interaction between quilt use and sleep position on respiratory function was observed. There was an adverse effect associated with synthetic quilt use on frequent wheeze and postexercise lung function among children who slept supine but not among children who did not sleep supine. It is of relevance to study the interaction between bedding and different sleep positions, an approach we have used previously in sudden infant death research.<sup>26</sup> For the issue of overlying synthetic quilts and child wheeze, if the adverse effect was mediated through some mechanism that involved the bedding being in close proximity to the airway (such as, but not restricted to, HDM allergen transfer), one would postulate that the association between overlying synthetic quilt use and adverse respiratory outcomes would be observed specifically among children sleeping supine, during which the face would be closer to overlying bedding, as was observed in the present study. In contrast, the adverse effect of an overlying synthetic quilt would be less evident for side- or prone-sleeping children, because other bedding items such as the mattress would be closer to the airway and thus relatively more important than any overlying items such as quilts. A diagrammatic representation of this is shown in Fig 1.

The strengths of this study are a high participation rate, the availability of lung-function and symptom-report data, and the use of frequent wheeze as a study outcome. Frequent wheeze is a better marker of HDM allergen-related wheeze than the global term "asthma," because HDM atopy is strongly related to frequent wheeze.<sup>19</sup> The use of a nested case-control analysis with matching on underbedding reduced the likelihood that underbedding variability contributed to the observed interaction. The cross-sectional design study does not limit the study materially, because the postulated interaction is based on short-term disease processes. Synthetic bedding has been postulated to induce adverse effects through HDM allergen loading,<sup>7</sup> the release of volatile organic compounds,<sup>18</sup> or altered endotoxin exposure.<sup>13</sup> Bronchial provocation with aeroallergen can produce either an immediate or late response with wheeze and FEV<sub>1</sub> reduction.<sup>27,28</sup> Volatile organic compounds can induce a decline in FEV<sub>1</sub> in asthmatic subjects within 1.5 hours of exposure.<sup>29</sup> Inhaled endotoxin can produce a dose-related bronchoconstriction within 6 hours.<sup>30</sup> Thus, bedding-

quilt use did not vary between side- and prone-sleeping children ( $P = .86$ ). The significant difference in quilt effect by sleep position persisted after adjustment for premature (<37 weeks' gestation) birth, breastfeeding history, sibling number, allergen-occlusive mattress cover use, overlying sheet use, home gas use, child exposure to tobacco smoke, or exposure to the other factors listed in Table 2. The interaction effect also persisted after adjustment for child hay fever, eczema, and family history of asthma (test for interaction:  $P = .01$ ). Third, we examined 6 different sleep-position-overbedding combinations with regard to frequent wheeze (Table 3). The baseline group for each pairwise comparison was sleeping supine under a feather quilt. All other sleep combinations were associated with a higher risk of frequent wheeze, and the difference in risk for synthetic quilt use was significant regardless of sleep position used under a synthetic quilt. Fourth, we attempted to examine the effect of pillow composition on frequent wheeze by sleep position. However, this was not possible because of low numbers: only 3 children who slept supine on a nonsynthetic pillow were reported to have frequent wheeze.

### Lung Function

The median FEV<sub>1</sub> in this sample was 1.44 L (interquartile range: 1.30–1.59 L). The results in Table 4 have been adjusted for child age, gender, height, distance run, ambient humidity during exercise, family history of asthma, child exposure to active smoking, and whether asthma medications were taken within 6 hours of testing. Increasing wheeze frequency over the past year was clearly associated with lower postexercise FEV<sub>1</sub> measures. Children with any wheeze episodes over the past year had a lower FEV<sub>1</sub> postexercise than children with no wheeze. Among children who slept nonsupine, synthetic quilt use was not associated with a significant FEV<sub>1</sub> reduction postexercise, compared with children not using this item. However, among children who did sleep supine, synthetic quilt use was associated ( $P = .05$ ) with a lower postexercise FEV<sub>1</sub> compared with supine sleepers under feather or other bedding (Table 4). Thus, an adverse effect for synthetic quilt use, particularly among supine sleepers, was observed for this measure of lung function, similar to the findings reported above for frequent wheeze.

TABLE 3. The Risk of Frequent Wheeze for Various Combined Sleep Arrangements Compared With Sleeping Supine Under a Feather Quilt

Combined Sleeping Arrangement		Cases, % (n = 117)	Matched Controls, % (n = 1144)	Matched OR* (95% CI)	P Value
Sleep Position	Overbedding				
Supine	Feather quilt	8.5	20.6	1.00 (reference)	—
Supine	Other overbedding	6.0	4.9	2.88 (0.83, 10.03)	.10
Supine	Synthetic quilt	26.5	17.7	2.67 (1.23, 5.80)	.01
Nonsupine	Feather quilt	27.4	26.0	1.87 (0.86, 4.08)	.12
Nonsupine	Other overbedding	6.8	6.5	6.84 (0.82, 56.75)	.08
Nonsupine	Synthetic quilt	24.8	24.4	2.38 (1.09, 5.18)	.03

\* Cases matched to controls with regard to age, gender, foam mattress use, electric blanket use, and sheepskin use.

TABLE 4. Change in FEV<sub>1</sub> Postexercise by Wheeze Frequency and Sleep Arrangement

Factor	No. of Children With Lung-Function Tests and Data Available	FEV <sub>1</sub> Change in mL Postexercise (95% CI)	P Value
Number of wheeze episodes in the past year			
None (reference)	320	0% (reference)	—
1-3	48	-5.5 (-8.80 to -2.2)	.001
4-12	16	-5.5 (-11.1 to 0.05)	.05
>12	2	-16.6 (-30.9 to -2.21)	.02
Supine sleep position	349	-0.1 (-2.6 to 2.4)	.94
Synthetic quilt use	406	-1.3 (-3.6 to 1.00)	.27
For children with nonsupine sleep position, synthetic quilt use	196	-1.0 (-4.7 to 2.8)	.61
For children with supine sleep position, synthetic quilt use	151	-3.6 (-7.0 to 0.03)	.05

Lung-function measures were adjusted for child height, age, gender, distance run, ambient humidity during exercise, family history of asthma, child exposure to active smoking, and whether asthma medications were taken within 6 hours of testing. Children with no usual sleep position were excluded. Children using  $\beta$ -agonists on the day of testing were excluded ( $n = 6$ ).

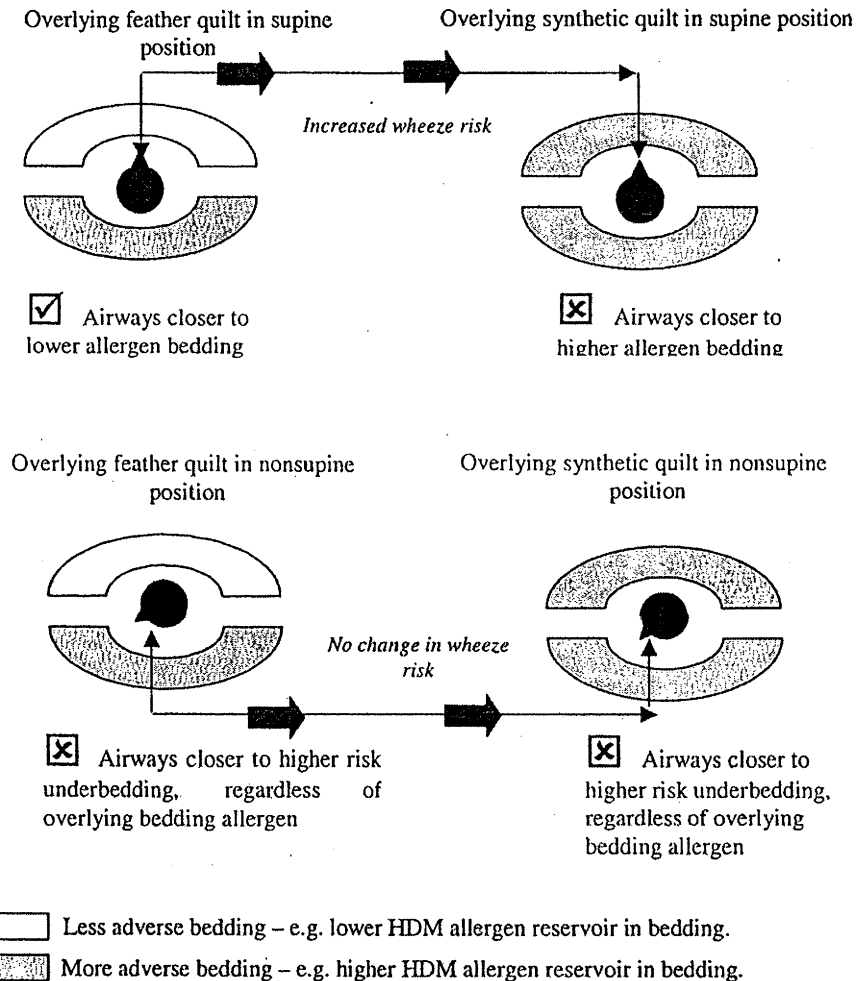


Fig. 1. Schematic representation of a hypothesized mechanism involving close proximity of bedding to the child's airway. The hypothesis is that the adverse effect of an overlying synthetic quilt is mediated by a mechanism involving close proximity to the airway. For example, the inhaled HDM allergen dose into a child's airways could be less if the airway is in close proximity to lower HDM allergen bedding such as feather quilts,<sup>6</sup> compared with higher HDM allergen bedding such as synthetic quilts,<sup>6</sup> underbedding,<sup>3</sup> or mattresses.<sup>4</sup>

induced bronchoconstriction could occur over a short time period. A potential weakness of the study is that frequent wheeze, bedding, and sleep position were based on parental report only. The report of wheeze frequency showed good agreement with measures of postexercise lung function. Additionally, the findings for synthetic quilts and lung function were similar to those for frequent wheeze. The lung-function decrement associated with synthetic quilt use among supine sleepers was small, but it was two thirds the magnitude of the decrement associated with recent wheeze and thus may be of

clinical relevance. Previously, the parent report of infant bedding has been shown to agree well with interviewer observations at home interview. The validity of a parental report of usual sleep position in children of this age group has not been established. Child sleep position is likely to change during the night,<sup>31</sup> which could lead to misclassification of usual sleep position. This misclassification would be likely to be nondifferential and thus reduce the study's ability to detect sleep-position effects.

However, the important issue is that the interaction between synthetic bedding and sleep position

cannot be explained by such misclassification. Sleep position was classified as a binary factor (supine/nonsupine), and both differential and nondifferential misclassification of a binary environmental factor will, if it has any effect, bias a multiplicative interaction effect toward the null value when the following conditions are met.<sup>32</sup> First, the 2 binary factors should be independent. The lack of association between synthetic quilt use and supine sleeping in Table 2 satisfies the criteria that the 2 binary factors should be independent.<sup>32</sup> A second condition is that the measures must classify the true exposures better than random.<sup>32</sup> Past validation work shows a high level of agreement between parental report and nurse observation of infant bedding.<sup>13</sup> Thus, parental report is likely to classify bedding correctly, certainly better than random. To our knowledge, the parental report of child usual sleep position at age 7 has not been validated. However, findings in this study related to sleep position and electric blanket use indicate that parental classification of usual sleep position is not random. Children sleeping on electric blankets were classified by parents as significantly more likely to sleep supine, consistent with past thermal work on sleeping infants.<sup>33</sup> That is, the sleep-position data do provide a pattern of results consistent with past work on thermal balance,<sup>33</sup> which would predict that children with electric blankets would avoid the prone position, which provides a reduced capacity to lose body heat. Thus, parental report, although it may not classify all sleep positions correctly, is likely to reflect the actual predominant sleeping position.

There is growing evidence that synthetic bedding materials are associated with increased childhood wheeze.<sup>9-11</sup> It is now a high priority to establish whether the association is causal in nature. Previous studies have shown that the association between synthetic upperbedding and severe wheeze has a high strength of association,<sup>13,18</sup> a dose-response relationship,<sup>13</sup> biological plausibility,<sup>7</sup> and ecological coherence.<sup>9-11</sup> Two recent birth cohorts have reported that a prospective relationship is evident.<sup>12,13</sup> However, experimental evidence is not available and may be difficult to obtain because of the ethics of applying a potentially deleterious exposure (synthetic bedding) to children with asthma. One of the counterarguments against a causal role for synthetic bedding with childhood wheeze was that the association may merely reflect selection bias even before wheeze development (ie, synthetic bedding was preferentially selected for children at risk of subsequent wheeze). However, the finding that the adverse effect of synthetic quilts was restricted to supine-sleeping children only is evidence against this, because it is unlikely that this selection bias differs by sleep position. This is supported by the findings of no interaction between sleep position and the 2 bedding items (sheepskin and allergen-occlusive mattress cover) that do seem to reflect selection according to the asthma recommendations existing at the time of the study. In 1997, Australian asthma recommendations were to avoid sheepskins and use impermeable mattress covers.<sup>25</sup> The interaction re-

ported here provides additional support for a causal interpretation,<sup>34</sup> because the adverse effect of synthetic quilts was most evident in children who would be more likely to be sleeping face-up near the quilt. In contrast, as predicted, the adverse effect of an overlying synthetic quilt was less evident for side- or supine-sleeping children, because other bedding items such as the pillow or mattress would be closer to the face and thus relatively more important than overlying quilts. The exact mechanisms that underlie this interaction are not understood yet. An increasing focus on the bedding environment immediately adjacent to the nose and mouth of children during sleep is required.

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## FRAUD IS WAY, WAY UP!

"The federal government is on its way to collecting a record amount of fines and settlements from the health-care industry. In the last 3 fiscal years, the government has amassed \$4.21 billion in fines, settlements, and restitution payments from its health-care investigations—well over the \$3.29 billion it collected in the prior 10 years combined, according to the Department of Health and Human Services Office of Inspector General. . . . [T]he federal government is poised to collect more than \$2 billion in payments from HCA Inc, Abbott Laboratories, AstraZeneca PLC, Bayer AG, Guidant Corp, GlaxoSmithKline PLC, Tenet Health Care Corp and Pfizer Inc. More settlements are expected."

Callahan P. *Wall Street Journal.* August 18, 2003

Noted by JFL, MD

Appendix 6

**Trevillian LF, Ponsonby AL, Dwyer T, Kemp A, Cochrane J, Lim LL-Y, Carmichael A. The infant sleeping environment and asthma at 7 years: a prospective cohort study. Am J Public Health 2005; 95(8):(In press).**

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**The infant sleeping environment and asthma at 7 years: a prospective cohort study.**

LF Trevillian<sup>a,b</sup>, A-L Ponsonby<sup>a,b,c</sup>, T Dwyer<sup>c</sup>, A Kemp<sup>d</sup>, J Cochrane<sup>c</sup>, LL-Y Lim<sup>b</sup>, and A Carmichael<sup>e</sup>

<sup>a</sup>Medical School, The Australian National University, Canberra, Australia, <sup>b</sup>National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia, <sup>c</sup>Menzies Centre for Population Health, University of Tasmania, Hobart, Australia, <sup>d</sup>Department of Allergy, Immunology and Infectious Diseases, The Children's Hospital, Westmead and Discipline of Paediatrics and Child Health, University of Sydney, Sydney, Australia, <sup>e</sup>Department of Paediatrics and Child Health, University of Tasmania, Hobart, Australia

Correspondence: Dr Leigh F Trevillian, National Centre for Epidemiology and Population Health, The Australian National University, Canberra ACT 0200, Australia.

Ph: +61-2-6125-8260 Fax: +61-2-6125-0740

E-mail address: leigh.trevillian@anu.edu.au

## **Abstract**

**Objective** To investigate the role of infant bedding items, not in isolation, but as part of a composite bedding environment with the development of wheeze in childhood.

**Methods** Prospective cohort study of 863 children who participated in an infant survey in 1988 and asthma study in 1995 (78% follow-up) in Tasmania, Australia. The three composite infant bedding categories (B<sub>0</sub>, B<sub>1</sub> and B<sub>2</sub>) corresponded to increasing numbers of the bedding items of synthetic pillow, quilt, cocoon and sheepskin. 1995 outcome measures included recent wheeze.

**Findings** Infant bedding was associated with subsequent recent wheeze (AOR B<sub>0</sub> 1.00 [reference]; B<sub>1</sub> AOR 1.07 [95%CI 0.72, 1.57]; B<sub>2</sub> AOR 2.10 [95%CI 1.15, 3.82]; p for trend = 0.05). This composite bedding effect was further enhanced by the home environment factors of bedroom heating, recent bedroom painting and absence of bedroom carpet. When any two or more of these environmental bedding-wheeze enhancers were present a strong dose-response was evident (p for trend = 0.01).

**Conclusion** Bedding exposure in infancy is prospectively associated with childhood wheeze and home environmental conditions may modify this association.

## Introduction

Reasons for the changing incidence of childhood asthma over time are unclear. The indoor environment, in particular house-dust mite (HDM) allergen exposure, is an area of concern.<sup>1</sup> High exposure to HDM allergens is associated with an increased risk of subsequent HDM sensitization but the role of HDM exposure in asthma is less clear.<sup>2</sup> Bedding is a significant source of HDM allergens with infant bedding such as synthetic pillows and quilts,<sup>3</sup> and sheepskins<sup>4</sup> harboring high HDM levels. Replacing used with new bed quilts reduced more than 10-fold airborne *Dermatophagoides* HDM allergen levels near the face during sleep.<sup>5</sup> HDM allergen levels in bedding have been shown to be more important than bedroom floor HDM levels in determining airway responsiveness<sup>6</sup> or asthma severity.<sup>7</sup> This may explain why a prospective association between infant bedroom floor HDM levels and asthma has been found in only one of three studies.<sup>8-10</sup> Furthermore, increased environmental exposure to endotoxins, found in the bedroom, has been postulated to influence the risk of asthma and allergic sensitization.<sup>11,12</sup>

Difficulty in measuring indoor exposures during infancy has been one problem hampering research into early life influences on childhood asthma. Detailed information on the infant sleep environment has not been readily available. The Tasmanian infant cohort provides such information. Previous studies on this cohort demonstrated infant exposure to synthetic bedding items such as pillow, quilt and cocoon was associated with child wheeze.<sup>13-15</sup> Sheepskin use was associated with HDM sensitization.<sup>16</sup> In contrast, bedroom carpet<sup>17</sup> and infant mattress type appeared less important.<sup>16</sup>

Moreover, with regard to childhood asthma, the environmental model for infant HDM exposure may not be one of single major independent risk factors but rather one of environmental determinants synergistically increasing infant HDM exposure. For example,

bedroom heating increases the HDM levels in bedding.<sup>18</sup> In addition to allergen exposure, environmental air quality may also be important with substances such as volatile organic compounds (VOCs) possibly potentiating allergen sensitization, whereas, endotoxin presence may affect HDM sensitization.<sup>11</sup>

An additional approach investigating the role of infant bedding and bedroom environment in asthma development is to (i) further quantitate bedding exposure measurement by considering bedding not as single items but as a composite and, (ii) investigate bedding-environment interactions. We utilize this approach, based on a theoretical model of HDM-loading in bedding, to investigate infant sleeping environment and subsequent childhood.

## Methods

### Study Design

The Tasmanian Infant Health Survey (TIHS) was a cohort study of infants born from 1988 through 1995 in Tasmania, Australia that operated from hospitals where approximately 93% of births occurred. Infants born were scored to assess the risk of sudden infant death syndrome (SIDS) using perinatal entry criteria.<sup>19</sup> Infants exceeding a scoring cutoff were eligible for inclusion together with all multiple births. The eligibility criteria and study methods are discussed elsewhere.<sup>19</sup> Data were obtained on three occasions, including a home interview during the fifth postnatal week. Data included parental, infant, home environmental, child-care factors and the infant's sleeping environment at age one-month.

In 1995, the cross-sectional Childhood Asthma Survey was conducted on all children who turned seven years of age in Tasmania.<sup>17</sup> We linked the 1995 asthma data of the 863 children who had an at-home interview at one-month of age in 1988 as part of the TIHS. Data included sleeping environment and asthma symptoms, using International Study of Asthma and Allergies in Childhood (ISAAC) questions.<sup>20</sup> The child's age (in completed years) at onset of wheezy breathing or asthma was obtained.

### Definitions

*Recent wheeze* refers to one or more wheeze episodes over the past 12 months. *Asthma ever* refers to a positive response to the ISAAC question, "Has your child ever had asthma?".<sup>20</sup> Bronchial hyperresponsiveness after exercise is related to these outcomes.<sup>14</sup> *Night wheeze* is the child's sleep being disturbed one or more nights per week in the past 12 months due to wheezing. *Frequent wheeze* refers to 12 episodes or more of wheeze over the past 12 months. *A family history of asthma* was defined as asthma in any of the infant's siblings, parents or grandparents at the time of the infant's birth.

### **Classification of Bedding Items**

Sheepskins comprised the animal hide with natural wool fibres attached. Infant cocoons manufactured and sold in Southern Tasmania during the study period most commonly comprised outer coverings of cotton/polycotton with a synthetic filling.<sup>15</sup> Pillows reported as foam/sponge/tontine/polyester/Dacron were classified as synthetic and a synthetic quilt in infancy was defined as the use of a synthetic quilt over the infant during cold weather. Use of sheepskin and/or cocoon at time of interview or intention to use either of these items in cold weather was recorded, thereby avoiding the effect of current season when interviewed.

A three-level composite bedding classification was made based on past work and the distribution of bedding exposures to HDM-rich synthetic pillows, quilts and cocoons, or sheepskin.<sup>3,4</sup> The reference group *Bedding Combination 0* (B<sub>0</sub>) represented infants with no synthetic items and no sheepskin.<sup>16</sup> *Bedding Combination 1* (B<sub>1</sub>) comprised either one synthetic item only (n=279) or one sheepskin only (n=121) or one synthetic item and one sheepskin (n=113). *Bedding Combination 2* (B<sub>2</sub>) comprised two or more synthetic items without sheepskin (n=57) or with sheepskin (n=14). More emphasis was on synthetic bedding items than sheepskin because of the previous reported associations with wheeze in this cohort.<sup>13-15</sup> Here, the term composite bedding refers to the increase from B<sub>0</sub> to B<sub>1</sub> to B<sub>2</sub>. The B<sub>2</sub> effect is B<sub>2</sub> versus B<sub>0</sub>, and the B<sub>1</sub> effect is B<sub>1</sub> versus B<sub>0</sub>.

### *Classification of Indoor Environmental Factors*

We coded possible effect modifiers as binary. Baby's bedroom heated was in response to current use at time of interview and also intended use of heating in cold weather. Recent painting refers to the infant's bedroom having been painted within the previous 12 months from the time of home interview. Absence of carpet means no wall-to-wall carpet in the infant's bedroom.

## Statistical Methods

Pair-wise correlations were obtained by Spearman's rank order correlation. Logit-based univariate odds ratios and 95 percent confidence intervals were calculated by logistic regression. To assess the role of the composite bedding exposures in infancy as a risk factor for asthma at the age of 7 years, multivariate logistic regression models controlled for multiple confounders simultaneously, providing adjusted odds ratios<sup>21</sup> for the categorical outcome variables "recent wheeze" and "asthma ever". We also examined "frequent wheeze" as a measure of asthma severity and "night wheeze" because bedding was the exposure of interest. Those factors found in univariate analysis, or a priori, to be associated with wheeze were examined as potential confounders. Using change-in-estimate methods, factors altering the exposure-wheeze association point estimate by 10 percent or more were included in the final model. We examined the confounding effect of a large number of factors including sibling number, in utero exposure to maternal smoking, air freshener use in infant's bedroom, cat or dog as a family pet during infancy, visible indoor mould and plastic mattress cover use in infancy, and low maternal education or paternal unemployment at child's birth. We explored the contribution of family asthma history to the association between bedding and wheeze as either a confounder or an intervening variable using stratification. Factors that altered the exposure-wheeze association by 10 percent or more were an at-birth family history of asthma, male sex, foam mattress use in infancy and maternal cigarette smoking during infancy. The cohort entry criteria, either separately or as a set did not alter any of the reported associations. We used the Wald test for linear trend of the categorical bedding variables by replacing the binary predictors with a single predictor, taking category rank scores.

A model was built with terms for composite bedding and each confounder to assess whether an association between a composite bedding classification and a respiratory outcome differed

by environmental factor status after controlling for confounders. The dependent variable was one of the respiratory outcomes examined. A second model, was built similar to the first but also with a term for the environmental factor and an interaction term between composite bedding and environmental factor. The resulting deduction in deviance obtained using the second model compared to the first was then assessed using the p-value associated with the log likelihood ratio test.<sup>21</sup> Tests for interaction often use a higher significance than  $p=0.05$ .<sup>22</sup> Here, interaction terms improving the model by  $p \leq 0.1$  are considered important. Stratified multivariate logistic regression explored the potentiation of more than one environmental factor on the bedding-wheeze effect. Discrete proportional hazard modeling<sup>21</sup> examined age of asthma onset or wheezy breathing by bedding. The potentiation of age of onset by environmental factors was determined by a stratified log rank test.<sup>21</sup> We conducted the analysis using statistical software, STATA 7.0.<sup>23</sup>



## Results

The characteristics of the study sample are shown in Table 1. Infants exposed to composite bedding B<sub>2</sub>, had a more than two-fold risk of recent wheeze and night wheeze by age 7 years compared with children who had none of these bedding items in infancy (Table 2). There was a dose-response relationship between exposure to increasing number of composite bedding items in infancy and the risk of recent wheeze and asthma ever in childhood. This trend for a higher number of composite bedding items and increasing risk of subsequent wheeze was also found with night wheeze and frequent wheeze. A parental history of asthma was not associated with selection of composite bedding combinations. Even among children without an at-birth family history of asthma, the risk of wheeze increased with more composite bedding items (Test for trend,  $p=0.03$ ).

We examined the influence of bedroom heating, bedroom carpet and recent bedroom painting on wheeze and the interactions of these factors with the use of composite bedding. There was no relationship between bedroom heating and bedroom carpet (Spearman  $r=0.052$ ); bedroom heating and recent painting (Spearman  $r=0.078$ ); bedroom carpet and recent painting (Spearman  $r=-0.029$ ). Nor were these factors associated with the composite bedding (Spearman  $r=-0.015$ ;  $-0.002$  and  $-0.083$  for bedroom heating, recent bedroom painting and bedroom carpet respectively). Bedroom heating, recent bedroom painting and the absence of bedroom carpet did not significantly predict wheeze with ORs of 1.08, 0.82, and 1.12 respectively. Carpet may be removed as part of an allergy-reduction measure in families with a history of asthma. In this cohort, there was no difference in the proportion of children with a family history of asthma (9.1%) that had no carpet in their bedrooms compared to children who did not have a family history of asthma without carpet in their bedroom (10.1%) ( $p=0.576$ ).

These three environmental factors altered the bedding-wheeze associations. The dose-response relationship of infant composite bedding on the risk of subsequent recent wheeze was particularly evident when the infant slept in a heated room (Table 3). In particular, B<sub>2</sub> was strongly associated with recent wheeze in childhood (adjusted OR 7.87; 95% CI 2.17, 28.51) when the infant's bedroom had been heated. The difference in the potentiation of the composite bedding effect by room heating was significant (Likelihood ratio test, p=0.051). Similarly, children with asthma ever demonstrated this potentiation of the composite bedding effect by room heating. No significant associations were found between each of the different types of heating used in the infant's bedroom and recent wheeze. The bedding-wheeze effect was potentiated by room heating irrespective of the heating type.

There was a greater increase on risk of subsequent wheeze by composite bedding for infants sleeping in a recently painted bedroom (Table 3). Among infants in recently painted rooms, infants exposed to a composite bedding arrangement of B<sub>2</sub>, had a more than five-fold increase in risk of recent wheeze by age 7 years than infants with B<sub>0</sub> bedding. We next examined whether the relative importance of composite bedding on wheeze would be greater in uncarpeted or carpeted rooms. Stronger composite bedding effects on wheeze were found in uncarpeted compared to carpeted bedrooms (Table 3). The potentiation of the composite bedding effect by these three environmental factors was also evident for night and frequent wheeze.

The effect modification patterns reported above for bedroom heating, recent bedroom painting and the absence of carpet, remained after adjustment for the other two environmental factors, either individually or together, plus the confounders listed at the bottom of Table 2. These three environmental factors appeared to independently potentiate the risk of composite bedding categories on wheeze. Moreover, Figure 1 shows when any two or more of these

environmental bedding-wheeze enhancers were present, the OR for the B<sub>1</sub>-wheeze association was 3.45; 95%CI 1.01, 11.83, and the OR for the B<sub>2</sub>-wheeze association was 14.94; 95%CI 1.94, 115.1. The difference for potentiation of the bedding classification B<sub>2</sub>-wheeze effect in the presence of from none to two or more environmental factors was significant (p=0.012).

Among infants with childhood asthma, increasing the number of composite bedding items was associated with an increased risk of subsequent earlier onset of asthma symptoms by age 7 years. Infants with B<sub>0</sub>, B<sub>1</sub> and B<sub>2</sub> had a mean age of onset of 3.7, 3.2 and 2.1 years respectively (Log-rank test for equality of survivor functions, p=0.002). The presence of the three environmental factors, identified as bedding-wheeze enhancers in infancy, also potentiated the shift by the bedding combinations to an earlier age of onset of asthma among children with a history of asthma ever.

## Discussion

This is the first report investigating composite infant bedding and subsequent wheeze to consider modification by the home environment. Wheeze risk in childhood increased linearly with increasing numbers of potentially high HDM-rich bedding items at one-month of age. This composite bedding effect was further modified by the indoor environment factors of bedroom heating, recent bedroom painting and absence of bedroom carpet. When two or more of these environmental factors were present the bedding-wheeze association was markedly exacerbated.

Strengths of this study include prospective sleeping environment data, minimizing recall bias, and the use of a composite bedding classification. At the time of assessment of wheeze, the research nurse was unaware of the infant bedding status. The results are not likely to be influenced by differential follow-up as the proportion of TIHS children followed-up from infancy did not differ by use of particular bedding items. The study sample was not representative of all live births in the geographical area as it consisted of infants born at a higher risk of SIDS, however, the TIHS cohort entry criteria are unlikely to affect the generalizability of these results. The eligibility criteria were well defined<sup>24</sup> and the potential effects of the entry scoring system components were considered in the multivariate analyses. Thus, the children in this study should not differ from other children to any large extent with regard to the biological development of asthma. Importantly, the bedding-wheeze associations were evident even among children without an at-birth family history of asthma. A potential weakness is the absence of a biological or physician assessment of asthma. The ISAAC questionnaire, however, is considered a valid instrument for the determination of current asthma symptoms; the report of 'wheeze' over the past 12 months has a sensitivity of 0.85 and a specificity of 0.81 for the physician diagnosis of asthma in childhood.<sup>25</sup>

Our findings emphasise the important role of infant sleeping environment on asthma development. Moreover, this study demonstrates features suggestive of a causal relationship<sup>26</sup> between composite bedding and wheeze: a high strength of association, a marked dose-response effect for wheeze, consistency in the bedding-wheeze effect and the significant earlier shift in age of onset of asthma by composite bedding. Further, the environment enhancers not only increased the magnitude of bedding-wheeze associations but also shifted to earlier age of asthma onset. These results are also consistent with past work. In the Tasmanian study, sensitization to HDM is increased in children exposed to sheepskin<sup>16</sup> or to synthetic bedding as compared to those using feather bedding in infancy.<sup>13</sup> Moreover, several cross-sectional<sup>27, 28</sup> and prospective<sup>14, 15</sup> studies have reported an association between synthetic bedding and childhood wheeze.

Several mechanisms provide biological plausibility for the increase risk of wheeze reported here. An increased exposure to HDM allergen levels, the model on which this report is based, has been reported with the use of synthetic or sheepskin bedding items<sup>3, 4</sup> in early childhood. Thus high HDM-rich bedding items may increase the risk of HDM sensitization and airways inflammation by placing a higher allergen load near the infant's airway.<sup>14</sup> This is further reinforced by new work which shows that the adverse effect of synthetic quilts on wheeze varies by sleeping position.<sup>29</sup>

Atopic individuals are over-represented at the severe end of the asthma spectrum, with earlier studies suggesting frequent wheeze may be a better marker of HDM-allergen-related airway disease than a history of asthma or milder symptoms.<sup>13, 28, 30, 31</sup> HDM allergen exposure is associated with increasing wheeze frequency.<sup>32</sup> Here, the risk of frequent wheeze in childhood also increased linearly with increasing numbers of potentially high HDM-rich

bedding items at age one-month. This is consistent with a bedding effect on HDM-allergen-related airway disease but is not definitive as child HDM-atopy status was not available.

Conflicting results regarding associations between mattress and respiratory symptoms or HDM sensitization have been reported.<sup>32,33</sup> Mattress HDM allergen levels may be a proxy for the measurement of other allergen sources closer to the subject.<sup>34</sup> A recent Cochrane meta-analysis found bedding changes aimed at reducing exposure to HDM allergens seem ineffective in improving the symptoms of asthma in HDM-sensitive asthmatics.<sup>35</sup> Overall, no statistically significant difference in improvement of asthma was found even among the subgroup for whom effective allergen reduction was documented.<sup>35</sup> The findings reported indicate the lack of effect may relate to the effective allergen reduction for mattress only, but not other allergen sources. Multiple components, not single items, and their relationship to the proximal sleeping microenvironment may all play a role in child asthma.

We did not determine HDM allergen levels. However, a single allergen measure of, for example, bedroom carpet<sup>9</sup>, which may not have consistent patterns of allergen distribution<sup>36</sup>, would not have encompassed the bedding and indoor environmental determinants leading to personal allergen exposure studied here. Thus, exposure models that take into account the multiple determinants of personal allergen exposure are now required to identify the mechanisms involved.

Various environmental factors influence asthmatic symptom development.<sup>37</sup> For atopic infants, the presence of other environmental exposures, in addition to aeroallergens has been hypothesised to be synergistic and increase the risk of asthma.<sup>38</sup> Here, the potentiation of the composite bedding-wheeze effect by indoor environmental factors could reflect various synergistic mechanisms. These include increased HDM exposure, increased allergen

sensitization, increased VOC-induced inflammation in vulnerable infant airways, or reduced exposure to endotoxin. The potentiation of the composite bedding effect on wheeze by room heating may be due to an enrichment of the allergen content of bedding, consistent with previous studies that reported room heating increased HDM load in bedding.<sup>18</sup> The finding here that bedroom heating potentiation did not vary by heating type is consistent with the effect being that of increased heat in the bedroom environment and not due to characteristics associated with the type of heating. The potentiation of the composite bedding effect on wheeze by recent painting may reflect that recently painted walls release VOCs<sup>39</sup> and their presence in the infant's bedroom may enhance sensitization to HDM by airway inflammation resulting in increased permeability and enhanced allergen presentation to the immune system<sup>40</sup>, and/or by VOC-induced Th2 deviation.<sup>41</sup> Several birth cohort studies have also found an exposure-response relationship between recent home redecoration, including wall painting, and an increased risk of wheeze<sup>39</sup> or asthma.<sup>42</sup>

The potentiating effect of having no bedroom carpet is intriguing. The promoting effect of no carpet did not operate independently but was seen in association with composite bedding exposure. Possibly the absence of bedroom carpet has reduced one habitat for HDM<sup>36</sup>, potentially increasing the relative importance of the bedding as a HDM allergen reservoir. Other possible mechanisms include that bedroom carpets, containing significantly more endotoxin than bedding<sup>43</sup>, may be a major reservoir for infantile endotoxin exposure<sup>44,45</sup>. As synthetic bedding may contain less endotoxin as compared to other bedding<sup>46</sup>, this could be counterbalanced by increased levels in the bedroom carpet. Although, the role of environmental endotoxin exposure in asthma development is unclear, several studies have postulated that endotoxin exposure in infancy may be protective.<sup>12,47</sup>

In conclusion, composite bedding exposure as an infant at age one-month predicts subsequent childhood wheeze, particularly if exacerbating home environment factors are present. Infants spend a significant proportion of their time in bed with consequent opportunity for prolonged exposure to adverse environmental influences. These findings indicate that a greater public health effort to achieve optimal infant sleeping environments for asthma prevention is required.



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**Table 1: 1995 Study Sample Characteristics (N=863) at age 7 years**

	%	N*
Mean age (years)	6.9 (SD= 0.3)	
Male sex	71.3	615/863
At birth family history of asthma	35.0	301/859
No siblings in 1995	5.8	48/823
Recent wheeze over past year	27.0	222/823
Night wheeze over past year	19.2	160/834
Asthma ever	32.4	280/863
Frequent wheeze over past year	4.8	30/631
<i>Bedroom factors in infancy</i>		
Synthetic pillowcase use at 1 month age	14.8	127/857
Synthetic quilt use at 1 month age	44.9	396/802
Cocoon use at 1 month age	2.4	19/802
Sheepskin use at 1 month age	29.8	256/859
Foam mattress use in infancy	62.2	531/854
Plastic mattress cover use in infancy	41.0	352/859
<b>Three-level Composite Bedding Classification</b>		
Combination B <sub>0</sub>	27.0	216/800
Combination B <sub>1</sub>	64.1	513/800

Combination B <sub>2</sub>	8.9	71/800
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*Environmental factors in infancy*

Heating in infant's bedroom	34.3	294/857
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Carpet in infant's bedroom	90.6	767/847
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Infant's bedroom painted within previous 12 months	33.5	287/856
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Maternal cigarette smoking during infancy	44.7	382/855
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Use of home gas appliances (cooking and/or living room heating) in infancy	3.3	28/856
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Presence of mould in home (excluding bathroom) in infancy	4.7	40/855
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Cat as pet during infancy	34.3	294/857
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Dog as pet during infancy	35.9	308/857
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*Parental factors*

Low maternal education at child's birth	22.2	191/859
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Paternal unemployment at child's birth	17.4	146/837
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\* Small N for some characteristics: bedding items (N=800)

Table 2. Association between Infant Composite Bedding Classification and Childhood Wheeze

		Unadjusted odds ratio				Adjusted odds ratio*			
% Children with infant bedding combination with wheeze		n/total n	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value	
Recent wheeze									
Combination 0	23.8	49/206	1.00 (reference)			1.00 (reference)			
Combination 1	25.7	126/490	1.11	0.76, 1.62	0.593	1.07	0.72, 1.57	0.744	
Combination 2	43.3	29/67	2.45	1.37, 4.37	0.003	2.10	1.15, 3.82	0.015	
Linear Trend					<i>P</i> = 0.014			<i>P</i> = 0.053	
Asthma ever									
Combination 0	29.6	64/216	1.00 (reference)			1.00 (reference)			
Combination 1	32.6	167/513	1.15	0.81, 1.62	0.439	1.15	0.81, 1.64	0.437	
Combination 2	45.1	32/71	1.95	1.12, 3.38	0.018	1.80	1.01, 3.18	0.045	
Linear Trend					<i>P</i> = 0.039			<i>P</i> = 0.072	

\* Adjusted for male sex, at birth family history of asthma, foam mattress use in infancy, maternal cigarette smoking during infancy.

Further adjustment for cohort entry criteria did not alter the results.

Note: The reference group *Bedding Combination 0* ( $B_0$ ) represented infants with no synthetic items and no sheepskin. *Bedding Combination 1* ( $B_1$ ) comprised either one synthetic item only ( $n=279$ ) or one sheepskin only ( $n=121$ ) or one synthetic item and one sheepskin ( $n=113$ ). *Bedding Combination 2* ( $B_2$ ) comprised two or more synthetic items without sheepskin ( $n=57$ ) or with sheepskin ( $n=14$ ).

**Table 3: Potentiation of Infant Bedding Effects by Indoor Environmental Factors on Wheeze**

		Recent wheeze			Asthma ever				
Bedding combinations by environmental factors		%	N	Adjusted Odds ratio* (95% CI)	p value	%	N	Adjusted Odds ratio* (95% CI)	p value
<b>Without room heating</b>									
Combination 0		27.0	37/137	1.00 (reference)		33.8	49/145	1.00 (reference)	
Combination 1		24.2	74/306	0.84 (0.2, 1.34)	0.454	32.6	105/322	0.91 (0.59, 1.40)	0.673
Combination 2		38.5	20/52	1.39 (0.69, 2.79)	0.354	41.8	23/55	1.14 (0.59, 2.21)	0.703
				Linear Trend p=0.653				Linear Trend p=0.898	
<b>With room heating</b>									
Combination 0		17.4	12/69	1.00 (reference)		21.1	15/71	1.00 (reference)	
Combination 1		28.0	51/182	1.77 (0.86, 3.65)	0.120	32.3	61/189	1.90 (0.97, 3.73)	0.063
Combination 2		60.0	9/15	7.87 (2.17, 28.51)	0.002	56.3	9/16	7.07 (2.09, 23.85)	0.002
				Linear Trend p=0.004				Linear Trend p=0.003	
<b>Difference in bedding effect by room heating</b>				<i>Likelihood ratio test</i>	<i>P=0.051</i>			<i>Likelihood ratio test</i>	<i>P=0.048</i>
<b>Without painting</b>									
Combination 0		27.2	39/141	1.00 (reference)		32.4	48/148		
Combination 1		26.5	82/310	0.89 (0.57, 1.41)	0.633	31.5	103/327	0.98 (0.64, 1.51)	0.944
Combination 2		43.1	22/51	1.65 (0.82, 3.31)	0.162	37.7	20/53	1.20 (0.60, 2.40)	0.606
				Linear Trend p=0.383				Linear Trend p=0.730	



With Painting									
Combination 0	15.4	10/65	1.00 (reference)	23.5	16/68	1.00 (reference)	0.075		
Combination 1	24.6	44/179	1.97 (0.89, 4.36)	0.094	34.6	64/185	1.81 (0.94, 3.49)	0.075	
Combination 2	43.8	7/16	5.39 (1.44, 20.25)	0.013	66.7	12/18	7.22 (2.25, 23.22)	0.001	
Linear Trend p=0.013									
Likelihood ratio test P=0.095									
Difference in bedding effect by room painting p=0.039									

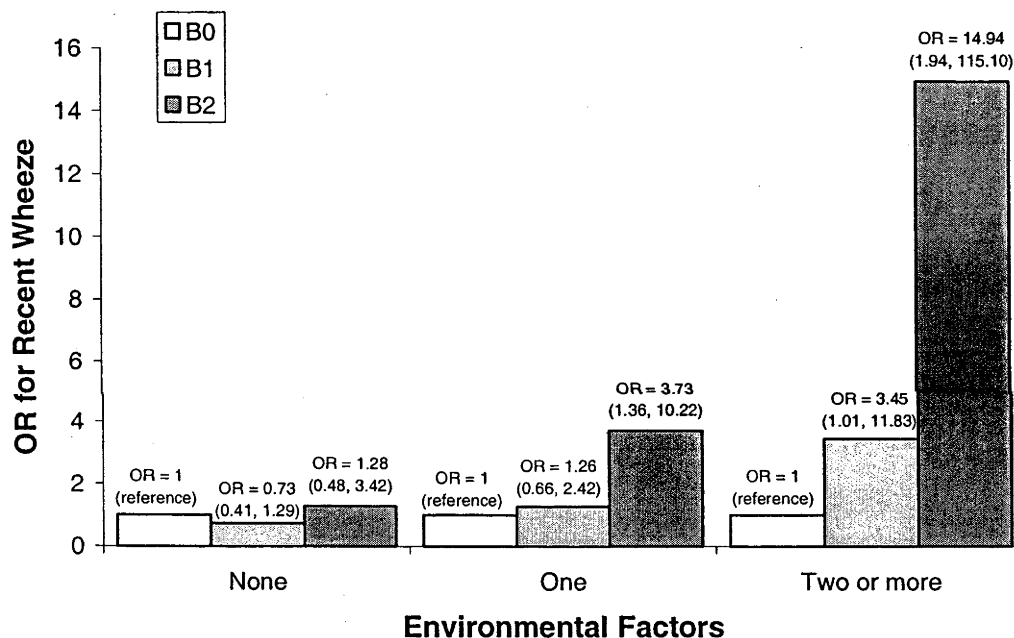
Without Carpet									
Combination 0	13.3	2/15	1.00 (reference)	33.3	5/15	1.00 (reference)	0.487		
Combination 1	30.4	14/46	2.51 (0.47, 13.55)	0.284	41.7	20/48	1.61 (0.42, 6.19)	0.487	
Combination 2	58.3	5/12	8.13 (1.14, 58.20)	0.037	53.9	7/13	2.40 (0.46, 12.48)	0.298	
Linear Trend p=0.032									
Likelihood ratio test P=0.003									
Difference in bedding effect by room carpet P=0.001									
With Carpet									
Combination 0	24.7	46/186	1.00 (reference)	29.6	58/196	1.00 (reference)	0.621		
Combination 1	25.5	112/440	1.01 (0.67, 1.51)	0.966	31.7	146/461	1.10 (0.76, 1.60)	0.621	
Combination 2	40.7	22/54	1.82 (0.94, 3.53)	0.075	43.9	25/57	1.72 (0.92, 3.23)	0.090	
Linear Trend p=0.200									
Likelihood ratio test P=0.003									
Difference in bedding effect by room carpet P=0.001									

\*Adjusted for male sex, at birth family history of asthma, foam mattress use in infancy, maternal cigarette smoking during infancy. Further adjustment for cohort entry criteria did not alter the results.

Note: The reference group *Bedding Combination 0* (B<sub>0</sub>) represented infants with no synthetic items and no sheepskin. *Bedding Combination 1* (B<sub>1</sub>) comprised either one synthetic item only (n=279) or one sheepskin only (n=121) or one synthetic item and one sheepskin (n=113). *Bedding Combination 2* (B<sub>2</sub>) comprised two or more synthetic items without sheepskin (n=57) or with sheepskin (n=14).

**Figure 1. Relationship between the Number of Environmental Factors (Bedroom Heating, Recent Bedroom Painting, Absence Of Bedroom Carpet) and Potentiation of Composite Bedding- Wheeze Effect by Bedding Combination B<sub>0</sub>, B<sub>1</sub> And B<sub>2</sub>**

The reference group is B<sub>0</sub>. The difference in effect for potentiation of the bedding combination B<sub>1</sub>- wheeze effect, from none to two or more of the environmental factors is p=0.017. The difference in effect for potentiation of the bedding combination B<sub>2</sub>- wheeze effect, from none to two or more of the environmental factors is p=0.012.



Note: The reference group *Bedding Combination 0* (B<sub>0</sub>) represented infants with no synthetic items and no sheepskin. *Bedding Combination 1* (B<sub>1</sub>) comprised either one synthetic item only (n=279) or one sheepskin only (n=121) or one synthetic item and one sheepskin (n=113). *Bedding Combination 2* (B<sub>2</sub>) comprised two or more synthetic items without sheepskin (n=57) or with sheepskin (n=14).