7 Birthweight, weight growth and diabetes risk

In this chapter the programming hypothesis is tested: that low birthweight, and/or disrupted growth (especially catch-up growth), is associated with subsequent risk of diabetes among adults. The chapter is organised into two parts. The first part describes the Cherbourg infant health clinic data, including birthweights, and statistically derived estimates of birthweights. It then analyses the patterns of weight growth of study participants from birth to five years. The second part examines the programming hypothesis, through analysis of birthweight and weight growth in relation to diabetes risk factors as measured in the survey.

7.1. Background: birthweight and patterns of weight growth in Cherbourg

This section describes the background to participants’ child health records. Birthweight and weight growth to five years are then examined to determine typical patterns of child growth in Cherbourg.

7.1.1. Cherbourg child health records

Exceptionally clean and nice (Nurse’s entry in a Cherbourg child’s medical records, 1958).

The Infant Health Clinic (IHC) began in Cherbourg in October 1950 and continued until November 1985, during which time 2156 children attended the clinic. The earliest birth-year of a child attending the clinic is 1947. All children who were born at or living at Cherbourg attended the clinic regularly, usually weekly, until they were ‘school age’ (about five years old). Coverage by the clinic was almost universal, with gaps in records occurring only when children were living off-settlement, for example, while their mothers were working elsewhere or the children were staying with relatives outside Cherbourg. The frequency of clinic attendance, and therefore the detail of the weight growth records available, arises from a system that was in place for many years, whereby mothers were fined if their children did not attend the clinic regularly (Tarita Fisher 2000, personal communication). Some children attended the clinic when they were visiting family at the settlement.
At each clinic visit the child was weighed and their general health status observed. Characterisations of health status were strongly related to the disciplinary culture of the settlement; many of the notes describe how the child was clothed, or how clean they appeared, or whether they were accompanied or arrived for their regular appointment on time (see opening quotation above). These clinic inspections were carried out by nurses as Cherbourg did not have a residential doctor until 1985. The weight measures taken by the clinic have been validated elsewhere (Dugdale et al. 1990c).

Participants were not chosen for the study based on the availability of their records as this would have compromised the representativeness of the study sample of current Cherbourg adults. In addition, it was far more feasible to select from living individuals and link them to their child records than to attempt to follow up the more than 2000 infants, many of whom have since died.

Of the 216 people who took part in the field study (September to December 2000), child clinic records are available for 156. There are no birthweight records available for those who were born before 1950. Given that diabetes prevalence (in particular diagnosed diabetes) increases with age, birth records are less likely to be available for participants with diabetes (Table 7.1). Participants with available records and those without may potentially differ on other factors unrelated to age and diabetes diagnosis, such as place of birth and where they spent their childhood. These effects are expected to be limited, however, as place of birth was found not to be associated with birthweight for those who were born elsewhere but whose birthweight had been recorded by the Cherbourg IHC (Section 9.1).
Table 7.1. Availability of participants’ child health records, according to diabetes diagnosis.

<table>
<thead>
<tr>
<th>Records available</th>
<th>Females</th>
<th>Males</th>
<th>Total % available&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diagnosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (41.27)</td>
<td>23 (52.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never-diagnosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (31.38)</td>
<td>12 (34.17)</td>
<td>.543</td>
</tr>
<tr>
<td>Gestational</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (30.78)</td>
<td>3 (33.00)</td>
<td>.591</td>
</tr>
<tr>
<td></td>
<td>85 (34.34)</td>
<td>38 (45.16)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Numbers of participants in each category; mean age in years (on their birthday in 2000) shown in brackets.

<sup>b</sup>p value from independent samples t-tests (two-tailed) of the hypothesis that age of participants did not differ according to record availability.

<sup>c</sup>Of category, females and males combined.

Each participant in the study was asked as part of the consent form for their permission to link their IHC records to the data collected in the surveys. Of the 156 participants who had records available, 12 women and two men did not consent for their records to be linked to the survey data, leaving a total of 142 records which could be analysed with regard to risk factors. It is unlikely that the records of those who did not consent differ in any systematic or significant manner, other than sex (see below), from the records of those who gave their consent, for example, in age (Table 7.2).
Table 7.2. Participants’ consent to link their child health records to the results of the diabetes survey.

<table>
<thead>
<tr>
<th>Consent</th>
<th>Females&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Males&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Total consent&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (mean age)</td>
<td>No (mean age)</td>
<td>Sig.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes (mean age)</td>
<td>No (mean age)</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>25 (41.32)</td>
<td>1 (40)</td>
<td>n/a</td>
<td>22 (41.95)</td>
<td>1 (37.00)</td>
</tr>
<tr>
<td>Never-diagnosed</td>
<td>39 (30.82)</td>
<td>11 (33.36)</td>
<td>.361</td>
<td>47 (33.32)</td>
<td>1 (37.00)</td>
</tr>
<tr>
<td>Gestational</td>
<td>9 (30.78)</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Total</td>
<td>73 (34.39)</td>
<td>12 (33.92)</td>
<td>0.889</td>
<td>69 (36.07)</td>
<td>2 (37.00)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Numbers of participants in each category (mean age in years on their birthday in 2000).

<sup>b</sup> Two-tailed t-test of the hypothesis of no age difference between those who gave permission and those who did not give permission for their child records to be linked to their survey results. Performed only for the category of never-diagnosed females as there were insufficient numbers in the other categories for analyses.

<sup>c</sup> Number of females and males combined.

A significantly greater proportion of female than male participants did not give their consent (Chi-square: p=0.016, value=5.832). A greater proportion of the randomly selected women (never-diagnosed) did not consent to have their birth records used than women with current diagnosed diabetes or who had gestational diabetes, although this difference was not quite significant (Chi-square: p=0.050, value=5.973). This difference is most likely due to the personal relevance of the study, and perceptions of how important their own contributions might be.

Data entry and conversion

Weight data and the date of each visit were transcribed from the archival microfilm records to a database (Microsoft Access), using the identity codes assigned during the surveys, as described in Section 5.3. This amounted to 19,227 records. Length (or height for older children) and head circumference, were available for only 13 participants; recording of these by the IHC only commenced in 1966 and coverage was sporadic. Likewise there is very little data on head circumference at birth (16 participants). There is no data on placental size in the IHC records, nor is there consistent information on maternal smoking and alcohol consumption; it is likely that at least some of the participants’ mothers did smoke and consume alcohol during pregnancy. The prevalence of smoking among women in the community was probably not as
high in the past as it is now (fewer older people than young people smoke, see Section 8.2.3, a difference not accounted for by former smokers). There is no explicit information on alcohol use among pregnant women. Until the 1980s, however, Cherbourg was a ‘dry’ community, so alcohol was unlikely to have been consumed readily while people were on-settlement. Nor, probably, did women working as domestics have ready access to alcohol. A study of Cherbourg births more recent than those in the scope of the present study found that maternal alcohol consumption had a significant negative association with birthweight (Powell and Dugdale 1999).

Early clinic data were measured in the imperial system (stones, pounds, ounces, inches); metric measures were introduced in the late 1970s. Imperial measures were converted into metric for ease of comparison between participants and with outside references.

7.1.2. Fitted birthweights

Of the 142 IHC records to be linked to the survey data, birthweights were recorded for 72. Age greater than 50 years and place of birth other than Cherbourg are the reasons for missing data. Forty of the remaining 70 participants had weight recorded within the first two weeks of birth. A reliable estimate of birthweight for these participants would increase the sample size by more than 50%.

Previous researchers using this dataset have used the first weight measurement as equivalent to birthweight if it was taken within two weeks of birth (Dugdale et al. 1990a; Dugdale et al. 1990c; Dugdale et al. 1994). Patterns of early postnatal growth, however, vary greatly between individuals. Some initial weight loss is common immediately following birth, with a subsequent positive trajectory of weight gain commencing after this loss. Other individuals start gaining weight rapidly and immediately after birth. It is therefore preferable to take individual variation in growth into consideration when estimating birthweight, especially when the dataset available is small. Although catch-up and catch-down growth could not be measured directly in individuals in the absence of data, the flexibility of the method used to predict missing birthweights and the fact it was only used for those who were weighed within two weeks of birth does take into account individual variation.
Curves were fitted to the data wherever there were three or more measurements recorded within the first month (splines were chosen as they fit the data closely while remaining flexible).\textsuperscript{58}

Two of the 40 participants who were weighed within two weeks of birth were excluded from birthweight estimation as there were only two recorded measurements, insufficient to extrapolate birthweight with any accuracy. Two curves were fitted for each of the 38 participants, using splines derived from each individual’s growth pattern, one with 15 degrees of freedom and the other with 10 degrees of freedom. In most cases, there was very little difference between the two predictions. In two cases, the difference between the estimates produced by the two methods was greater than 200g, therefore these two cases were omitted to minimise error. Splines using 15 degrees of freedom appeared to fit the data slightly better when assessed visually, therefore the estimates derived from these are used in analyses of birthweight.

Estimating birthweight in this manner increased the birthweight sample size by 36 to 108. Birthweight in relation to adult diabetes risk could then be examined for 50% of the study participants. This sample size, though not particularly large, is sufficient for valid comparisons to be made of associations with risk factors. Any intergroup differences (i.e. between diagnosed and never-diagnosed participants) will need to be substantial if they are to be found statistically significant.

The mean age at which first weight was recorded (in the absence of birthweight) was 9.64 days (range 1 to 14 days) (Table 7.3). On average, the estimated birthweights were 306.39g lighter than first recorded weight.

\textsuperscript{58} Jenss curves were fitted by Dr Ann Cowling, Statistical Consulting Unit, The Australian National University. Details of the method used and its validation are provided in Appendix G.
Table 7.3. Estimated birthweight and first recorded weight

<table>
<thead>
<tr>
<th></th>
<th>Estimated birthweight (a)</th>
<th>First recorded weight (b)</th>
<th>a-b</th>
<th>Age at first visit (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=20</td>
<td>Mean</td>
<td>3242.92</td>
<td>3538.01</td>
<td>-295.09</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>608.66</td>
<td>597.33</td>
<td>219.58</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=16</td>
<td>Mean</td>
<td>3249.72</td>
<td>3570.25</td>
<td>-320.53</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>477.92</td>
<td>582.23</td>
<td>188.94</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Mean</td>
<td>3245.94</td>
<td>3552.34</td>
<td>-306.39</td>
</tr>
<tr>
<td>n=36</td>
<td>Standard deviation</td>
<td>546.82</td>
<td>582.44</td>
<td>204.06</td>
</tr>
</tbody>
</table>

The birthweight estimation method was tested by calculating differences between estimated and recorded birthweights for the 72 infants for whom the latter was available. Predicted birthweights tended to be slightly, but not significantly, lower than recorded birthweights, for both females and males (Table 7.4). Although small, this difference may be real in that it could reflect a variation in antenatal care; those whose birthweights were recorded probably received better antenatal care, a factor well recognised to result in fewer low birthweight babies (de Costa and Child 1996; Fejo and Rae 1996; Mackerras 2001).

Table 7.4. Test for difference between recorded and estimated birthweights

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recorded (38)</td>
<td>Estimated (20)</td>
</tr>
<tr>
<td>Mean</td>
<td>3275.6</td>
<td>3242.9</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>515.8</td>
<td>608.7</td>
</tr>
<tr>
<td>p value(^a)</td>
<td>.830</td>
<td>.350</td>
</tr>
</tbody>
</table>

\(^a\) Independent samples \(t\)-test (two-tailed) of the hypothesis of no difference between birthweights which had been recorded and the estimates for the missing birthweights. Number of participants within each category are shown in brackets.

The actual and estimated birthweights of participants were tested to determine if they came from the same distribution. There were no significant differences in distribution between actual and estimated birthweights for either females or males (Table 7.5).
Table 7.5. Kolmogorov-Smirnov test: actual and estimated birthweights of participants

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolmogorov-Smirnov Z</td>
<td>.479</td>
<td>.740</td>
</tr>
<tr>
<td>p value</td>
<td>.976</td>
<td>.644</td>
</tr>
</tbody>
</table>

Tests the hypothesis that the two samples come from the same distribution.

How representative of the IHC coverage is the sample?

The current mean birthweight for Australia as a whole is 3360g, with females weighing slightly less than males (3297g and 3420g) (ABS and AIHW 2001). The mean for all recorded birthweights in Cherbourg has been lighter than this on average over the three-and-a-half decades of the IHC, and again females are born weighing approximately 100g less than males (means 3130g and 3228g respectively). This difference is also reflected in the birthweights of participants in this study (means 3264 g and 3361g respectively, estimated weights included).

The birthweights of participants were approximately 150g to 250g heavier than the current average birthweights for Indigenous infants in Queensland (Section 3.2.1), and study participants were also slightly (but not significantly) heavier as babies than the entire IHC data sample. This is likely to be a reflection of poorer survival of low birthweight babies. In addition, diagnosed diabetics also make up a greater proportion of the study sample than of the whole community (about 40% rather than 20%), which may skew the birthweights somewhat towards heavier babies if their mothers had been diabetic while pregnant.

Participant birthweights (actual and estimated) were tested against all recorded birthweights to determine whether there were significant differences between the samples in the means and distributions. The means, standard deviations, range and quartiles for each are shown in Table 7.6. The distributions of participant and the remaining IHC birthweights were significantly different from each other overall (Table 7.7).

59 1999 data, includes stillbirths.

60 In the analyses of birthweights referring to ‘all recorded’ birthweights from the IHC, only actual birthweights are used; no birthweight estimates are included, nor are weights measured within two weeks of birth. Analyses of the participants’ birthweights alone include the estimates derived for this study (unless specified otherwise).
Table 7.6. Comparison of birthweight distributions between participants (includes estimates) and all IHC recorded birthweights. Measurements given in grams.

<table>
<thead>
<tr>
<th></th>
<th>Participant recorded birthweights (grams)</th>
<th>Participant estimated birthweights (grams)</th>
<th>IHC recorded birthweights (grams) (not including participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n=72 )</td>
<td>( n=36 )</td>
<td>( n=1308 )</td>
</tr>
<tr>
<td>mean</td>
<td>3341</td>
<td>3245</td>
<td>3170</td>
</tr>
<tr>
<td>SD</td>
<td>629</td>
<td>546.8</td>
<td>546</td>
</tr>
<tr>
<td>minimum</td>
<td>2126</td>
<td>2285</td>
<td>1350</td>
</tr>
<tr>
<td>maximum</td>
<td>5528</td>
<td>4636</td>
<td>5775</td>
</tr>
<tr>
<td>25(^{\text{th}}) percentile</td>
<td>2883</td>
<td>2875</td>
<td>2820</td>
</tr>
<tr>
<td>50(^{\text{th}}) percentile</td>
<td>3331</td>
<td>3296</td>
<td>3160</td>
</tr>
<tr>
<td>75(^{\text{th}}) percentile</td>
<td>3685</td>
<td>3548</td>
<td>3530</td>
</tr>
</tbody>
</table>

The range of birthweights for the IHC was slightly greater (lower minimum and greater maximum), reflecting both the larger sample and most likely poorer survival of those born at the extremes of birthweight. This is supported by the very few low birthweight babies (<2500g) among the study participants. The lightest babies among the study participants are approximately 800g heavier than the lightest babies recorded by the IHC.

Of the 108 recorded and estimated birthweights, 13 participants (12%) had birthweights below 2500g and seven (6.5%) greater than 4500g.

Table 7.7. Kolmogorov-Smirnov test: participants’ birthweights (recorded only and recorded with estimated for females and males, and all participants birthweights) compared with IHC records (minus participants)

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recorded participants' birthweights</td>
<td>All participants' birthweights (includes estimates)</td>
</tr>
<tr>
<td>Kolmogorov-Smirnov Z(^ a )</td>
<td>1.311</td>
<td>1.656</td>
</tr>
<tr>
<td>p value</td>
<td>0.055</td>
<td>0.008</td>
</tr>
</tbody>
</table>

\(^ a \) Tests the hypothesis that the two samples come from the same distribution.
Secular trends in birthweight

There was a small decline in birthweight as recorded at Cherbourg from 1952 to 1985 (Figure 7.1a). This decline over time, although slight, was found to be significant in this analysis (Pearson correlation = -0.098, p=0.001), although previous investigations did not find the decline significant (Dugdale et al. 1990a; Dugdale et al. 1994). This discrepancy is most probably due to the different criteria for birthweight; the present analysis only included recorded birthweights, while previous analyses have included first weight when it was measured within two weeks of birth. As the value of $r$ is very low, even slight variation in the data used could have an impact on the significance level.

This decline in birthweight over time is reflected in the survey participant birthweights (Figure 7.1b). Although this trend is not significant (Pearson correlation = -0.098, p=0.312), it provides further evidence that participants’ birthweights are a representative sample of the community. Birthweights at Cherbourg increased again in the early 1990s (Dugdale et al. 1994), a period not covered in the current analysis. Figure 7.1a shows a hiatus for birthweight records in the late 1950s. Rather than an unusually low birth rate during these years, it is more likely that there is an administrative reason for this gap in the data.

The decline in recorded birthweights from the 1950s to the 1980s is due to an increase in the proportion of babies who weigh less than 2500g at birth, from 5% to 13% (Dugdale et al. 1990a). Rather than illustrating a decline in infant health, this probably reflects a reduction in stillbirths among low birthweight infants; as only the weights of live births were recorded, a greater number of low birthweight infants were probably surviving to term and as live-births. Birth order among participants was not found to be significantly correlated with birthweight (Section 9.1), so any birth order effect might be minimal.

Powell and Dugdale (1999) found that the main factors relating to lower birthweight for babies born to Cherbourg mothers in recent years were factors associated with gravidity (first births and more than four previous births), alcohol consumption and sexually transmitted infections. These were associated with other lifestyle factors such as smoking, and poor nutrition. Although anaemia was prevalent among mothers (65%) this was not found to affect birthweight significantly. Powell and Dugdale (1999) also found that once lifestyle factors were considered, Aboriginality was not a substantial contributor to low birthweight, contributing to a difference of 112g.
Figure 7.1. Linear regression by year of birth of all recorded birthweights in Cherbourg, 1952-1985 (a) and participant birthweights for age (b). N.B. (b) includes predicted weights.
Birthweight is not necessarily a ‘responsive indicator of community well-being’ (Dugdale et al. 1990c, p. 29) as there is likely to be a substantial lag between improved conditions and increased birthweight, as a woman’s own birthweight contributes substantially to the birthweight of her children. Birthweight is therefore not as sensitive to environmental conditions as postnatal growth, which over recent decades has moved closer towards international references (Section 3.2.3).

7.1.3. Postnatal growth

Since birthweight is simply a cross-sectional measure of body size on the continuum between fetal and adult size, any long lasting effects of birthweight and the prenatal environment are likely to be mediated through postnatal growth (Lucas et al. 1999).

Birthweight and W/A are the only measures of growth that are available for use in the present study. Heavier children also tend to be taller (Section 3.2.3), and so W/A remains a useful composite measure of child growth for this study, especially as children at Cherbourg were measured so frequently. The mean number of visits made by participants seen by the clinic was 135.4, over a period of 5 years. The timing of changes in growth trajectories can therefore be established for individuals, and tested for differences between diabetes risk categories.

An overall picture of how month-by-month growth of the participants in the present study compares with the CDC 2001 reference is shown in Figure 7.2. The data were simplified so that weights at specified ages could be compared. Birthweight, plus weight at one, three, six, nine, 12 months, and every six months to 66 months were used. Weights were measured so frequently that the weight taken closest to the particular age was used, with the following considerations:

1. as growth rate is most rapid in the early months, less variation from the specified age was tolerated than for later ages, so that if weight had been measured within four days either side of one and three months it was included, or within seven days either side for weights at six and nine months, or up to two weeks either side for older ages; and

2. occasionally measurements were included if they fell just outside this period if there had been no change or very little change in weight between one measurement and the next through the specific age in question.

If recorded measurements fell to either side of the target age (for example, three days before and
three days after), the older age was used. The mean difference between the actual age at measurement and the target age was 4.5 days. If this is expressed as a proportion of the particular age, the mean difference is 0.01 of the accumulated age. For example, a weight taken at an actual age of 6.07 months has a difference of 0.07 months between the actual age and the target age (six months), which is approximately 0.01 of the accumulated age (0.07 divided by 6).

Although there are no significant differences between the weight growth of girls and boys at Cherbourg (Dugdale et al. 1990c), there is a trend for girls to have higher weights at earlier ages and lower weights at later ages (Figure 7.2). Overall, females had slightly increased weight growth in the first few months, in relation to males and to the CDC data, but had fallen behind males on sex-specific z-scores by 36 months. These differences between Cherbourg females and males in their z-scores were not significant, although they approached significance at nine months (t-test: p=0.052). Figure 7.2 illustrates a pattern of rapid growth in the first three months in relation to the CDC 2001 data, which is most likely due to catch-up growth. This is followed by a period of faltering up to about 15 months, a subsequent period of rapid growth.
(again probably catch-up growth) to approximately 36 months, and then a period of reasonably steady growth, in relation to the reference to 66 months, which is only slightly slower than the reference. It also illustrates that the outliers are more likely to be above the international reference in the early months but well below at later ages. This lends support to the probability that a number of children are born large (due to maternal diabetes) but that postnatal environmental circumstances are less than optimal for growth.

**Secular trends in postnatal growth**

Health outcomes for Indigenous infants and children have improved greatly over the last few decades. Infant mortality in Cherbourg has declined from approximately 250 per thousand live births in 1952, through 150 in 1960s, 40 in the 1970s (still twice the rate for Queensland at the time) to approximately 16 per thousand live births in the 1980s (Dugdale et al. 1990a; Dugdale 1996). Dugdale (1980) found that there was no change in growth of infants to parallel the early decline in infant mortality, suggesting that nutrition was not wholly responsible. Even when infant mortality was very high there were few children who were categorised as severely malnourished (<60% of the reference) (Dugdale et al. 1990c). If programming is to appear as significant in this community, it must operate at low levels of malnutrition.

Postnatal growth patterns in Cherbourg have changed slightly since records began. In 1952, 40% of infants in Cherbourg measured less than 90% of the NCHS 1977 reference median (Muller et al. 1984). There has been an increase in mean W/H/A measurements since then, with most children meeting the NCHS 1977 reference by the 1980s (Dugdale et al. 1994). The mean weights of five-year-old children increased from 90% of the NCHS reference median in 1952 to meet the median in 1982 (Dugdale 1996) but still 20% of children were below 90% at this time (Muller et al. 1984). This increase in the mean over time may reflect an increase in the proportion of children who were over 120% of the reference (Dugdale et al. 1990c), rather than an overall increase. Adequate weight gain is therefore not always equivalent to health, and comparison with the international reference may be inappropriate (Dugdale et al. 1990c). For example, Cameron et al. (1998) found that children of low SES in South Africa were likely to have greater weight throughout the first year compared with international references, while Smith et al. (2000) found in a recent study of Aboriginal infants in northern Western Australia.

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61 1977 NCHS reference.
that weight exceeded the NCHS reference after two weeks even though birthweight had been ‘only moderately depressed’ (Smith et al. 2000, p. 124).

Patterns of disease in Cherbourg children have undergone transition over the last 50 years. In the 1950s, diarrhoeal disease was prominent, but its relative importance declined over the decades (Dugdale 1996). Increases in median growth towards the NCHS reference median coincided with changes in the types of diseases that dominate child morbidity and mortality. In Cherbourg there has been a relative decrease in gastroenteritis and a relative increase in respiratory and other disease since the 1950s, from a more typical ‘developing’ pattern towards a more ‘developed’ pattern (Dugdale 1996). The reduction in enteric diseases is probably causally related to observed increases in child growth.

Changed feeding practices are thought to have had little to do with the change in Cherbourg infant growth, as breast-feeding declined markedly in the first ten years of the IHC, but then remained somewhat constant for at least the next ten (Dugdale 1980) (Figure 7.3). The differences in growth between breast-fed and formula-fed infants were found to be negligible in Cherbourg, with a slight non-significant increase in mortality among formula-fed infants (Dugdale 1980).

![Percentage of infants breast-fed](image)

Although there has been an overall increase in weight growth in Cherbourg since the 1950s, families maintain their growth rankings within the community, i.e. those who were relatively
heavier than their peers themselves as infants tend to have children who are also relatively heavier (Alsop-Shields and Dugdale 1995). The growth of infants was found to be correlated with the growth of their mothers but not of their fathers; ‘good’ growth in one generation of a family (defined matrilineally) was likely to be followed by ‘good’ growth in the next (Alsop-Shields and Dugdale 1995), and these patterns are transmitted through at least two generations (Dugdale et al. 1994). The authors conclude that family practices are more important than hereditary factors and that these persist within matriline. It could also be that biologically ‘programmed’ influences of mothers’ early growth and nutrition are affecting the growth of their children. Dugdale et al. (1994) describe Cherbourg as having a uniform social structure, and they therefore conclude that differences in child growth between families are not attributable to socioeconomic differences. Relative to the total Australian population, this depiction might be true, given that the community as a whole is fairly socioeconomically disadvantaged and there are not the magnitude of inequalities one might observe between, for example, Double Bay and Redfern in Sydney, but there are some socioeconomic differences at Cherbourg that are apparent (for example, ‘Snob Hill’, Section 4.4.5). There is also the historical dichotomy between ‘camp kids’ and ‘dormitory kids’ might still show its influences today. These socioeconomic differences may become more apparent over time.

Some investigators have recently suggested that catch-up growth may be important in predisposing a person to diabetes and other metabolic disorders, rather than simply their smallness at birth or in an early stage of childhood (for example, see Stern et al. 2000, Section 1.1.1). Any associations between birthweight and later disease might therefore be modified by patterns of postnatal growth, in particular by catch-up growth (Rasmussen 2001). Whether a child is big or small may not be as important in aetiology of later disease as whether growth follows an average, steeper or shallower trajectory.

### 7.2. Methods

This section links participants’ child weight growth with their subsequent adult risk factors as measured in the survey.

#### 7.2.1. Quantifying growth variation (1): determining IUGR

The likelihood that a given individual was IUGR was assessed using early postnatal growth in relation to birthweight. IUGR infants tend to exhibit rapid catch-up growth in the first few months after birth (Section 3.2.3). To determine weight growth velocity (grams per month),
individual birthweight was compared with weights at one and three months of age, estimated as described in Section 7.1.3 above.

Participants were then divided into the following four groups (N.B. medians are sex-specific and based on all available participant data):

- **Group 1**: lower than median birthweight and lower than median velocity (low-low)
- **Group 2**: lower than median birthweight and higher than median velocity (low-high)
- **Group 3**: higher than median birthweight and lower than median velocity (high-low)
- **Group 4**: higher than median birthweight and higher than median velocity (high-high)

Participants were grouped in this manner for growth velocity to one month of age and growth velocity to three months of age. Participants in Group 2 are those most likely to have experienced IUGR and subsequent catch-up growth, while those in Group 3 are those most likely to have been large for gestational age (possibly related to maternal diabetes) and to have undergone early postnatal catch-down growth.

### 7.2.2. Quantifying growth variation (2): birth to five years

In addition to likely IUGR, diabetes risk was analysed in relation to birthweight (including fitted birthweight as described above) and to two further growth parameters: mean weight deviation from the Cherbourg reference median within five distinct growth periods, and indices of change between each of these periods. This involved two processes: deriving a local growth reference and quantifying individual variation from the reference median.

**Step 1: deriving a local growth reference**

Given that growth comparisons were to be made between individuals within Cherbourg, an internal growth reference was calculated. An internal reference enables comparison between individuals and illustrates the patterns of growth for the community.

Kuczmarski *et al.* (2002) suggest that 400 to 500 individuals are required in a sample to achieve precision of the centiles. The data in the present study contains only 142 participants, well below the recommended level, but these have the benefit of being longitudinal rather than cross-sectional data, so individual timings of variation in growth velocities are not lost. The purpose of the locally derived reference is to make comparisons within the data set in relation to subsequent adult diabetes risk, rather than as a clinical tool to assess individuals as they
develop. In Cherbourg, conditions were generally those of deprivation relative to all of Australia; the growth reference is therefore not assumed to represent healthy growth, although those included in the sample all survived into adulthood, suggesting that the sample may be healthier than one containing children who did not survive into adulthood.

The growth reference that was calculated for Cherbourg is intended to be representative of the growth of surviving children in the community; not all the participants in the study were used in deriving the reference, as this would have meant an over-representation of diagnosed diabetics. All available weight growth data from the randomly selected (never-diagnosed) participants was included in the reference calculations, in addition to a random sample of the diagnosed participants to make up approximately 20% of the number of individuals used for calculating the reference, as this is the proportion of diagnosed people within the Cherbourg community. This was to ensure the sample used to calculate growth references was as representative as possible of the community.

For the present study, females and males were considered separately and a growth curve calculated for each. The details of the methods used to calculate the local reference are provided in Appendix H. These growth curves (10th, 25th, 50th, 75th and 90th percentiles) are shown in Figures 7.4 and 7.5 for females and males in relation to the CDC 2001 reference.

The two ‘bumps’ apparent in the Cherbourg reference between weights of between approximately 12 and 14kg and 18 to 20kg are artefacts of the data; raw data for Cherbourg weights show scarce measurements between these two sets of possible weights, suggesting a transition in the scales that were used, i.e. one set of scales for lighter children, another for heavier children. They may also reflect small sample size. Further smoothing of the data would have removed these aberrations, but would also have compromised the accuracy of the curve as a reflection of the data.

Reference calculations were performed by Dr Ann Cowling, Statistical Consulting Unit, The Australian National University.
Figure 7.4. Cherbourg female growth reference in relation to the CDC 2001 reference, showing 10th, 25th, 50th, 75th, and 90th percentiles. Solid lines = local reference percentiles, dotted lines = CDC reference percentiles. Vertical reference lines at 3, 6, 15 and 36 months divide growth into discrete periods which are used in subsequent analyses (see below).
Figure 7.5. Cherbourg male growth reference in relation to the CDC 2001 reference, showing 10th, 25th, 50th, 75th, and 90th percentiles. Solid lines = local reference percentiles, dotted lines = CDC reference percentiles. Vertical reference lines at 3, 6, 15 and 36 months divide growth into discrete periods which are used in subsequent analyses (see below).

These illustrate much greater postnatal weight growth variability among males, while female growth resembles the CDC 2001 reference more closely. Male growth faltering in relation to the international reference is much more marked; the Cherbourg median for males aged between 6 and 36 months is more closely aligned with the CDC 25th percentile, with recovery to the median occurring after 36 months. The heaviest males, those in the 90th percentile, are substantially heavier than the 90th percentile for the CDC data.
Step 2: weight deviation and change of growth indices

A method to characterise each individual’s pattern of weight growth from 0-5 years was developed. Individual data were plotted against the median of the reference curve that had been calculated for the Cherbourg sample. To determine the characteristic pattern of growth during particular time periods, the growth curve was divided into five contiguous periods:

A = 0<3 months;
B = 3<6 months;
C = 6<15 months;
D = 15<36 months; and
E = 36<60 months.

A smoothing spline was applied to each individual’s data, and the areas above and below the median were calculated for each of the five growth periods. Details of these calculations are provided in Appendix I.\(^{63}\) Classifying the data in this manner meant that growth for some periods could be included in the analysis, even for individuals with patchy records (for example, due to a temporary absence from the community).

The five child growth periods were chosen as they represent responses to important influences on growth. The first growth period, birth to three months (A), is frequently characterised by rapid growth, perhaps indicating that IUGR has occurred (Section 3.2.3). The second period, three to six months (B), is another period of normally rapid growth, but where faltering begins in some individuals, most likely in relation to the weaning process (Figure 7.3 indicates that fewer than half the infants in the study were probably still breastfed at three months). Six to 15 months (C) is typically characterised by growth faltering, sometimes severe, shown by a flattening of the reference curve. Again this is probably due to weaning-associated malnutrition and infection (Figure 7.3 indicates that fewer than one in five infants were probably still breastfed at six months, and none by 12 months). A period of rapid catch-up growth from 15 to 36 months (D) follows, while steady and sustained growth usually occurs between 36 to 60 months.

\(^{63}\) Deviation from the reference was calculated by Dr Ann Cowling, Statistical Consulting Unit, The Australian National University.
(E). Despite greater overall postnatal growth variability among males, these patterns are similar for females and males.

The splines calculated for each individual were assessed visually to determine goodness of fit (Appendix I). Growth periods without an acceptable goodness of fit (because of gaps in the data) were not included in subsequent analyses. The area difference was then standardised into the mean deviation from the median for a given period, expressed in kilograms.

A second method to further characterise individual growth involved calculating an ‘index of change’ between these successive growth periods to establish whether there were significant relative changes in mean weight deviation between the growth periods in comparison to the reference. This indicates the direction of the change over time (positive or negative) in relation to the reference. It provides a useful means of quantifying faltering and recovery; for example, an individual might be substantially heavier than the median in one period, still heavier in the second but by a much smaller mean amount, producing a negative index indicating slowed growth relative to the median.

Indices of change were therefore calculated as follows:

- Index 1: B - A
- Index 2: C - A
- Index 3: D - A
- Index 4: E - A
- Index 5: C - B
- Index 6: D - B
- Index 7: E - B
- Index 8: D - C
- Index 9: E - C
- Index 10: E - D

Where:

- A = mean deviation 0<3 months
- B = mean deviation 3<6 months
- C = mean deviation 6<15 months
- D = mean deviation 15<36 months
- E = mean deviation from 36<60 months

Linear models were applied to assess the relationships between adult diabetes risk factor variables and birthweight, IUGR, weight deviation, and indices of change. Relationships were tested between growth parameters and the surveyed measurements of FBSL, obesity and central
obesity, blood pressure, and the categories of case or control, where child weights were treated as the explanatory variable and surveyed measure as the response using logistic regression. In the logistic analyses, the risk factors were treated as whether a risk was present or absent, based on the thresholds discussed in Section 6.2. Analysis of variance (ANOVA) was used to test relationships between both age and family history and child weight growth, with age and family history treated as explanatory variables and growth as response variables. Female and male participants were analysed separately, as childhood weight influences on adult measures of obesity, for example, may be sex dependent. Analyses including age as a covariate were included, as measures of diabetes risk tend to increase with age. Odds ratios were also calculated for risk and child weight quintiles. Detailed results tables are presented in Appendices J and K.

Loess curves were also applied to the data to further explore the shapes that relationships might take. Loess curves were chosen because they do not make assumptions about the shape of the relationship and enable more complex patterns to be perceived. As many of the relationships appear to be quadratic when graphed with Loess curves (Appendix L) (fitting 50% of the data, three iterations), quadratic associations between surveyed measures and growth data were tested. Quadratic regressions were performed only for the participants who had never been diagnosed, to simplify relationships, i.e. diagnosis itself might have an effect on risk factor relationships, for example in trying to control blood sugar levels or lose weight. This has the additional benefit of reducing the potential influences of age on these associations (older participants were more likely to have been diagnosed with diabetes). Quadratic relationships that were found to be significant (p<0.05), or those which approached significance (p<0.1), are illustrated (x axis = explanatory variable, y axis = dependent variable).

## 7.3. Results

### 7.3.1. IUGR and adult diabetes risk

Do infants who were born small and grew more rapidly during the first one and three postnatal months, and are therefore more likely to have been IUGR, have a greater risk of developing subsequent diabetes?

Growth velocity (grams per month) is shown in Figure 7.6 between birth and one month and birth and three months of age.
Figure 7.6. Individual’s growth velocity (grams per month) from birth to one month and birth to three months, (a) females, (b) males. N.B. x-axis denotes categories and is non-linear for birthweight.
Most children had greater weight velocity to one month than to three months, suggesting that growth was initially more rapid and then slowed. Based on birthweight and velocity of weight growth between birth and one month, 10 from 47 (21.3%) females and 10 from 44 (22.7%) males were found likely to have been IUGR, determined by below median birthweight and above median postnatal weight growth velocity (low-high). For velocity between birth and three months, the numbers were similar, 10 from 50 (20%) females and 11 from 47 (23.4%) males. There were no cohort effects found; age was not significantly associated with the groupings (see Appendix J for detailed results table).

Participants who were most likely to be IUGR infants (low-high) did not consistently have greater diabetes associated risks (females: Figures 7.7 to 7.14; males: Figures 7.15 to 7.22. N.B. Group 1: low-low; Group 2: low-high; Group 3: high-low; Group 4: high-high).

Among females, for weight growth velocity to one month in relation to birthweight, those who grew more slowly, whether low or high birthweight, had higher mean FBSL than those who grew more rapidly (Figure 7.7). Those with lower birthweights were shorter as adults on average than those with higher birthweights (Figure 7.8), and weighed slightly less (Figure 7.9). For BMI, there was very little difference between the groups, although those who were low birthweight and grew more slowly (Group 1) had slightly lower mean BMI (Figure 7.10). There was also very little difference between groups for waist circumference, with both the low-low and the high-high groups having slightly lower measurements than the other two groups. Blood pressure, both systolic and diastolic, was highest on average among the low-high group and lowest among the high-high group (Figures 7.12 and 7.13). Pulse rate was lowest among the high-high group of females, and highest among the two slower growing groups (Figure 7.14).

For weight growth velocity between birth and three months among females, FBSL were on average highest among those in the low-high group and lowest in the high-high group (Figure 7.7). Again females who were born smaller had reduced attained adult stature in relation to larger babies, regardless of their growth velocity to three months (Figure 7.8), while adult weight was lowest in the low-low group and fairly even between the other three (Figure 7.9). This was similar for BMI, although those in the low-high group had slightly higher mean BMI (Figure 7.10). For waist circumference, the low-high group again had a slightly higher mean while the lowest mean was for the low-low group (Figure 7.11). Systolic pressure was fairly even across three of the groups, while those in the high-high group had the lowest systolic pressure (Figure 7.12). A smooth gradient of declining diastolic pressure between Groups 1 to 4
is apparent as weight increases (low-low, low-high, high-low, high-high) (Figure 7.13). Again pulse rate is lowest in the two higher velocity groups (Figure 7.14).

Few of these differences were significant. Among females, pulse was found to differ significantly (ANOVA: p=0.05); those in Group 3 (high birthweight, low velocity) had the highest pulse rate (mean=88.4 bpm) and those in Group 4 (high birthweight, high velocity) had the lowest rate (75.9 bpm). Differences in diastolic pressure approached significance for weight velocity to one month (ANOVA: p=0.085); those in Group 2 (the IUGR group) had the highest diastolic pressure (mean=91.30mmHg) and Group 4 (high birthweight, high velocity) had the lowest (mean=75.10mmHg). Although among females for weight velocity between birth and three months in relation to birthweight, differences were significant for both height (ANOVA: p=0.032) and weight (ANOVA: p=0.048) they were not significant for BMI (ANOVA: p=0.174), and approached significance for pulse (ANOVA: p=0.051). Groups with the highest and lowest mean risk factor measurements where differences between groups were significant (or approached significance) were:

- **height** – Group 3 (high birthweight, low velocity): 1.64m; Group 1 (low birthweight, low velocity): 1.58m
- **weight** – Group 2 (IUGR likely): 89.46kg; Group 1 (low birthweight, low velocity): 69.26kg
- **pulse** – Group 1 (low birthweight, low velocity): 88.77bpm; Group 4 (high birthweight, high velocity): 78.92bpm.

![Figure 7.7. FBSL by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.](image-url)
Birthweight, weight growth and diabetes risk

Figure 7.8. Attained adult height by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.9. Adult weight by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.10. Adult BMI by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.
Birthweight, weight growth and diabetes risk

Figure 7.11. Adult waist circumference by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.12. Systolic blood pressure by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.13. Diastolic blood pressure by group (females). Weight growth velocity (grams per month) calculated at one month and at three months.
Among males, for weight growth velocity to one month in relation to birthweight, highest mean FBSL was in the low-high (IUGR) group, and the lowest in the high-low group (Figure 7.15). Those with lower than median birthweights were shorter as adults than those with higher birthweights, regardless of weight growth velocity to one month (Figure 7.16). The heaviest adults on average were those in the high-high group, while the lightest were the high-low group (Figure 7.17). The more rapid growers had slightly higher mean BMI as adults than those who grew more slowly (Figure 7.18) and slightly higher mean waist circumference (Figure 7.19). Mean systolic and diastolic blood pressure was highest among those who were most probably IUGR (low-high) and lowest among the slower growers (Figures 7.20 and 7.21). Pulse was highest in the low-high group and lowest in the low-low group (Figure 7.22).

For weight growth velocity between birth and three months among males, FBSL was again highest in the low-low group and lowest in the high-low group (Figure 7.15). Attained height increased steadily across groups, the shortest were those in the low-low group and the tallest in the high-high group (Figure 7.16). Males with higher growth velocity were on average heavier than those who grew more slowly (Figure 7.17). Mean BMI was lowest in the high-low group (Figure 7.18), as was waist circumference (Figure 7.19). Males in the low-high group had the highest systolic and diastolic blood pressures (Figures 7.20 and 7.21). Pulse rate was lowest in both the low-low group and the high-high group (Figure 7.22).

Among males, there were no significant associations between likely IUGR and later risk, although differences in systolic blood pressure approached significance for groups at three
Birthweight, weight growth and diabetes risk

months (ANOVA: p=0.090), with Group 2 (the likely IUGR individuals) having the highest systolic pressure (mean=143.09mmHg) and Group 1 (low birthweight, low velocity) having the lowest (mean=126.83mmHg).

Figure 7.15. FBSL by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.16. Attained adult height by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.
Figure 7.17. Adult weight by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.18. Adult BMI by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.19. Adult waist circumference by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.
Figure 7.20. Systolic blood pressure by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.21. Diastolic blood pressure by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.

Figure 7.22. Pulse rate by group (males). Weight growth velocity (grams per month) calculated at one month and at three months.
That there were so few relationships found to be significant may be primarily due to the small sample sizes available. The magnitude of the detectable differences for each risk factor required to produce statistically significant results from such a sample is considerable. Tables 7.8 provides estimates for the detectable differences in each risk factor with the available sample, and Table 7.9 shows estimates of the sample sizes required to produce significant results with the magnitude of the differences in means found between groups in the available sample.

Table 7.8. Estimates of the detectable differences for each risk factor (includes height, weight and pulse)\(^a\)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting BSL (mmol)</td>
<td>±3.05</td>
<td>±3.53</td>
</tr>
<tr>
<td>Height (m)</td>
<td>±0.57</td>
<td>±0.81</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>±20.94</td>
<td>±18.77</td>
</tr>
<tr>
<td>BMI</td>
<td>±7.91</td>
<td>±5.17</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>±16.67</td>
<td>±14.28</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>±19.48</td>
<td>±17.08</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>±13.01</td>
<td>±12.12</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>±12.4</td>
<td>±15.05</td>
</tr>
</tbody>
</table>

\(^a\) Estimates calculated using PS Power and Sample Size Calculations version 2.1.30. Estimates were calculated using an alpha level of 0.05 and a power level of 0.8.
Table 7.9. Estimates of sample sizes required to produce statistically significant results with the magnitude of differences observed in the sample available

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting BSL (mmol)</td>
<td>430</td>
<td>145</td>
</tr>
<tr>
<td>Height (m)</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1260</td>
<td>2810</td>
</tr>
<tr>
<td>BMI</td>
<td>770</td>
<td>135</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>260</td>
<td>1045</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>175</td>
<td>135</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>445</td>
<td>105</td>
</tr>
</tbody>
</table>

* Estimates calculated using PS Power and Sample Size Calculations version 2.1.30. Estimates were derived using an alpha level of 0.05 and a power level of 0.8 and are rounded to the nearest 5.

7.3.2. Birthweight, weight deviation and indices of weight change

Are diabetes risk factors (including overall risk and FBSL) associated with birthweight or patterns of weight deviation during particular growth periods, or with relative change in weight growth between growth periods? All results of linear modelling and calculated odds ratios (OR) are presented in Appendix K.

**Overall risk of diabetes**

Among females, whether a participant was categorised as a case (diagnosed plus high-risk, Section 6.3) or control (low-risk) was not significantly related to any child growth parameter with linear modelling. There were some non-significant trends, however, between weight deviation at B (3 to 6 months: \( p=0.099 \)) and C (6 to 15 months: \( p=0.092 \)). Those in the highest quintile for several growth parameters were slightly more likely to be in the cases category: Index 4 OR=2.06 (1.33-3.18); Index 7 OR=1.74 (1.06-2.86); Index 8 OR=1.72 (1.06-2.79); Index 9 OR=2.09 (1.36-3.21); and Index 10 OR=1.93 (1.22-3.04). Although the confidence
intervals are wide, the trend of more rapid growth associated with higher overall diabetes likelihood is consistent.

Among males, birthweight was significantly related to whether a participant was a case or a control ($p=0.049$), although the difference was only 50g between the groups (mean = 3384.8g and 3334g respectively). Both slow early growth and more rapid later growth put males at slightly increased risk of being categorised as a case. Those in the lowest quintile at Index 3 and those in the highest quintile at Index 10 were more likely than others to be cases (OR=1.77 (1.02-3.07) and 1.65 (1.01-2.70)).

**Age**

Patterns of weight growth may have changed over time, so that any growth related diabetes risk may affect different age groups differentially. How have early childhood growth patterns changed over time?

Among females, a person’s age was significantly associated with mean weight deviation at C (6 to 15 months: $p=0.015$), Index 9 (E-C: $p=0.008$) and Index 10 (E-D: $p=0.001$) (Figures 7.23 to 7.25). This suggests that the weights of children between 6 and 15 months have generally increased over time (younger participants were heavier at this age than older participants), while younger participants also had lower values at indices 9 and 10, suggesting that their rate of catch-up growth had slowed in relation to older participants. Non-significant trends were apparent for 36 to 60 months (E: $p=0.061$) and for Index 4 (E-A: $p=0.095$).
Figure 7.23. Relationship between mean weight deviation 6 to 15 months and participant age at time of survey (females) (95% CI of the mean).
Rsq = 0.0373

Figure 7.24. Relationship between mean index 9 and participant age at time of survey (females) (95% CI of the mean).
Rsq = 0.1295
Among males, age was only significantly related to growth at Index 9 (E-C: p=0.040) and Index 10 (E-C: p=0.003) (Figures 7.26 and 7.27). This suggests, similarly to females, that rate of catch-up growth of younger participants has slowed in relation to this period among older participants, with a non-significant trend between age and Index 2 (C-A: p=0.087).
Fasting blood sugar level

Is adult FBSL associated with early childhood weight growth?

There were no significant linear relationships between birthweight, any period of weight deviation or indices and FBSL that were independent of age among women or men. There was a non-significant trend among males for birthweight (p=0.077) (age was not significantly involved in this relationship) (Figure 7.28). This relationship does, however, exhibit an inverted U-shape, as might be expected if both low and high birthweights contributed to subsequent adult diabetes risk. An estimated sample size of approximately 60 would be required to produce statistically significant results here. Among women, those who were heaviest in later childhood in relation to earlier weight were at slightly increased risk of having an abnormal FBSL: Index 4 OR=1.944 (1.41-2.68); Index 7 OR=1.68 (1.15-2.48); and Index 10 OR=1.82 (1.26-2.63).
Birthweight, weight growth and diabetes risk

In quadratic regression analyses, FBSL was significantly associated only with Index 7 among females \((p=0.044, \text{Rsq}=0.192)\), so that heavier weight at 36 to 60 months relative to weight at three to six months was associated with higher FBSL (Figure 7.29).

**Obesity**

Is adult body mass associated with early child growth? Significant relationships between BMI and growth parameters are summarised in Table 7.10.
Table 7.10. Summary of significant relationships between early child growth parameters and subsequent adult BMI (binary logistic regression)

<table>
<thead>
<tr>
<th>growth parameter</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: mean weight deviation 36 to 60 months</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Index 4 (E-A)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Index 8 (D-C)</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>Index 9 (E-C)</td>
<td>0.041</td>
<td>0.037</td>
</tr>
<tr>
<td>Index 10 (E-D)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>birthweight</td>
<td></td>
<td>0.024</td>
</tr>
</tbody>
</table>

Females in the lowest quintiles for each of these growth parameters appeared to be at lower risk of becoming obese adults, while those in the highest quintiles appeared to be at increased risk, but these were not statistically significant (Appendix K).

For males, those in the highest quintiles for growth periods B (3 to 6 months), C (6 to 12 months) and E (36 to 60 months) were at increased risk of becoming obese adults: B OR=2.4 (1.12-5.17); C OR=2.74 (1.32-5.69); and E OR=2.14 (1.03-4.42).

Significant quadratic relationships for never-diagnosed females (summarised in Table 7.11) are shown in Figures 7.30 to 7.36. In general, these too show a positive relationship between child growth measures and BMI, indicating that girls who are heavier in the later growth periods (from 36 months) and those who show more rapid later growth relative to their earlier weights are more likely to have higher BMIs as adults.

There were no significant quadratic relationships between child growth and adult BMI among males, although there were trends for associations at indices 1 (B-A: p=0.0757, Rsq=0.180) and 2 (C-A: p=0.094, Rsq=0.121) (Figures 7.37 and 7.38). Some of these relationships appear linear (females Index 6, Figure 7.33; males Index 1, Figure 7.37).
Table 7.11. Summary of significant relationships between early child growth parameters and subsequent adult BMI (quadratic regression, never-diagnosed participants)

<table>
<thead>
<tr>
<th>growth parameter</th>
<th>p value</th>
<th>Rsq</th>
</tr>
</thead>
<tbody>
<tr>
<td>D: mean weight deviation 15 to 36 months</td>
<td>0.022</td>
<td>0.237</td>
</tr>
<tr>
<td>E: mean weight variation 36 to 60 months</td>
<td>0.027</td>
<td>0.208</td>
</tr>
<tr>
<td>Index 3 (D-A)</td>
<td>0.026</td>
<td>0.242</td>
</tr>
<tr>
<td>Index 6 (D-B)</td>
<td>0.038</td>
<td>0.198</td>
</tr>
<tr>
<td>Index 7 (E-B)</td>
<td>0.046</td>
<td>0.218</td>
</tr>
<tr>
<td>Index 8 (D-C)</td>
<td>0.020</td>
<td>0.250</td>
</tr>
<tr>
<td>Index 9 (E-C)</td>
<td>0.049</td>
<td>0.181</td>
</tr>
</tbody>
</table>

Figure 7.30. Quadratic regression curve for females (never-diagnosed), BMI for mean weight deviation 15 to 36 months.
Birthweight, weight growth and diabetes risk

Figure 7.31. Quadratic regression curve for females (never-diagnosed), BMI for mean weight deviation 36 to 60 months.

Figure 7.32. Quadratic regression curve for females (never-diagnosed), BMI for index 3.

Figure 7.33. Quadratic regression curve for females (never-diagnosed), BMI for Index 6.
Birthweight, weight growth and diabetes risk

Figure 7.34. Regression curve for females (never-diagnosed), BMI for Index 7.

Figure 7.35. Regression curve for females (never-diagnosed), BMI for Index 8.

Figure 7.36. Regression curve for females (never-diagnosed), BMI for Index 9.
Central obesity
Is the presence of central obesity among adults significantly associated with their weight growth as children?

Using binary logistic regression, central obesity was not found to be significantly associated with any growth parameter among women or men. Among males, there were non-significant trends for weight at birth (p=0.073), weight deviation at 6 to 15 months (C: p=0.082) and 36 to 60 months (E: p=0.082). Among women, those who were heaviest and grew more rapidly during early childhood were more likely to be centrally obese adults: B OR=1.43 (1.17-1.75); C OR=1.36 (1.31-1.62); Index 1 OR=1.38 (1.14-1.67); Index 2 OR=1.35 (1.12-1.61); and Index 3 OR=1.31 (1.10-1.56) Among males, those who were heaviest at 6 to 12 months or 36
to 60 months were more likely to be centrally obese: C OR=2.11 (1.08-4.10) and E OR=2.14 (1.14-4.00).

Among never-diagnosed females, several significant quadratic associations were found between adult waist circumference and child growth (Table 7.12). These relationships are illustrated in Figures 7.39 to 7.45. Again the relationships are positive, with waist circumference increasing with both weight in the later child growth periods and with greater relative growth in later periods in relation to early periods. For Index 3, the strongest association appears to be at lower relative weights suggesting that even a little catch-up growth at this time makes a substantial difference, while at indices 8 and 9 relationships seem strongest at higher relative weight, suggesting that those whose relative weights are much higher after 36 months relative to their weight during the typical period of catch-up have higher waist circumferences – perhaps they experienced delayed catch-up growth after 36 months. Some of these relationships (Figures 7.39, 7.41 and 7.43) appear linear.

There were no significant quadratic relationships found between growth and waist circumference among never-diagnosed males.

Table 7.12. Summary of significant relationships between early child growth parameters and subsequent adult waist circumference (quadratic regression, never-diagnosed participants)

<table>
<thead>
<tr>
<th>growth parameter</th>
<th>p value</th>
<th>Rsq</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: mean weight deviation at 36 to 60 months</td>
<td>0.009</td>
<td>0.273</td>
</tr>
<tr>
<td>Index 3 (D-A)</td>
<td>0.010</td>
<td>0.304</td>
</tr>
<tr>
<td>Index 4 (E-A)</td>
<td>0.325</td>
<td>0.297</td>
</tr>
<tr>
<td>Index 6 (D-B)</td>
<td>0.017</td>
<td>0.259</td>
</tr>
<tr>
<td>Index 7 (E-B)</td>
<td>0.018</td>
<td>0.305</td>
</tr>
<tr>
<td>Index 8 (D-C)</td>
<td>0.008</td>
<td>0.298</td>
</tr>
<tr>
<td>Index 9 (E-C)</td>
<td>0.013</td>
<td>0.271</td>
</tr>
</tbody>
</table>
Birthweight, weight growth and diabetes risk

Figure 7.39. Quadratic regression curve for females (never-diagnosed), waist circumference for weight deviation 36 to 60 months.

Figure 7.40. Quadratic regression curve for females (never-diagnosed), waist circumference for index 3.

Figure 7.41. Quadratic regression curve for females (never-diagnosed), waist circumference for index 4.
Birthweight, weight growth and diabetes risk

Figure 7.42. Quadratic regression curve for females (never-diagnosed), waist circumference for index 6.

Figure 7.43. Quadratic regression curve for females (never-diagnosed), waist circumference for index 7.

Figure 7.44. Quadratic regression curve for females (never-diagnosed), waist circumference for index 8.
Blood pressure

Is higher blood pressure among adults associated with their weight growth as children? Using logistic regression, neither systolic nor diastolic pressure were found to be significantly associated with any growth parameter among either women or men. Non-significant trends for diastolic pressure were found for Index 6 (D-B: p=0.098) and Index 8 (D-C: p=0.058) among women. Among women, those who were lightest and grew most slowly (lowest quintile) were at increased risk of systolic hypertension as adults: B OR=3.20 (1.05-9.78); D OR=5.00 (1.82-13.76); E OR=3.75 (1.42-9.88); Index 2 OR=3.47 (1.16-10.38); and Index 4 OR=3.80 (1.30-11.09). Similarly for diastolic pressure among women: D OR=2.78 (1.22-6.35); Index 6 OR=2.71 (1.16-6.3); and Index 9 OR=2.47 (1.09-5.61). For birthweight, however, it was those in the highest quintile who were at increased risk: OR=2.55 (1.15-5.62). Among men, those in the extreme quintiles (1 and 5) at Index 1 were at reduced risk of systolic hypertension in comparison with those in the middle range: OR=.246 (.061-.965). There were no significant associations between quintiles of growth parameters and diastolic hypertension among men.

In quadratic regression analyses among never-diagnosed women, systolic pressure was associated with birthweight (p=0.0483, Rsq=0.169) (Figure 7.46). No relationships were found for males. Diastolic pressure was significantly associated with mean weight deviation at 36 to 60 months (p=0.0302, Rsq=0.181) among women showing an almost linear positive relationship (Figure 7.47), but again not with any measure of child growth among men.
Family history
Is a positive family history of diabetes significantly associated with measures of child growth? Among females, those in the highest quintile for Index 6 were slightly more likely to have a positive family history: OR=1.43 (1.17-1.75), but there were no significant associations among males.

7.4. Conclusions
Main findings
There are very few participants in this study who could be classified as low birthweight, i.e. weighing less than 2500g, quite likely a reflection of the poorer neonatal survival of low
Birthweight babies as participants represent only those who survived to adulthood. Heavy babies are also at increased obstetric and neonatal risk. A number of participants were very large at birth, which suggests that their mothers had diabetes during pregnancy. Although thresholds are useful in terms of neonatal survival, they may be less suited to determining risk of disorders such as diabetes. For example, several Barker group studies found that babies toward the lower end of the ‘normal’ birthweight range were also at increased risk of later disease; the most important threshold for survival at one end of the life-span may not be equally relevant or useful in predicting outcome at the other (Rasmussen 2001). McCance et al. (1994) too note that among Pima Indians, most of those who develop diabetes had normal birthweight.

Child growth and nutritional status reflect the social and epidemiological circumstances in which they occur, although these effects are not necessarily uniform for girls and boys (Crooks 1999). Although the growth potential of most Aboriginal children is similar to international reference data (Gracey 1991), growth of males in Cherbourg is much poorer than females in relation to the CDC 2001 reference. It may be that some external influences to do with nutrition and infection are inhibiting catch-up growth that may otherwise occur. This could be why so few relationships between early weight growth and adult diabetes risk were apparent for males. SES strongly influences birthweight and postnatal growth, and is responsible for most postnatal growth variation within populations (Mueller et al. 2001). Young children are potentially the most vulnerable to poor circumstances (Skoufias 1998), as they are developing rapidly.

Malnutrition and infection also play a greater role than ethnicity in children showing disrupted growth patterns and failure to reach this potential (Dugdale et al. 1990c). From the analyses made in this data set, it seems that the poorer environmental community circumstances are having their main effects on infants between three and 15 months of age. This is a sensitive period of infant growth, often coinciding with weaning, so children at this age are most vulnerable to environmental insults; urban children, for instance, generally have better growth status than those in rural areas (Cameron et al. 1998).

IUGR does not appear to be associated with an increased risk of diabetes among adults in Cherbourg. Where IUGR is likely, as determined by lower than median birthweight and higher than median weight at three months, adult weight among female adults is significantly greater. This means that the girls who have greater weight velocity within their first three months are likely to be heavier adults; however, they also tend to be slightly taller given that BMI was not significantly different. Yajnik (2002) found other risk factors associated with height that were
Birthweight, weight growth and diabetes risk

not found here; four-year-old children who were taller than expected given their parent’s mid-
height exhibited higher risk factors for CVD, but this is consistent with a relationship between
more rapid growth and later diabetes risk.

Where significant relationships were found between infant or childhood weight and adult
diabetes risk, weight in childhood, and especially faster weight growth relative to the median,
appear to be positively related to adult diabetes risk factors, especially among women.
Although there are some consistencies in quadratic relationships between child growth
parameters and adult risk factors for diabetes in this population, associations are fairly weak, as
reflected by the low R-squared values. A larger sample may have yielded stronger results, but it
is more likely that the relationships, where they do exist, are extremely complex, with many
other factors coming in to play.

Almost all significant associations (or those approaching significance) between childhood
growth and adult risk of diabetes are positive. The exception to this is for birthweight among
males in which it seems that those at both extremes, the lowest and highest quintile, have
*reduced* chance of developing some risk factors. This suggests that low weight in childhood has
the opposite effect to that expected under the programming hypothesis, so that rather than low
weight at birth and low weight during early childhood being a risk factor for diabetes, it seems
that heavy children – relative to the community median – are more at risk in this population.
This is consistent with more recent research on programming, however, which suggests that
catch-up growth is an important factor, in that those most at risk seem to be not only those
children who are heaviest during later childhood, but where later weight is heavy in relation to
early weight.

Where U-shaped relationships existed between growth and risk as demonstrated by quadratic
relationships, they were fairly inconsistent and goodness of fit was poor, as demonstrated by the
low R-squared values, and again there was no consistency between females and males. This
may be because of small sample size.

The most consistent general relationships found in this study are between higher weight in later
childhood relative to weight in early childhood among females (i.e. more rapid growth in
relation to other children) and obesity and central obesity among adult women. The positive
association between rapid childhood growth and later adult risk factors among women does not
mean, however, that rapid growth in childhood ‘causes’ obesity in adulthood. Adult obesity
may be the result of continuing on a trajectory that was ‘programmed’ by this early pattern, or it
may be the outcome of factors that also contributed to early rapid weight gain. As children learn much of their eating and lifestyle behaviours from their parents, it may be that as children they were exposed to overnutrition, or possibly a diet high in simple carbohydrates and fat, causing rapid childhood weight gain, and this continued into adulthood.

**Maternal diabetes**

One of the major confounding factors may be a very high prevalence of diabetes among the mothers of participants when they were pregnant, which would both increase birthweight and increase diabetes risk. However, Powell and Dugdale (1999) found in the early 1990s that gestational diabetes was no more common among Cherbourg Aboriginal mothers than for non-Aboriginal mothers from the same region (<2%), which suggests that perhaps gestational diabetes is not a significant factor leading to increased birthweight. Gestational diabetes is, however, defined as diabetes first diagnosed during pregnancy and thus precludes women who are known to be diabetic before their pregnancy commences. It is likely that there remains a greater proportion of pregnant women with diabetes in Cherbourg – and perhaps other Aboriginal communities – than in the Australian population as a whole.

Controlling for maternal diabetes was attempted, but too few participants could say whether or not their mother was diabetic, let alone whether she was diabetic while pregnant: among female participants, 29.3% reported that their mother was diabetic at some stage, and 16.3% said that she was not diabetic, while among males, only 7.5% reported having a mother who was diabetic, while 28% said that she was not. The now routine screening for gestational diabetes was not available during the time when participants’ mothers were pregnant with them. This could explain why any associations between early weights and diabetes risk were found to be positive. U-shaped associations have been found between birthweight and diabetes risk in other populations (Section 2.4.3); although such associations appear to occur in this population the patterns were inconsistent and rarely significant, perhaps due to the low numbers of participants. Assumptions and generalisations, for example in regarding IUGR rather than prematurity as the main contributing factor to lower birthweight, have been made based on the weight of the evidence. Such assumptions, although necessary, may in fact reduce some differences that might otherwise have been found to be significant.

If a mother had diabetes in pregnancy her child would also be more likely to be born large, but large infants tend to have slowed growth rather than more rapid growth (‘catch-down’) so if this were the case one would expect that lower weight gain exhibited in the first few post-natal
months would also be related to diabetes risk in adulthood, not higher weight throughout childhood and more rapid growth as found here. Among males there were very few significant relationships found, suggesting that some important aetiological influences operate differentially according to sex, at either a physiological or social level. That relationships were found among females but not males is consistent with the findings from a French study by Trudeau et al. (2001), that adult obesity is more easily predicted among girls than boys based on childhood weight, and in particular, childhood weight change.

**Catch-up growth**

Catch-up growth between birth and two years has been associated with obesity at five years (Ong et al. 2000). Those who undergo such rapid growth postnatally are likely to have had restricted prenatal growth. Ong et al. (2000) therefore suggest that mechanisms which regulate catch-up growth may influence associations between small birth size and adult disease risk.

This has implications for the response to growth faltering of a child. (It should, however, be remembered that even children who are average or quite large within the Cherbourg frame of reference are relatively small compared with the international references.) The emphasis in child health promotion has been to promote catch-up growth in infants and children after a period of faltering; to achieve maximal and sustained catch-up growth (Preece 1998). Catch-up growth is associated with the immediate benefit of reducing morbidity and mortality from infection (Victora and Barros 2001).

Child health as measured by growth was probably much poorer before the advent of the regular check-ups at the clinic. The regular contact would have presumably detected sickly children with severely faltering growth thus providing opportunity for intervention. While keeping malnutrition to a minimum, this intervention may in fact have served to increase later risk of disease.

The results of the present study suggest that this practice might be potentially detrimental to the future health of that child. It could be that remaining small but maintaining an otherwise ‘appropriate’ trajectory is a better option. Being a relatively large child might only be detrimental if growth is not occurring at a moderate pace, although Parsons et al. (2001) found that children who had achieved a greater proportion of their adult height by the age of seven years were much more likely to be obese as adults. Contrary to the present study, they also found that association between early small size and later large size was associated with higher adult BMI only among men. Barker et al. (2001) too concluded the effects of health of low
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Social class were greatest among men who had been born thin but had accelerated growth as children. This may be due to differential feeding practices according to size. Stafford and Lucas (1998) found for example that mean fat intake among infants who were small was slightly higher than for normal weight infants, and that it might be the amount of fat consumed at an early age which increases risk, especially if it is sustained. This could indeed ‘program’ a preference for higher fat foods among these children, as preferences for higher fat foods may remain, resulting in continued consumption of a diet that is higher in fat than their initially heavier peers.

Rapid weight gain among children who subsequently become obese adults may also simply signal the beginnings of a trajectory towards adult obesity, rather than being causal. Relative change rather than absolute size at given ages was more important. That smaller young children have been found to be more at risk of diabetes in previous studies, is perhaps simply because of their greater propensity for upward centile crossing, rather than because they were small at an early age.

Normal birthweight, but fetal malnutrition?

The timing of maternal nutritional deprivation is likely to have some effect on both birth outcome and later disease risk. For example, Susser and Stein (1994) found in a study of prenatal exposure to the Dutch famine that those exposed during the first four months were more likely to be obese as adults, while those exposed in the latter half of pregnancy were less likely to be obese. The authors suggest this might be due to altered hypothalamic function, or to rapid maternal weight gain in later pregnancy or probably both together. Maternal weight was found to explain to a large extent the association between birthweight and adult BMI in a UK sample, and this may be more important than child birthweight (Parsons et al. 2001). Unfortunately in the present study, mother’s weights were not known thus such relationships cannot be examined.

The implications of this for the current study are very interesting. For decades most young women (the mothers of the study participants) were sent off the settlement to work as domestics in conditions that would not have been conducive to positive energy balance, due to high levels of physical activity and possibly less than adequate nutrition (Section 4.3). Many of them would have been adolescent with their own growth demands when they became pregnant. Pregnancy among young women working as domestics was seen as shameful and women were sent back to the settlement; perhaps there was a tendency for women to have hidden their
pregnancy for as long as they could, and continued to work. On returning to the settlement, these women would then have presented late for antenatal check ups, if at all, and conceivably have had quite reduced nutritional stores. Back at the settlement they probably then received better care and nutrition than before, hence enabling a kind of ‘rebound’ in the birthweights of their infants.

Of course this is simply conjecture and the details of individual mothers’ experiences cannot be verified for this study, but this is an interesting and possible scenario that may have been repeated again and again over many decades for the women of Cherbourg. It does mean that even if a vast majority of birthweights fall within the ‘normal’ range, it does not preclude infants from being exposed to poor nutrition in utero, especially in early pregnancy. A pattern of early prenatal exposure to inadequate nutrition for children who were growing up in Cherbourg is more likely than later exposure.

**Conclusions**

Overall, the evidence to support programming due to low infant and child weight is at best weak. That large infants and young children were found more likely to exhibit adult risk factors for diabetes, rather than those who had been small, was unexpected given the premises of the programming hypothesis. Patterns of rapid childhood weight gain relative to early weight, however, suggest that catch-up growth, or at least upward centile crossing, might be important contributing factors to adult diabetes risk. The results are most consistent among women, as greater later childhood weight relative to early childhood weight is associated with all three modifiable risk factors of obesity, central obesity and blood pressure. Among men, childhood growth patterns are associated with family history of diabetes but not with any of the modifiable risk factors.

That patterns of association between parameters of child growth and adult diabetes risk are inconsistent between females and males, although fairly consistent within each sex, suggests that there are sex differences in child growth influences on risk, either in kind or degree. There are differences between women and men in their adult risk exposure to diabetes as well, apparent in the following two chapters: Chapters Eight explores the likely proximal influences on diabetes risk of nutrition and lifestyle factors, while Chapter Nine explores additional social variables that may have a less direct impact. Implications of sex difference in both responses to childhood growth patterns and socialised exposure to risk are further discussed in Chapter Ten.