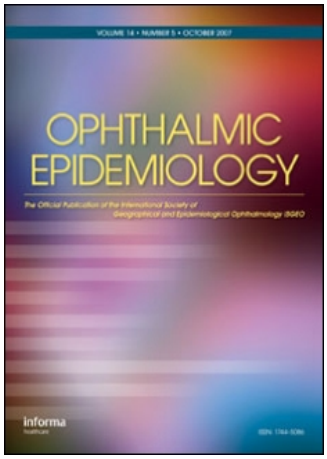
This article was downloaded by:[Mackey, David]
On: 27 December 2007
Access Details: [subscription number 788999488]
Publisher: Informa Healthcare
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Ophthalmic Epidemiology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713734444

The Association Between Maternal Smoking in Pregnancy, Other Early Life Characteristics and Childhood Vision: The Twins Eye Study in Tasmania

A. L. Ponsonby [ab]; S. A. Brown [ac]; L. S. Kearns [cd]; J. R. MacKinnon [ef]; L. W. Scotter [d]; J. A. Cochrane [a]; D. A. Mackey [acde]
[a] Menzies Institute, University of Tasmania, Australia
[b] Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia
[c] Center for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia
[d] Ocular Diagnostic Clinic, Royal Victorian Eye and Ear Hospital, Australia
[e] Department of Ophthalmology, Royal Children's Hospital, Melbourne, Australia
[f] Department of Ophthalmology, Royal Hospital for Sick Children, Yorkhill, Glasgow, Scotland

Online Publication Date: 01 November 2007
To cite this Article: Ponsonby, A. L., Brown, S. A., Kearns, L. S., MacKinnon, J. R., Scotter, L. W., Cochrane, J. A. and Mackey, D. A. (2007) 'The Association Between Maternal Smoking in Pregnancy, Other Early Life Characteristics and Childhood Vision: The Twins Eye Study in Tasmania', Ophthalmic Epidemiology, 14:6, 351 - 359
To link to this article: DOI: 10.1080/01658100701486467
URL: http://dx.doi.org/10.1080/01658100701486467

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article maybe used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

Ophthalmic Epidemiology, 14:351–359
ISSN: 0928-6586 print / 1744-5086 online
Copyright © 2007 Informa Healthcare USA, Inc.
DOI: 10.1080/01658100701486467

informa
healthcare

The Association Between Maternal Smoking in Pregnancy, Other Early Life Characteristics and Childhood Vision: The Twins Eye Study in Tasmania

A. L. Ponsonby,[1,2] S. A. Brown,[1,3] L. S. Kearns,[3,4] J. R. MacKinnon,[5,6] L. W. Scotter,[4] J. A. Cochrane,[1] and D. A. Mackey[1,3,4,5]

[1] *Menzies Institute, University of Tasmania, Australia*
[2] *Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia*
[3] *Center for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia*
[4] *Ocular Diagnostic Clinic, Royal Victorian Eye and Ear Hospital, Australia*
[5] *Department of Ophthalmology, Royal Children's Hospital, Melbourne, Australia*
[6] *Department of Ophthalmology, Royal Hospital for Sick Children, Yorkhill, Glasgow, Scotland*

ABSTRACT

Purpose: **To investigate the association between maternal smoking in pregnancy, early-life environment and childhood vision.** ***Methods:*** **Twin and triplet children enrolled in the Twins Eye Study in Tasmania underwent a comprehensive ophthalmic examination and their parents/guardians retrospectively answered a questionnaire regarding crawling, walking and other measures. A subset of these twins was also in the Tasmanian Infant Health Survey, which prospectively collected data on antenatal smoking, gestation, birth weight and other factors.** ***Results:*** **The mean age of the 346 individuals (172 multiple birth sets) at the time of examination was 9.25 $\pm$ 2.4 years. Mean unaided visual acuity was 0.0 (6/6). The mean spherical equivalent was +0.87D, and decreased with increasing child age ($p < 0.01$). A prospective analysis, accounting for birth set clustering and relevant confounders, showed increasing levels of maternal smoking in the third trimester was associated with poor stereoacuity on the Titmus test (worse (>) than 100″, $p = 0.05$) and Lang test ($p = 0.001$) and also with the presence of esotropia ($p = 0.02$). These associations persisted after adjustment for infant postnatal smoke exposure at one month of age. Poor stereoacuity on Titmus stereo test circles was associated with late age of first crawling (RR = 1.23 (1.06, 1.42) $p = 0.005$ per month) and late age of first walking (RR 1.18 (1.05, 1.22) $p = 0.001$ per month).** ***Conclusions:*** **Antenatal smoking was independently associated with poor stereovision and the presence of esotropia. Poor stereoacuity may be associated with delayed age at first crawling or walking.**

INTRODUCTION

Normal visual function (acuity, refraction, alignment, and stereoacuity) is of great importance in children's ability to learn and interact with their environment. Both genetic and environmental factors have been proposed to contribute to visual problems in childhood. Twin studies are a method of determining the relative genetic and environmental contribution to a disease or trait.[1] They can be used to identify causative genes as well as to investigate possible environmental associations.

The Twins Eye Study in Tasmania (TEST) was established to determine the heritability of childhood visual function and other ocular parameters. A subset of these twins was also part of the Tasmanian Infant Health Study (TIHS) cohort,[2,3] allowing us to cross reference with prospectively collected data on fetal and infant environment. Detailed prospective data were available for many factors including fetal and infant tobacco smoke exposure.[2] In previous studies, maternal smoking in pregnancy has been reported to be associated with strabismus or poor stereopsis in childhood.[4–6] However, the relative contribution of antenatal smoking by trimester independent of postnatal exposure

Received 15 November 2006; accepted 31 May 2007.
Keywords: Visual acuity, Binocular function, Antenatal smoking, Stereoacuity strabismus
Correspondence to:
David A Mackey
Center for Eye Research Australia
University of Melbourne
Department of Ophthalmology
Royal Victorian Eye and Ear Hospital
1/32 Gisborne St.
East Melbourne Vic 3002
Australia.
e-mail: D.Mackey@utas.edu.au

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

to smoke has not previously been evaluated. We examined the influence of environmental factors in antenatal and early life on eye outcomes in childhood, with an emphasis on stereoacuity and strabismus, because these entities have been previously linked to antenatal smoking.[4–6]

MATERIALS AND METHODS

Infant cohort data

From 1988 to 1995, a birth cohort study, the Tasmanian Infant Health Survey (TIHS), investigating infants at-risk of sudden infant death syndrome, took place in Tasmania, Australia.[2] It operated from six obstetric hospitals where approximately 93% of births occurred. All live-born infants from multiple pregnancies were eligible and a perinatal scoring system based on maternal age, infant sex, birth-weight, feeding intention, season of birth, and second stage of labor was used to select at-risk singletons. Infants with major medical anomalies, still hospitalized at 3 months, placed for adoption or planning to reside outside Tasmania were excluded.

The infant sample was predominantly Caucasian. Standard study measurements were collected by research staff at three stages. First, an interview was conducted when the infant was approximately 4 days old. Information was collected on sociodemographic factors, maternal smoking during pregnancy, antenatal alcohol consumption and other antenatal factors. Because the effects of smoking on vision are likely to vary by the fetal developmental stage of tobacco smoke exposure, we used recorded data on antenatal smoking by trimester of pregnancy.

Medical record data on the delivery including birth weight, gestational age, head circumference at birth, length at birth, Apgar scores at 1 and 5 minutes were obtained and infant anthropometry at 4 days was measured. Secondly, a home interview was conducted during the fifth postnatal week. Infant exposure to postnatal smoke was defined as the mother usually or sometimes smoking in the same room as the infant.[2] This variable is significantly related to higher infant urinary cotinine, a biomarker of nicotine exposure, even among infants whose mothers smoked postnatally.[2] This indicates that infants of mothers who smoke will have greater smoke exposure if the mother smokes nearby to the infant, highlighting the importance of recording not only maternal smoking habit, but whether the infant is exposed to active smoking in the same room. Thirdly, a phone interview was conducted when the infant was 12 weeks of age.[2]

Child eye follow-up study

Twins in the TEST were recruited from 1) A follow-up study of TIHS, 2) Mail-out to all Tasmanian twins on the Australian Twin Registry (aged 5–16 years), 3) Local media publicity. Exclusion criteria were major disability (e.g., cerebral palsy) or systemic illness (e.g., cancer). Participants underwent an extensive ophthalmological exam conducted by ophthalmologists and orthoptists over 60 minutes. Visual acuity with and without glasses was measured using a LogMAR chart at 3 meters. If vision was less than 0.0 (6/6), then visual acuity with pinhole was also measured. A cover test was performed at near and at distance to detect latent and manifest strabismus. Version eye movements were examined. Convergence near point was measured objectively with a RAF gauge (Clement Clarke, London).

Stereoacuity was measured at 40cm using the Lang I stereo test (Lang, Zurich) and/or Titmus stereo test (Stereo Optical Co, Chicago). Tests were performed according to the manufacturers' instructions. Cycloplegic autorefraction (Hark599, Humphrey, San Leadro, California) was taken 20–30 minutes after the instillation of one drop of 1% cyclopentolate to each eye.

Other measures included central corneal thickness, axial length, intraocular pressure, and stereo disc photography but these are not analyzed in this report. Amblyopia was defined as a difference in best-corrected visual acuity of 2 or more LogMAR lines between the eyes, regardless of whether a unilateral ambyogenic factor was present. Poor stereoacuity by Lang stereotest was the inability to see any picture on the card (0/3). Poor stereoacuity on Titmus stereotest was defined as being worse than (>) 100 seconds arc. This cut-off was chosen to reflect likely poor function rather than age-related development in stereoacuity. For example, among normal Saudi males of six years, the upper 95% confidence interval for mean stereopsis is 79 secs.[7] Strabismus was defined as any heterotropia at near and/or distance fixation without glasses.

Examiners were required to follow a strict protocol to ensure the standardization of vision assessment and results were only recorded after child training and an assessment that the child comprehended the task. When parents attended, a best corrected visual acuity and non-cycloplegic auto-refraction was also performed on them.

Parents / guardians were asked to complete a questionnaire, which was posted out in advance, regarding the child's crawling age and style, age of walking, use of a baby-walker, early motor development, and other aspects of the child's early life. Importantly, the eye examiner was blind to any antenatal characteristics (such as whether the mother smoked during pregnancy) and was not aware of the parental questionnaire content at the time of conducting the eye examination.

DNA samples were obtained to allow zygosity and other genetic testing for future genetic studies, which are not the subject of this paper. Written informed consent was obtained from parents and the children were not forced to undergo any examination they were uncomfortable with. The TEST was approved by the ethics committees of the following institutions: The University of Tasmania (Hobart) and The Royal Hobart Hospital. This study was conducted in accordance with the declaration of Helsinki and subsequent revisions.

Statistical methods

The distribution of eye outcomes was determined and if not normally distributed, categorical outcomes were made (Table 1). Pair-wise correlations between eye outcomes were obtained with Bonferonni adjustment for multiple comparisons.[8] For univariate risk estimates and associated confidence intervals,

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

Table 1. Ocular examination results

Ocular Characteristic	Prevalence %	Prevalence n/N	Within birth-set Spearman's correlation r	Within birth-set Spearman's correlation p value
Uncorrected visual acuity in better eye =6/9 (0.2 LogMAR) or worse	4.3	14/326	0.40	<0.01
Convergence near-point >5 cm	35.1	109/311	0.31	<0.01
Myopia (MSE less than 0.5D in one or both eyes)	7.0	21/301	0.04	0.58
Amblyopia	3.8	13/344	0.15	0.05
Hypermetropia with a MSE of +3D	3.2	11/344	0.39	<0.01
No strabismus or phoria	78.5	266/339	—	—
Esotropia (near or distance)	6.9	23/339	0.03	0.70
Esophoria (near or distance)	2.1	7/339	−0.02	0.84
Exotropia (near or distance)	6.3	21/339	−0.06	0.46
Exophoria (near or distance)	6.6	22/339	0.18	0.02
Titmus Stereo acuity range 1″–59″	69.1	235/340	0.32	<0.01
Titmus Stereo acuity range 60″ ≤ 100″	17.7	60/340	—	—
Titmus Stereo acuity range >100″–800″	9.1	31/340	—	—
No stereo acuity (Titmus)	4.1	14/340	—	—
Stereo acuity worse than 100 sec, including absent stereo acuity	13.2	45/340	0.33	<0.01
Lang car test (550″) failure	7.5	26/346	0.53	<0.01
Lang star test (600″) failure	6.7	23/346	0.51	<0.01
Lang cat test (1200″) failure	6.1	21/346	0.54	<0.01
All Lang tests failed	5.8	20/346	0.58	<0.01

*Across the four categories of stereoacuity on Titmus testing.

generalized linear models with a logit link and binomial error structure were used.[9] To obtain adjusted relative risk estimates and associated 95% confidence intervals, we used general estimating equation models with random and fixed effects and a logit link and binomial error structure.[10]

These models took into account the correlation within birth sets.[11] We identified potential confounders by literature review and an assessment of how candidate factors related to both the exposures and outcomes of interest.

For most associations, we examined over 30 potential individual confounders. These included antenatal smoking, antenatal alcohol consumption, birth-weight, length at birth, head circumference at birth, gestation, maternal and paternal age at birth, maternal education by time of birth, paternal employment status at birth, private medical insurance at birth, sex, child age at interview, exclusive breastfeeding at home visit, maternal and other household residents smoking postnatally, number of residents at infant home visit, and weight, length, and head circumference at home visit. For each of these factors, we examined how it related to the putative exposure (e.g., maternal smoking) and also the eye outcome.

Change in estimates of the exposure-outcome association was then examined after individual and multiple adjustments for confounders. Because of sample size, additional confounders were examined sequentially rather than including all as covariates in the same model. Relevant adjusted findings are reported, but not all analyses are reported due to the amount of potential confounding evaluated. Private health insurance at birth and maternal education level were used as markers of socioeconomic status.

We examined dose response trends using either linear regression (Figure 1) or the Wald test associated with categorical exposures, replacing the binary predictors with a single predictor, taking category rank scores. The prospective component was powered to detect univariate odds ratios of 2.5 or greater at $p < 0.05$ for antenatal smoking at a prevalence of 23% for outcomes of 10% prevalence.[12] Zygosity subgroups were not examined in this report because of ongoing zygosity work and limited sample size but we report on the within birth set Spearman's correlation for eye outcomes. In this paper, results with $p < 0.05$ are considered statistically significant. Analyses were conducted using STATA 9.0. (Statacorp 2005: Statistical Software: Release 9, College Station, TX).

RESULTS

From 2000–2002, 346 individuals (167 twin pairs and 4 sets of triplets) were seen, representing a volunteer sample from over 2,000 multiple births in Tasmania from 1985 to 1998. The mean age at time of examination was 9.25 years (SD ± 2.4) with an age range from 5 to 16 years. Boys comprised 50.6% (175/346) of the sample. Prospective TIHS data were also available for 83% (288/346) of these infants. Not all children and parents completed all parts of the eye examination and questionnaire measures.

General features

The uncorrected mean visual acuity was similar for right and left eyes, mean values 0.008 (± SD 0.14) and 0.008 (± SD 0.15) LogMAR units, respectively. This equates to 6/6 Snellen equivalent. Both distributions were peaked (kurtosis 14.8, 16.9) and skewed to the right (skewness 2.54, 2.78). The mean spherical equivalent (MSE) by cycloplegic autorefraction was +0.87D (SD ± 1.07), again with a peaked (kurtosis 8.80) and slightly

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

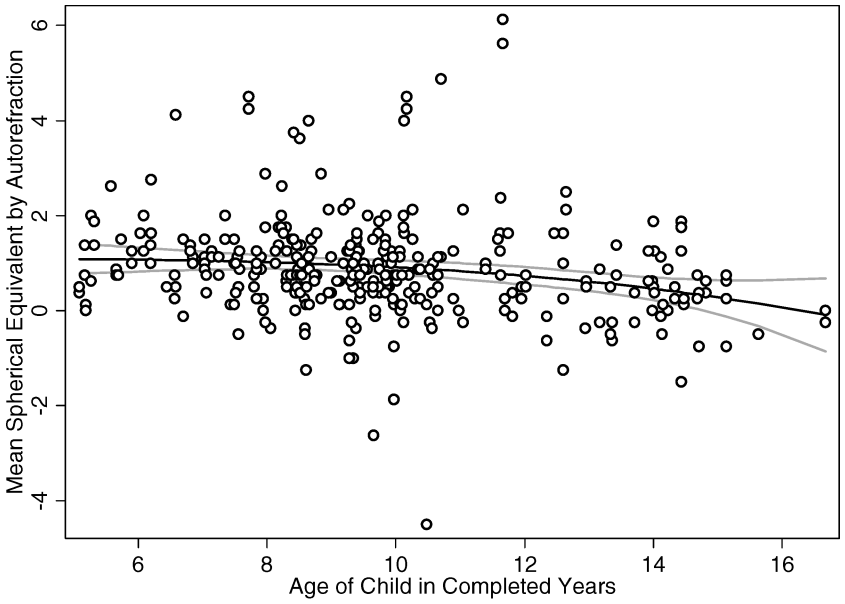


Figure 1. Plot of mean spherical equivalent autorefraction by age of child in years and a fitted fractional polynomial regression line with associated 95% confidence interval. Test for linear trend of decreasing MSE by age, $p < 0.001$.

right skewed distribution (skewness 0.87). The best-corrected mean visual acuity was -0.13D (SD $\pm$ 0.11). This equates to 6/4.8 plus 1 letter.

Eleven children had significant hypermetropia with at least a MSE of +3 D, averaging both eyes (Table 1). Of these children, 3 had an anismetropia, of 2 D based on MSE. The distribution of other categorical eye outcomes is shown in Table 1. We examined the correlation for ocular outcomes within each multiple birth set. The highest correlations were found for stereoacuity and uncorrected visual acuity (Table 1).

Parents reported past eye history as follows: a set of premature DZ twins had retinopathy of prematurity requiring bilateral retinal cryotherapy; one pair of MZ twins had bilateral esotropia surgery; one pair of twins had reported previous corneal ulcers; one individual had a unilateral dermoid; one individual had a unilateral mild cataract; two children required nasolacrimal duct probing; one child had a fully recovered chemical burn to the eye, and one child had reported delayed visual maturation.

Table 2 shows that several of the eye outcomes were strongly correlated. Poor uncorrected visual acuity was significantly related to amblyopia, myopia, poor stereoacuity and esotropia. Poor stereoacuity on both Titmus and Lang testing and esotropia were closely related. Boys and girls had a similar distribution of eye outcomes. Increasing child age was associated with lower MSE values (Figure 1) and increasing near-point of convergence ($p = 0.03$). The prevalence of myopia (< -0.5D) by age category was: 5 to 7 yrs 1.4% (95% CI 0.04, 7.6); 8 to 9 yrs 5.8% (95% CI 2.4, 11.6); 10 to 13 yrs 10.6% (95% CI 5.0, 19.2); 14 to 16 yrs 16.7% (95% CI 4.7, 37.4); test for trend ($p = 0.002$). This trend persisted ($p < 0.01$) after taking into account sex and birth set clustering.

Antenatal and infant environmental factors — prospective report

Two-hundred eighty-eight children from 143 multiple birth sets who participated in this study also had additional prospective infant data available from the TIHS. These 288 children represented 83% (288/346) of TEST children examined in 2000–2002 and 22% of all Tasmanian multiple births born between 1988 and1995. These children were representative of all Tasmanian multiple births with regard to low birth weight and prematurity but were less likely to have a mother who smoked in pregnancy (23.6% (68/288) vs. 34.9% (340/974), $p < 0.01$).

These children were followed up at a mean age of 9.8 (SD $\pm$ 2.1) years. Males comprised 49% (141/288) of this sample. The mean birth weight was 2,481 g (SD $\pm$ 580) and the mean gestation was 36.2 weeks (SD $\pm$ 2.72). A large proportion of the twin sample (43%, 124/288) were born prematurely (<37 weeks gestation) and the same proportion (43%, 124/288) were of low birth-weight (<2.5 kg). Prematurity was associated with low birth-weight, as expected (RR 4.99, 95% CI: 3.46, 7.17).

Nearly a quarter (23.6%, 68/288) of these children were exposed to maternal smoking *in utero*. One hundred eighty four of these 288 children also participated in another concurrent study investigating cardiovascular disease, which recruited TIHS cohort multiplets born between 1991 and 1993. This study provided current maternal smoking at time of child interview,[13]

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

Table 2. The correlation between eye outcomes with a Bonferroni adjustment for multiple comparisons

	Uncorrected visual acuity = 6/9 (0.2) or worse in best eye	Mean spherical equivalent	Myopia (less than 0.5 dioptres in one or both eyes)	Amblyopia	Poor stereoacuity on Titmus stereotest (worse than 100″)	Poor stereoacuity on Lang stereotest (all Lang tests failed)	Esotropia	Exotropia	Convergence near –point >5 cm
Uncorrected visual acuity =6/9 (0.2) or worse in best eye	**1.00**								
Mean spherical equivalent	0.09	**1.00**							
Myopia (less than 0.5 dioptres in one or both eyes)	0.21**	**−0.45****	**1.00**						
Amblyopia	**0.41****	0.17	0.01	**1.00**					
Poor stereoacuity (worse than 100″)	**0.45****	**0.26****	−0.02	**0.37****	**1.00**				
All Lang tests failed	**0.29****	0.21**	−0.06	0.15	**0.60****	**1.00**			
Esotropia	0.14	0.13	0.18*	0.01	**0.29****	**0.48****	**1.00**		
Exotropia	−0.03	−0.01	−0.04	−0.01	0.01	0.09	0.09	**1.00**	
Convergence near-point >5 cm	0.05	0.04	−0.03	0.10	0.10	−0.01	0.05	0.13	**1.00**

Note:**P < 0.001; * 0.05<P> 0.001, No asterisk, P > 0. 05. Correlation >0.25 in magnitude indicated in bold.

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

consequently maternal smoking data were only available for these 184 children participating in both studies.

Maternal smoking

Maternal smoking during pregnancy was associated with increased risk of poor stereoacuity by Titmus and Lang testing, and also the presence of esotropia (Table 3), with p-values of 0.05 or less observed for dose response trends for third trimester smoking. Maternal smoking during the third trimester was not associated with exotropia (test for trend, $p = 0.17$) or poor visual acuity. The correlation between antenatal and early postnatal maternal smoking was high ($r = 0.86$, $p = 0.001$) and it was not possible to assess their independent effects or that in one trimester compared to another trimester due to the high level of agreement across these time periods.

However, data on postnatal infant smoke exposure (infant sometimes or usually exposed to active smoking by mother or other in the same room at one month of age) were available as well as maternal postnatal smoking habit, so we were able to unravel antenatal and postnatal infant smoke exposure, as the latter was not as tightly linked to antenatal maternal smoking as maternal postnatal smoking habit alone. After adjustment for infant exposure to postnatal smoke, antenatal smoking in the third trimester remained significantly associated with poor stereoacuity on Titmus ($p = 0.05$) and Lang testing ($p = 0.001$) and the presence of esotropia ($p = 0.008$).

In contrast, infant exposure to postnatal smoke was not significantly associated with these outcomes (Table 3). We examined whether the third trimester smoking patterns were independent of maternal smoking in childhood for the 184 children on whom current childhood smoke exposure data were available. Increasing antenatal smoking in the third trimester remained significantly ($p < 0.05$) associated with all three outcomes after adjustment for mother smoking at child interview.

The association between antenatal maternal smoking and poor stereoacuity was then examined, taking into account birth clustering and potentially confounding factors. Increasing maternal smoking in the last trimester remained significantly associated with increasing risk of poor stereoacuity by Lang test failure and the presence of esotropia, with a smaller but nonsignificant tendency for poor stereoacuity on Titmus test, after adjustment for birth weight (grams) or gestation (weeks), maternal and paternal age, antenatal alcohol intake, low maternal education, private health insurance, paternal unemployment, low birth weight, head circumference at birth, length at birth, sex, Apgar score at 1 minute, and bottle-feeding at one month of age. Importantly, the trend for increased risk of esotropia with increasing smoking during the third trimester was evident ($p = 0.047$) even among those ($n = 247$) with no family history of strabismus for relatives outside the birth set. After excluding children with amblyopia, the association between increasing maternal smoking in the last trimester and Lang test failure or presence of esotropia remained.

We examined how the following factors related to poor stereoacuity on the Titmus test: low birth weight (<2500 g), prematurity (<37 weeks), male sex, maternal antenatal alcohol ingestion, paternal age at birth, maternal age at birth, infant apnoea, bottle feeding at one month of age, weight, length or head circumference at one month of age, household resident number, paternal unemployment at birth, low maternal education, parental marital status, or private health insurance at birth. No significant associations were observed. For example, exclusive breastfeeding at one month was not associated with poor stereoacuity (ARR (adjusted relative risk) 1.12 (0.61, 2.08)).

Crawling and walking

The mean ages at start of crawling and walking were 8.8 months (SD ± 2.2) and 13.5 months (SD ± 2.6), respectively. Most children (86%, 295/343) crawled on all-fours as an infant. One third, 33.5% (116/ 346) used a baby walker. Both age at first crawling (RR = 1.23 per month (95% CI: 1.06, 1.42) $p = 0.005$) and walking (RR 1.18 per month (95% CI: 1.05, 1.22) $p = 0.001$) were associated with poor stereoacuity on the Titmus test.

Similarly, poor stereoacuity on the Lang test was also associated with later age of first crawling (RR = 1.28 per month (95% CI: 1.09, 1.48) $p = 0.005$) and walking (RR 1.21 per month (95% CI: 1.10, 1.33) $p = 0.001$). However, age at first crawling or walking was not associated with esotropia. The median age at commencement of walking by stereoacuity on Titmus testing is shown in Figure 2. Later walking age remained associated with a higher risk of poor stereoacuity on both the Titmus and Lang test after accounting for birth set clustering, age, sex, prematurity, private insurance, or paternal age.

DISCUSSION

This study has detailed prospectively collected data on maternal smoking and a thorough ophthalmic examination performed on children in the later stages of their visual development. In this twin sample, as in other Australian studies,[14,15] myopia was uncommon among primary school age children. The median refraction was +0.75D, which was less myopic than reported by Rose et al.[15] who reported MSE of +0.4D at age 6 and –1.15D at 15 years. Of importance, we may be overestimating myopia by 0.5D as an artifact of the cycloplegic autorefraction.[16] The mean uncorrected visual acuity was 0.0 (6/6), which is slightly better than that reported by Robaei et al.[14]

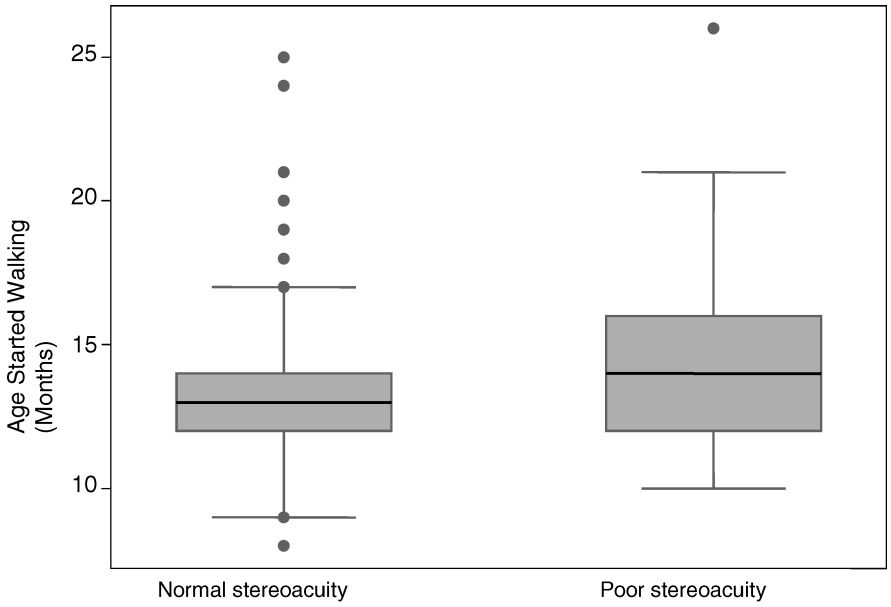
The proportion of children with myopia increased with age, associated with an age-related decrease in MSE refraction consistent with other reports.[15] More prevalent eye conditions were poor stereoacuity on Titmus test and strabismus. Strabismus (esotropia or exotropia) was present in 13%, which is higher than in previous studies.[15,17] This may partially reflect the twin sample, with an over-representation of low birth weight births, previously associated with a higher likelihood of these conditions.[6] Even among an unselected school sample of children aged 3–12 years in New South Wales, 39.2% failed one or more of four binocular vision tests.[18] Here, poor stereoacuity on Titmus test was positively and strongly correlated with Lang test failure

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

Table 3. The prospective association between maternal smoking and stereoacuity and esotropia

Smoking exposures (reference group)	Poor stereoacuity on Titmus stereotest (worse than 100″ of arc) %	n/N	Relative risk (95%CI) after adjustment for age and sex	Poor stereoacuity on Lang stereotest (0/3 objects) %	n/N	Relative risk (95%CI) after adjustment for age and sex	Esotropia %	n/N	Relative risk (95%CI) after adjustment for age and sex
Antenatal smoking—first trimester									
(no cigarettes/day)	12.7	28/221	1.00 (reference)	5.4	12/224	1.00 (reference)	7.0	15/213	1.00 (reference)
1–10 cigarettes/day	3.6	1/28	0.28 (0.04, 1.96)	3.6	1/28	0.65 (0.09, 4.84)	7.1	2/28	1.02 (0.25, 4.21)
11–20 cigarettes/day	31.3	5/16	2.46 (1.10, 5.52)	25.0	4/16	5.19 (1.85, 14.61)	0.0	0/16	0.00 (0.00, 4.62.)
21–40 cigarettes/day	12.5	2/16	0.95 (0.25, 3.66)	6.3	1/16	1.28 (0.18, 9.32)	18.8	3/16	2.51 (0.79, 7.99)
More than 40 cigarettes/day	50.0	2/4	4.28 (1.43, 12.84)	50.0	2/4	10.21 (2.96, 35.26)	50.0	2/4	7.50 (2.45, 23.00)
Test for linear trend			$p = 0.11$			$p = 0.003$			$p = 0.03$
Antenatal smoking—second trimester									
(no cigarettes/day)	12.2	28/229	1.00 (reference)	5.2	12/232	1.00 (reference)	6.8	15/221	1.00 (reference)
1–10 cigarettes/day	11.5	3/26	0.92 (0.30, 2.87)	11.5	3/26	2.35 (0.70, 7.85)	7.7	2/26	1.10 (0.26, 4.59)
11–20 cigarettes/day	21.4	3/14	1.74 (0.60, 5.04)	14.3	2/14	3.05 (0.74, 12.5)	7.1	1/14	1.03 (0.15, 7.29)
21–40 cigarettes/day	21.4	3/14	1.73 (0.60, 5.01)	14.3	2/14	2.92 (0.72, 11.88)	21.4	3/14	3.10 (1.01, 9.50)
More than 40 cigarettes/day	50.0	1/2	4.11 (0.95, 17.67)	50.0	1/2	10.40 (2.17, 49.73)	50.0	1/2	7.47 (1.71, 32.55)
Test for linear trend			$p = 0.08$			$p = 0.005$			$p = 0.02$
Antenatal smoking—third trimester									
(no cigarettes/day)	12.3	28/227	1.00 (reference)	5.2	12/230	1.00 (reference)	6.9	15/219	1.00 (reference)
1–10 cigarettes/day	4.2	1/24	0.34 (0.05, 2.36)	4.2	1/24	0.83 (0.11, 6.11)	4.2	1/24	0.60 (0.08, 4.35)
11–20 cigarettes/day	27.8	5/18	2.22 (0.97, 5.11)	22.2	4/18	4.94 (1.73, 14.12)	11.1	2/18	1.58 (0.39, 6.43)
21–40 cigarettes/day	21.4	3/14	1.72 (0.59, 5.00)	14.3	2/14	2.94 (0.72, 11.97)	21.4	3/14	3.08 (1.00, 9.43)
More than 40 cigarettes/day	50.0	1/2	4.06 (0.95, 17.47)	50.0	1/2	10.59 (2.21, 50.81)	50.0	1/2	7.39 (1.70, 32.24)
Test for linear trend			$p = 0{\cdot}05$			$p = 0.001$			$p = 0.02$
Infant exposed to mother or other smoking in the same room at one month									
(No)	13.5	28/207	1.00(reference)	7.14	15/210	1.00(reference)	8.5	17/199	1.00(reference)
Yes	13.6	8/59	1.00(0.48, 2.08)	8.5	5/59	1.22(0.46, 3.25)	6.8	4/59	0.80 (0.28, 2.26)

Downloaded By: [Mackey, David] At: 02:44 27 December 2007



Note: Poor stereoacuity was defined on Titmus testing as being worse than 100″.
Difference in median age at start of walking: Kruskal-Wallis test, p=0.014.

Figure 2. Box Plot of the distribution of age at start of walking by child stereoacuity.

(as expected) and moderately correlated with poor visual acuity, amblyopia and esotropia.

The twin sample was representative of all twin births in Tasmania with regard to low birthweight and prematurity and compared to the Finnish multiple birth cohort from 1991–1993 shows a similar proportion of low birthweight (43% vs. 40%) and premature infants (43% vs. 45% respectively).[19] The follow-up sample from the TIHS had a lower than expected proportion of mothers who smoked during pregnancy, consistent with a higher participation rate for non-smoking families. Although this is likely to have influenced prevalence estimates, it is unlikely to bias the associations between maternal smoking and poor stereopsis as it would be unlikely that the follow-up of smokers would be differential by stereoacuity status. The lack of association between smoking in pregnancy and poor visual acuity makes it unlikely that mothers who smoked during pregnancy would have been especially likely to encourage child participation if the child had visual acuity problems.

As in previous studies,[4–6] maternal smoking was associated with impaired stereoacuity and also the presence of esotropia. The strongest adverse effects were observed for maternal smoking of more than forty cigarettes per day (Table 3) and dose response trends were observed. The main contribution of this prospective report is the demonstration for the first time that increasing maternal smoking in the last trimester was independently associated with poor stereoacuity, particularly as measured by Lang test failure, and also with esotropia after adjustment for infant postnatal smoke exposure and maternal smoking in childhood. For poor stereoacuity by Titmus testing, the trends were in the same direction but only of borderline significance.

The weaker patterns observed for stereoacuity by Titmus rather than Lang testing may reflect that a more severe cut-off was used to define poor stereoacuity by Lang testing. Alternatively, the stronger association between maternal smoking and greater Lang failure may be attributed to monocular or lateral displacement cues in the Titmus circles test. It has been suggested when viewed monocularly through polarized lenses, a non stereoscopic lateral displacement of one of the four Titmus circles is readily apparent in the first four sets of Titmus circles.[20,21] This was demonstrated by Cooper and Warshowsky (1977)[22] where individuals who suppressed an eye could use this cue to respond correctly to the Titmus circles. Conversely, Random dot stereotests such as Lang lack these monocular and line contour cues,[23] thus could explain a greater Lang failure in twin participants.

The study did not have sufficient power to assess the contribution of this trimester independent of smoking during the other trimesters. The strong dose response trends evident for Lang test failure and esotropia persisted after adjustment for potential confounders such as low maternal education, and birth weight. These findings provide further evidence that antenatal smoking is likely to be causally related to poor stereoacuity and esotropia in childhood.

There was a clear association between later age at first crawling or walking and poor stereoacuity. This is an intriguing finding with several explanations. First, antenatal or perinatal central nervous system (CNS) damage may have led to both delayed walking and reduced stereoacuity.[24] Neonatal CNS damage is related to developmental delay, including delayed motor milestones and also related to a reduction in stereoacuity.[24]

Downloaded By: [Mackey, David] At: 02:44 27 December 2007

Secondly, infants with poor stereoacuity may have been less confident to start taking steps due to poorer depth perception. Thirdly, delayed walking may lead to poor stereoacuity. That is, sensory–driven neural activity assists infant brain development, including visual functional maturation.[25] An anomalous binocular experience during early childhood can severely disrupt stereoacuity development and the vulnerable age with regard to accommodative esotropia appears to be 10.8–20 months.[26] This encompasses the stage of walking commencement. Further work, with the prospective recording of motor milestones and serial measures of stereoacuity, is required to evaluate this issue. Delayed crawling and walking could also be further investigated as indicators for early referral for pediatric ophthalmic evaluation.

Overall, this twin study with a prospective component has provided further evidence that maternal smoking in pregnancy has an adverse impact on children's vision. The novel finding of a positive association between delayed crawling or walking and stereoacuity has potential implications for vision screening in infancy but prospective data are now required.

ACKNOWLEDGMENTS

We would like to thank the twins and their families for participating in the study, the Australian Twin Registry, and the Tasmanian Ophthalmologists and Orthoptists. We would like to thank Johan Poulsen, Tze'Yo Toh, and Alex Hewitt for their assistance in the eye examinations and Angela Pezic for assistance with graphical presentation. This work was supported by the Clifford Craig Medical Research Trust, The Ophthalmic Research Institute of Australia, and The NHMRC grant 350415. David Mackey is in Receipt of a Pfizer Australia Fellowship Award.

REFERENCES

1. Martin N, Boomsma D, Machin G. A twin-pronged attack on complex traits. *Nat Genet.* 1997; 17:387–392.
2. Dwyer T, Ponsonby AL, Couper D. Tobacco smoke exposure at one month of age and subsequent risk of SIDSA prospective study. *Am J Epidemiol.* 1999; 149:593–602.
3. Ponsonby AL, Couper D, Dwyer T, et al. The relation between infant indoor environment and subsequent asthma. *Epidemiology.* 2000; 11:128–135.
4. Christianson RE. The relationship between maternal smoking and the incidence of congenital anomalies. *Am J Epidemiol.* 1980; 112:684–695.
5. Hakim RB, Tielsch JM. Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. *Arch Ophthalmol.* 1992; 110:1459–1462.
6. Chew E, Remaley NA, Tamboli A, et al. Risk factors for esotropia and exotropia. *Arch Ophthalmol.* 1994; 112:1349–1355.
7. Almubrad T. Statistical stereo-acuity norms in Saudi children. *Clin Exp Optom.* 2006; 89:155–1599.
8. Armitage P, Berry G, Matthews JNS. *Statistical Methods in Medical Resea*rch. Oxford, UK: Blackwell Scientific Publications, 1994.
9. McCullagh P, Nelder JA. *Generalized Linear Models.* London: Chapman and Hall, 1989.
10. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: and orientation. *Am J Epidemiol.* 2003; 157:364–375.
11. Carlin JB, Gurrin LC, Sterne JA, et al. Regression models for twin studies: A critical review. *Int J Epidemiol.* 2005; 34:1089–1099.
12. Garcia-Closas M, Lubin J. Power and sample size calculations in case-control studies of gene-environment interactions: comments on different approaches. *Am J Epidemiol.* 1999; 149:689–692.
13. Morley R, Carlin JB, Dwyer T. Maternal calcium supplementation and cardiovascular risk factors in twin offspring. *Int J Epidemiology.* 2004; 33:1304–1309.
14. Robaei D, Rose K, Ojaimi E, et al. Visual acuity and the causes of visual loss in a population-based sample of 6-year-old Australian children. *Ophthalmology.* 2005; 112:1275–1282.
15. Rose K, Younan C, Morgan I, et al. Prevalence of undetected ocular conditions in a pilot sample of school children. *Clin Experiment Ophthalmol.* 2003; 31:237–240.
16. Toh T, Kearns L, Scotter L, et al. Post-cycloplegia myopic shift in an older population. *Ophthalmic Epidemiol.* 2005; 12:215–219.
17. Brown S, Jones D. A survey of the incidence of defective vision and strabismus in kindergarten age children- Sydney, 1976. *Aust Orthop J.* 1977; 15:24–28.
18. Junghans B, Kiely PM, Crewther DP, et al. Referral rates for a functional vision screening among a large cosmopolitan sample of Australian children. *Ophthalmic Physiol Opt.* 2002; 22:10–25.
19. Klemetti R, Gissler M, Hemminki E. Comparison of perinatal health of children born from IVF in Finland in the early and late 1990s. *Hum Reprod.* 2002; 17:2192–2198.
20. Reinecke R, Simons K. A new stereoscopic test for amblyopia screening. *Am J Ophthalmol.* 1974; 78:714–721.
21. Simons K, Reinecke R. A reconsideration of amblyopia screening and stereopsis. *Am J Ophthalmol.* 1974; 78:707–713.
22. Cooper J, Warshowsky J. Lateral displacement as a response cue in the titmus stereo test. *Am J Optom Physiol Opt.* 1977; 54:537–541.
23. Cooper J. Clinical stereopsis testing: Contour and random dot stereograms. *J Am Optom Assoc.* 1979; 50:41–46.
24. Mercuri E, Anker S, Guzzetta A, et al. Visual function at school age in children with neonatal encephalopathy and low Apgar scores. *Arch Dis Child Fetal Neonatal Ed.* 2004; 89:F258–F262.
25. Penn A, Shatz C. Brain waves and brain wiring: the role of endogenous and sensory-driven neural activity in development. *Ped Res.* 1999; 45:447–458.
26. Fawcett S, Wang Y, Birch E. The critical period for susceptibility of human stereopsis. *Invest Ophthalmol Vis Sci.* 2005; 46:521–525.