**Intergenerational effect of early life growth on offspring height: evidence from the Hertfordshire Cohort Study**

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**Short running title:** Intergenerational effect of infant growth

**Social media quote**

Positive associations were found between grandparental weight gain over the first year of life and the heights of their children and grandchildren. This indicates that early life growth patterns may be important intergenerational height predictors.

**Synopsis**

Study question:

The aim of this study was to examine the influence of the early life weight gain of grandparents on the adult heights of their children and grandchildren.

What’s already known:

Previous intergenerational research has established positive associations between birthweight and height across generations.

What this study adds:

This study demonstrates an association between grandparental growth in early life and the heights of their children and grandchildren. The results of these analyses highlight the influence of weight gain in early life on the adult stature of subsequent offspring.

**Abstract**

**Background**

Previous intergenerational (parent to child) and transgenerational (grandparent to grandchild) studies have shown there is a link between parental and offspring birthweight.

**Objectives**

The aim was to explore the association between the early life weight gain of an individual and the adult height of their children and grandchildren.

**Methods**

Study participants across three generations of the Hertfordshire Cohort Study (HCS) were included in this study. Health visitors recorded the birthweight (kg) and weight at 1 year (kg) of the original (F0 generation) HCS participants when they were born in Hertfordshire between 1931 and 1939. A conditional infant weight gain score for F0 participants was calculated using birthweight and weight at 1 year, and self-reported height (cm) of their children (F1 generation) and their grandchildren (F2 generation) was obtained from postal questionnaires. Due to lack of clustering within family lines, linear regression analysis was used to compare intergenerational relationships.

**Results**

Data were available from 139 F0, 148 F1, and 198 F2 participants. A positive association was found between parent birthweight (F0) and offspring adult height; on average, a 1 kg increase in F0 birthweight was associated with a 2.04 cm increase in F1 adult height (beta 2.04, 95% confidence interval (CI) -0.03, 4.10). A positive association was found between F0 conditional weight gain during the first year of life and offspring (beta 1.53, 95% CI 0.45, 2.62) and grandchild height (beta 1.06, 95% CI 0.03, 2.10). Positive associations were also found between F0 weight at 1 year and offspring (beta 1.83, 95% CI 0.79, 2.87) and grandchild height (beta 0.91, 95% CI -0.10, 1.91).

**Conclusion**

This study demonstrates an association between grandparental weight gain in early life and the heights of their children and grandchildren. The results of these analyses highlight the importance of early life weight gain on the adult stature of subsequent offspring.

**Keywords**

Intergenerational health; family health; population health; social determinants of health

**Word Count:** 2455 words

**Background**

Many studies have contributed to evidence for the foetal origins hypothesis that health in early life influences health in adulthood,1, 2 and it has been previously shown that low birthweight and stunted adult height are associated with poorer adult health outcomes.3 Famine studies conducted in The Netherlands and China have reported that exposure to famine in early infancy has implications for eventual height3 and obesity risk4 in adulthood, indicating that growth in early life influences health along the lifecourse. This increasing evidence has meant there is growing interest in how parental and grandparental birthweight, early weight gain, and adult height, all markers of health in infancy and later life, may impact on the health of future generations. Studies have shown that there is a link between maternal birthweight and offspring birthweight, with the risk of an infant having low birthweight increasing if the infant’s mother was also born with low birthweight.5, 6 The inverse is also true: women who were heavier at birth tend to have babies with higher birthweights.7 Interestingly, research has shown that mother-daughter correlations for birthweight are stronger than mother-son birthweight associations. Some studies have found relationships between paternal and offspring birthweight; however these associations are often weaker than those for maternal and infant birthweights.8-11

Previous studies have also investigated the intergenerational transmission of height. Kelly et al (2014) found that height at nine years of age is positively associated with the stature of a child’s mother, father, and paternal grandfather, with associations of girls’ heights being stronger between daughters and their mothers than between daughters and their fathers.12 Maternal height has also been found to be associated with both offspring adult height and conditional height growth during childhood.13 There is also evidence for a positive relationship between an individual’s birthweight and final adult height, and that this relationship holds across generations.14

Although most of the intergenerational literature focuses on correlations between parents and children, transgenerational studies examining the transmission of birthweight and height along three generations (from grandparents to parents to grandchildren) have produced results that echo those presented in parent-child studies. Several previous studies have identified associations between birthweight10, 15-17 and height12, 18 across three generations. Similarly to findings from intergenerational studies, correlations between grandparent and grandchild birthweight have been stronger along maternal than paternal lines.16

Recent research has focused on the mechanisms through which birthweight and height are transmitted across generations. One explanation is that while the transmission of physical attributes between family members is driven by genetics, these genetic expressions may be constrained or supported by environmental factors.19, 20 Of particular interest is how nutrition and growth in early life affects not only an individual, but also the growth of that individual’s children and grandchildren.1 It may be that, much like birthweight and adult height, an individual’s early weight gain and weight at one year of age can influence the size of their progeny.21-23

This paper aims to build on these previous studies by examining the intergenerational association between early life weight gain and offspring height. Using data collected from three generations of Hertfordshire Cohort Study participants, associations between the early growth of an individual (defined here as birth weight, conditional weight gain in the first year of life, and weight at 1 year) and the adult heights of their children and grandchildren will be explored.

**Methods**

**Study sample**

The study sample comprised original Hertfordshire Cohort Study (HCS) participants (F0 generation) and their children (F1 generation) and grandchildren (F2 generation). The HCS is a large, prospective, population-based cohort study of men and women born in the English county of Hertfordshire between 1931 and 1939. The original HCS has been previously described in detail; however, in brief, in the early 20th century, ledgers containing the early life details of 42,974 babies, including birthweight (pounds converted to kilograms) and weight at one year (pounds converted to kilograms), were populated by health visitors in Hertfordshire. Members of the HCS F0 generation were initially selected into the cohort if details of their early life were recorded in these ledgers, and if they were still residing in the county in the late 1990s.24 Of the 8,650 liveborn babies recorded in the ledgers and found to be still living in Hertfordshire, 3,225 became HCS cohort members. This is illustrated in Figure 1. Since the first contact with the F0 generation in 1998-2004, these HCS cohort members have taken part in various follow-up postal questionnaires, face-to-face interviews, clinics, intervention studies, and focus groups.25

In 2017 ethical approval was obtained (REC reference: 16/LO/1225) to contact F1 and F2 generation descendants via the F0 HCS participant. These F1 and F2 participants had previously expressed an interest in the Hertfordshire intergenerational study, had provided their contact details, and given permission to be contacted about further studies. Descendants over the age of 16 years and resident in the United Kingdom were eligible to participate. The recruitment of F1 and F2 participants is displayed at the bottom of Figure 1. Postal questionnaires were sent to 1090 F1 and F2 subjects, of which 712 questionnaires were returned. The questionnaires included sections on sociodemographic information and self-reported birthweight (kg), current height (cm) and current weight (kg).

A total of 446 F1 generation study participants and 266 F2 study participants returned postal questionnaires. However, in order to allow for comparisons to be made between generations, only those families with data available across all three generations were included in this study. To ensure that using three-generation families did not introduce selection bias, sensitivity analyses were run to test potential differences between F0 participants with both F1 and F2 family members recruited and F0 participants with only F1 or F2 family members recruited. In these t-tests, there were no differences in age, birthweight, weight at 1 year, conditional weight gain over the first year of life or height between these two groups of F0 participants.

**Statistical analysis**

In common with previous HCS publications, sex-specific conditional infant weight gain scores were calculated, which are equivalent to a standard deviation (SD) score for weight at one year independent of birthweight.26 Characteristics of study participants were described using means and SDs for normally distributed continuous variables, and frequencies and percentages for binary and categorical variables.

Often an offspring was linked to only 1 parent or grandparent, and this limited clustering prevented the use of multilevel models. Due to the lack of clustering within family lines, linear regression analysis was used to compare intergenerational associations between outcomes of interest. Models examined the relationships between F0 birthweight, conditional weight gain at 1 year, and weight at 1 year, and F1 and F2 adult height. Results were presented as regression coefficients with associated 95% confidence intervals (95% CI). All regression models were adjusted for sex and age at which offspring adult height was measured. The Stata statistical software package (version 14.0) was used for all analyses.27

**Results**

The descriptive statistics of the study sample used are contained in Table 1. Data on 485 study participants were included: 139 F0, 148 F1, and 198 F2 generation study participants. The mean age of F0 participants at HCS baseline was 66 years and just under 47% were women. The mean age of F1 study participants was 55 years and nearly 75% of the F1 respondents were female. The mean age of F2 participants was 25 years and there were equal numbers of male and female study participants. The average height of F0 participants was 169.3 cm, and the mean self-reported height of F1 participants was 169.4 cm and 175.3 cm for F2 participants. The mean birthweight of F0 participants was 3.5 kg, and at 1 year the mean weight of these study participants was 10.0 kg. The mean birthweight was similar across all three generation with the average birthweight of F1 study participants being 3.4 kg and 3.5 kg for F2 participants.

The results of regression analyses to assess associations between F0 early life variables and adult height of offspring and grandchildren are presented at the top of Figure 2. A positive association was found between the birthweight of the F0 study participants and the adult height of the F1 study participants; on average a 1 kg increase in F0 birthweight was associated with a 2.04 cm increase in F1 adult height. No association was found between F0 birthweight and F2 adult height.

A positive association was found between the weight at 1 year of the F0 study participants and adult height in the F1 generation, as seen in the centre of Figure2. On average a 1 kg increase in F0 weight at 1 year was associated with a 1.83 cm increase in adult height of F1 participants. In addition, on average a 1 kg increase in weight at 1 year was associated with an increase of 0.91 cm in the height of F2 participants.

A positive association was found between F0 conditional weight gain during the first year of life and adult height of both F1 and F2 generations, as displayed at the bottom of Figure 2. On average, an SD increase in F0 conditional infant weight gain was associated with 1.53 cm and 1.06 cm increases in the average height of the F1 and F2 study participants, respectively.

**Comment**

**Principal findings**

In this study, we examined the association between an individual’s weight gain in early life and the height of their offspring and grandchildren. Birthweight was found to be positively associated with offspring height, and for the first time, it has been demonstrated that weight at 1 and conditional weight gain in infancy were associated with descendant height in both the F1 and F2 generations.

**Strengths of the study**

This study has many strengths. It is the first study of its kind to investigate the association between early life weight gain in the F0 generation and the adult height of subsequent generations, and it highlights the importance of looking at growth patterns as predictors of size across generations. Intergenerational research has established positive associations between birthweight and height; however, in this study of the influence of the early life of grandparents on the heights of their children and grandchildren, weight at 1 year and conditional weight gain over the first year of life were the more influential growth factors, indicating that in addition to birthweight, early life growth patterns may be important intergenerational height predictors.

**Limitations of the data**

In some literature on growth across generations, there are differences in intergenerational associations between males and females. 5-8, 10 However, one limitation of this current study is that it was not possible to assess potential sex differences, as nearly three-quarters of the F1 generation were female. While recruitment was not targeted by sex, a higher proportion of female F1 participants returned postal questionnaires, meaning that generalizability of the results presented here may be limited. Another limitation of this study is that heritability could not be estimated, as maternal and paternal data were only available for a handful of study participants. A larger sample size would allow for mediation analyses investigating how F0 birthweight or conditional weight gain over the first year of life may mediate the relationship between F1 and F2 height. While limited sample size meant that this paper could not examine sex differences in height transmission, future research into the influence of early growth patterns on the heritability of height using familial data could further illustrate the relationship between sex and the intergenerational transmission of height by conditional growth in infancy.

While the sample precluded analyses by sex, loss to follow up between baseline HCS and the current study should not have negatively influenced the representativeness of the results. Previous work has established that the baseline HCS cohort was comparable to the Health Survey for England participants in 1996 and 199824, indicating that the HCS was nationally representative at the time of baseline data collection, and sensitivity analyses described above demonstrated that F0 participants with both children and grandchildren participating in the study did not differ substantially from those F0 with only children or grandchildren in the sample. The HCS does have a healthy responder bias, which could have affected which participants responded to the intergenerational survey questionnaire; however, this is unlikely to have influenced the association between early growth and offspring height across the generations.

**Interpretation**

A potential explanation for the association between grandparental infant growth and the stature of their children and grandchildren lies in epigenetic theory. According to Pembrey et al (2014), “any effect transmitted to F2 generation via F1 gametes might arise purely in response to the altered development or metabolism of the F1 generation arising from the F0 exposure,”26 meaning that in the current study, it is possible that the environments encountered by F0 HCS participants in infancy, which influenced their growth over the first year, may also have modified the development of their gametes, which in turn mediated the growth of their children (F1) and their grandchildren (F2).

Previous studies have shown that people who grow poorly in infancy, childhood, and adolescence become shorter adults, and shorter height in adulthood is associated with higher risk of morbidity.3, 27-29 There is evidence that shorter adults go on to have children and grandchildren with lower birthweights and shorter statures,7, 10, 28 and that this transmission of size along generations is not due to cultural or genetic exposures alone.30 Growth over the first one thousand days of life is critical to establishing adult stature and in some cases, promoting adult health,3, 28, 31 as growth failure leading to stunting can be established by two years of age.3 Stein et al (2010) found that adult height was strongly associated with growth failure even before one year of age. Over the past 150 years, there has been a secular trend in increasing height in high-income countries.26 It is possible that the influence of early weight gain on stature across generations is a mechanism for the increase in height over the last century, as twin studies have estimated the heritability of postnatal weight gain is 80%.32 However, as the F1 and F2 height data used in this study were self-reported and therefore at risk of measurement error, further research is needed to disentangle the influence of genetics on secular height trends.**Conclusions**

This study demonstrates an association between grandparental growth in early life and the heights of their children and grandchildren. The results presented here highlight the potential importance of weight gain in early life on the adult stature of subsequent offspring. Further studies which extend these findings by examining associations along male and female lines are now indicated. Although currently a discovery cohort, with replication, the implications of these associations could be far reaching and suggest the persisting effect of intrauterine growth trajectories in the next generation and thereafter.

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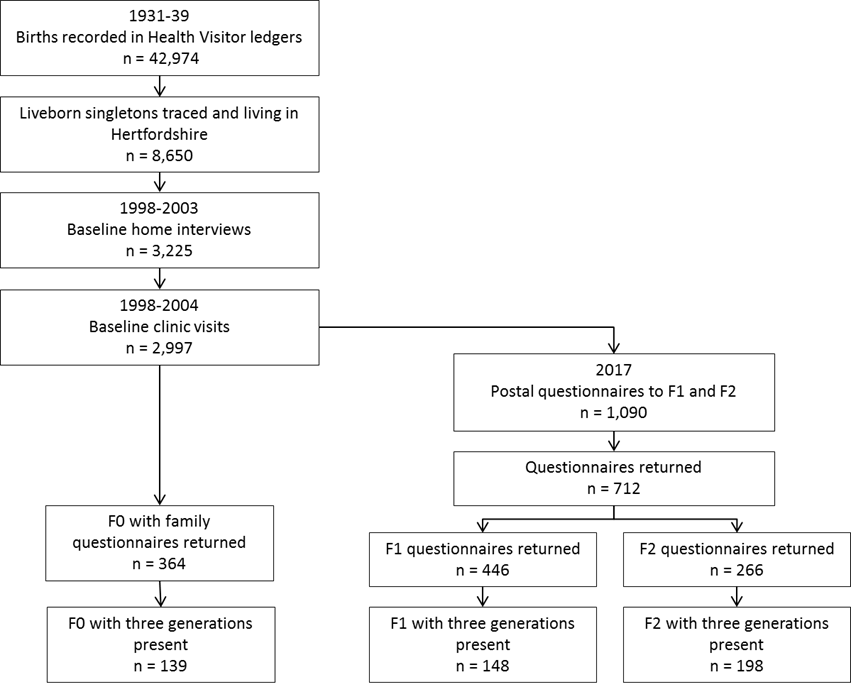
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**Table 1: Descriptive statistics of F0, F1, and F2 participants**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **F0 (n=139)** | | **F1 (n=148)** | | **F2 (n=198)** | |
|  | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| Age (years) | 66.1 | 2.8 | 55.4 | 3.9 | 25.1 | 5.8 |
| Birthweight (kg) | 3.5 | 0.5 | 3.4 | 0.6 | 3.5 | 0.6 |
| Weight at 1 year (kg) | 10.0 | 1.0 | - | - | - | - |
| Conditional weight gain during1st year (SD score) | 0.1 | 0.9 | - | - | - | - |
| Height (cm) | 169.3 | 8.9 | 169.4 | 9.1 | 175.3 | 10.0 |
|  | **N** | **%** | **N** | **%** | **N** | **%** |
| Female | 65 | 46.8 | 110 | 74.3 | 99 | 50.0 |

**Figure 1: HCS three generation recruitment**

**Figure 2: Associations between F0 early life growth and descendants’ adult height**

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