

## **NATURE AND NURTURE IN EARLY FEEDING BEHAVIOUR**

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## **Abstract**

Obesity has reached epidemic proportions and research into prevention is increasingly focusing on the earliest stages of life. Avidity of appetite has been linked to a higher risk of obesity, but studies in infancy were scarce. The Gemini twin cohort was established to investigate genetic and environmental determinants of weight trajectories in early childhood with a focus on appetite and the home environment.

Gemini families have been supplying questionnaire data at regular intervals, starting when the twins were 8 months old. Analyses of data on infant appetite and weight have provided a number of important findings. Firstly, a prospective study found that appetite in infancy drives weight gain more strongly than weight drives appetite, although the two processes do co-exist. A further study using a subsample of twins discordant for appetite ruled out the possibility of familial confounding, suggesting a causal role for appetite in weight. Heritability estimates for appetitive traits were moderate to high (53% - 84%). Finally, multivariate analyses indicated that roughly one third of the genes related to weight are also related to appetite and vice versa.

Environmental factors affecting appetite in infancy are under-studied, but some potential strategies for minimizing the risks of over or under-consumption in at-risk individuals are suggested.

## INTRODUCTION

Obesity is one of the world's great health challenges, and is increasingly seen in childhood. Obesity is complex because there is strong evidence for both environmental and genetic influences. Environmental changes are widely agreed to account for the rapid increases in weight over the last 40 years. But within-population variation in weight is as high – maybe higher – as ever, and twin and family studies show that weight is highly heritable (50-90%) [1]. Since the completion of the human genome project in 2003, studies have started to identify common genetic variants associated with weight variation. The fat mass and obesity-associated gene (FTO) was the first of these to be discovered and has the largest effect size, but there now 32 variants robustly associated with adult and child body mass index [2]. These can be combined to create a polygenic obesity risk score (PRS) that shows a quantitative association with BMI. One model put forward to resolve the apparent paradox of high genetic and environmental influence is behavioural susceptibility theory (BST) [3]. BST proposes that genetic risk operates through appetitive traits (responsiveness to external food cues and internal satiety cues) that confer susceptibility to the environment. As the environment becomes more 'permissive' so genetic expression increases, implying gene-environment interplay in the development of obesity. At the heart of this theory is the hypothesis that genes influence adiposity through appetitive mechanisms, and that this process begins very early in life.

### *Evidence for an appetitive model of obesity*

In support of an appetitive model of obesity, avidity of appetite has been associated with obesity risk in adults [4] and children. Obese children appear to be less satiety responsive (fill up less easily) [5], to eat faster [6], to value food more [7] and to be more food responsive (wanting to eat when seeing or smelling palatable food) [8] than their leaner peers.

There also appears to be a graded association between appetite and weight in population samples including normal weight and overweight/obese individuals. A number of studies have found that higher food responsiveness is positively associated with weight (and satiety responsiveness negatively) in a linear fashion (e.g. [3, 9], although as these studies were cross-sectional it was not possible to reject the possibility that the association worked in the opposite direction – higher weight resulting in increased appetite.

Prospective studies addressed this question, finding that large differences in appetite in infancy (indexed by sucking rate) were linked to subsequent growth. A faster sucking rate predicted adiposity at ages 1,2 and 3 years [10,11] although the effect was no longer observed at age 6. Likewise, Wright, Parkinson & Drewett [12] reported that appetite, rated at 6 weeks on a 5 point-scale from 'very poor' to 'very good', predicted weight gain to 12 months, but not at 7-8 years. Finally, infants who frequently emptied their bottle without parental encouragement were 69% more likely than those who rarely did so, to have excess weight (weight for age z score >1) at 12 months [13]. The suggestion is that appetite drives weight gain, but any reverse effect had yet to be explored.

### *Evidence for a genetic basis to appetite*

The heritability of weight is well-established in adults [1] children [14] and in infants [15]. In the latter, heritability of birth weight was quite low at a moderate 38%, but by 6 months it had risen to 62%; moreover, 57% of variation in weight change (the speed at which infants grew between birth and 6 months) was attributable to genetic factors, suggesting that the processes through which genes influence growth begin soon after birth. Twin correlations for adiposity in MZ and DZ twins are shown in Figure 1.

Insert Figure 1 around here

Recent studies in adults [16] and children [3,6,17] have indicated that appetitive traits are also highly heritable. However, studies of heritability of appetite in infancy were lacking and given the growing problem of childhood obesity, investigations of the genetic and environmental determinants of appetitive traits and their possible role in mediating genetic influences on weight were overdue.

### **THE GEMINI STUDY**

The observation that a large proportion of the genetic effect on body weight has already been expressed by the time children are 4 years old [18], led Professor Jane Wardle to establish Gemini – the Health and Development in Twins study. Gemini is a longitudinal cohort study of UK families with young twins sited within the Department of Epidemiology and Public Health at University College London. It is the largest twin study set up specifically to advance understanding of genetic and environmental influences on growth trajectories in early childhood, and has a focus on behavioural mechanisms in weight gain. Data have been collected on weight every three months from birth, and at multiple subsequent time points on the twins' appetite and eating behaviours, parental feeding practices and on aspects of the home environment in order to identify modifiable determinants of early excess weight gain.

The Gemini sample was recruited in January 2008. Using birth registration data, the Office of National Statistics approached the families of all twins born in England and Wales between March and December 2007 (n=6754). A little over half (n= 3435) consented to be contacted by the Health Behaviour Research Centre team of whom nearly 70% (n=2402) completed baseline questionnaires – 36% of the original target population. Of these 816 were opposite-sex twin pairs and 1586 were same-sex pairs – 749 identical (monozygotic, MZ) and 800 non-identical (dizygotic, DZ). Thirty-seven twin pairs were of unknown zygosity.

### **Why twins?**

Studying twins provides the opportunity to investigate the relative contribution to individual differences in any given trait (such as appetite) made by genes and the environment. MZ pairs share 100% of their genes, where DZ pairs share 50% on average, but both types of twins share their environments to a very similar extent – the 'equal environments assumption'. If MZ pairs are more similar for a given trait than DZ pairs, this suggests a heritable component to the trait in question; and the greater the difference between MZ and DZ similarity, the higher the heritability.

In terms of representativeness, the Gemini cohort is broadly comparable to the general population in terms of distribution across the country, and with national averages for twins in sex, zygosity, gestational age and birth-weight. However, Gemini families are older, healthier (indexed by smoking rates and fruit and vegetable consumption) and more likely to be married and to be White-British than the English and Welsh general population as a whole. For a full description of the rationale, aims, method and characteristics of participants in the Gemini study see van Jaarsveld et al [19].

## **Measures**

The findings discussed in this review are from data on weight and appetite collected at the first two time points a) at baseline when twins were on average 8.2 months old and b) at the first follow-up when the twins were on average 15.8 months old.

### *Infant weight*

From birth onwards, weights were based on health professionals' measurements recorded in each child's Personal Health Record (the Red Book). Parents either supplied photocopied pages from this document or copied the information into the questionnaire. Additional weight measurements were requested every three months.

### *Infant appetite*

Appetitive traits were measured using the Baby Eating Behaviour Questionnaire (BEBQ; [20]). This was based on the Child Eating Behaviour Questionnaire (CEBQ; [21]) and modified to assess appetite in the first 3 months of life when infants are solely milk-fed. It was completed retrospectively when twins were 8 months of age on average, and again at 15 months (in a slightly reworded form).

The BEBQ comprises 17 items measuring 4 appetitive traits, the first two of which are 'food approach' behaviours, and the latter two, 'food avoidant':

- Enjoyment of food (4 items) e.g. "My baby enjoyed feeding time" (baseline) and "My child enjoys eating" (follow-up)
- Food responsiveness (6 items) e.g. "Given the chance, my baby would always be feeding" (baseline) and "Given the chance my child would eat most of the time" (follow-up)
- Slowness in eating (4 items) e.g. "My baby fed slowly" (baseline) and "My child eats slowly" (follow-up)
- Satiety responsiveness (3 items at baseline and 5 at follow-up) e.g. "My baby got full up easily" and "My child gets full up easily"

All items were scored on a five point scale as never, rarely, sometimes, often and always with mean scores for each subscale ranging from 1 to 5. Higher scores indicated higher enjoyment of food and food responsiveness and lower eating speed and satiety responsiveness.

## RESEARCH QUESTIONS

Studies were conducted using the Gemini cohort to investigate the following questions:

- What is the direction of the association between appetite and weight gain?
- Does the association remain robust when controlling for confounder factors related to the shared family environment?
- Is appetite heritable in infancy?
- If so, do the same genetic influences underlie appetitive traits and weight?

### **The direction of the association between appetite and weight gain**

As discussed, existing data on the association between appetite and weight has been largely cross-sectional and the few existing prospective studies had not specifically investigated the possibility that appetite is a consequence of weight gain rather than a cause. Using measures of appetite at 3 and 15 months and of weight at 3, 9 and 15 months, the strength of the associations in both directions were tested using path analysis [22].

Results were that all 4 appetitive traits – greater enjoyment of food, speed of eating and food responsiveness, and lower satiety responsiveness - were prospectively related to higher weight and faster weight gain. All were relatively stable over time such that a baby with a large appetite at 3 months tended to have a large appetite at 15 months. Although weight at 9 months was also prospectively associated with appetite at 15 months, the association was far weaker, providing support for the behavioural susceptibility hypothesis – that there is a causal effect of appetite on weight.

### **Does the association remain robust when controlling for potential confounding factors related to the shared family environment?**

However, even this longitudinal study could not entirely rule out the possibility that some aspect of the shared home environment of children with larger or smaller appetites might account for differences in weight gain. In order to rule out familial confounding, data from a subsample - pairs of same sex DZ twins whose appetites were dissimilar at 3 months - were analysed [23]. This meant that all other potentially influential variables that twins share in common (e.g. maternal food intake in pregnancy or smoking, parental weight, SES, older siblings) were held constant and the causal effect of appetite on weight gain could be more robustly tested. Twins were deemed to be 'discordant' for appetite if their scores for the Food Responsiveness (FR) and/or Satiety Responsiveness (SR) subscales of the BEBQ at age 3 months differed by 1 standard deviation or more. This resulted in data from 228 pairs being entered into the analyses.

Despite there being no significant differences in birth weight between FR or SR discordant pairs, by 3 months those with a greater appetite were heavier than their sibling and by 15 months, were on average nearly a kilo heavier, which at that age equates to approximately 10% of body weight.

### **The heritability of appetite in infancy**

Using data from the baseline Gemini questionnaire when infants were on average 8 months of age, Llewellyn et al [24] conducted an investigation to determine the extent to which the four appetitive traits measured by the BEBQ were heritable in the very earliest stages of life – the first three months of exclusive milk feeding.

Intra-class correlations for MZ and DZ twins for the scale scores were calculated that showed that MZ twins were significantly more similar than DZ twins, although the size of differences varied between traits. Subsequent model-fitting analyses revealed moderate to high heritability estimates for the four traits and provided an indication of the contribution of environmental factors, both shared and non-shared by the twins (see Table 1)

Insert Table 1 around here

The genetic effect was large for Slowness in Eating (84%) and Satiety Responsiveness (72%) and moderate for Food Responsiveness (59%) and Enjoyment of Food (53%). These results confirm the important role that genes play in appetite variation from the very beginnings of postnatal life. That the heritability estimate for feeding rate (SE) was so high is consistent with previous findings for eating speed in older children [6] and taken together with evidence of an association between feeding speed and later adiposity [10], suggests that this trait may mediate genetically-determined growth rate in infancy. The 72% heritability estimate for Satiety Responsiveness is also broadly consistent with the previous estimate of 63% in 11 year olds [3] and stresses the importance of genes in the regulation of sensitivity to hunger and fullness.

The heritability of the other two appetitive traits, Food Responsiveness and Enjoyment of Food was only moderate (59% and 53% respectively) with a greater role for environmental factors than for SE and SR. In the case of SE, there was no shared environmental effect at all which is also consistent with Carnell et al's [3] findings in 11 year olds.

### **Do the same genetic influences underlie appetitive traits and weight?**

The high heritability of appetitive traits in infancy raises the question of whether the genes responsible are also implicated in weight gain. The first common variant to be implicated in adiposity in adults and children was the *FTO* gene with adults carrying the high-risk version being on average ~ 3 kilos heavier than those with the low-risk version. A large study of children also found that carrying the high-risk allele was associated with lower satiety sensitivity and that this mediated the relationship between *FTO* and weight [25]. Many more obesity-related genes have been identified such that it is possible to calculate an individual's risk score. A score comprising 28 known obesity-related variants was calculated for the same sample of children; as genetic risk of obesity increased, satiety responsiveness decreased, and satiety responsiveness mediated some of the association between the genetic risk score and weight [25, 26, 27] These studies support the idea that 'obesity genes' influence weight via their effects on appetite. However, they included only a very small number of

known variants. Twin studies allow researchers to explore the extent to which *all* the genes that influence appetite are broadly the same as those that influence weight, using inferential modeling.

This hypothesis was tested in the Gemini cohort, with the finding that approximately one third of the genes that influence certain appetitive traits (Slowness in Eating and Satiety Responsiveness) also influence weight [28]. Associations between weight and the other two traits measured (Food Responsiveness and Enjoyment of Food) were too small to permit the modeling of common pathways. This may be because very young infants have so little scope to influence their intake and it may be that at later ages the magnitude of the observed association would be larger. Again, the results support the behavioural susceptibility hypothesis suggesting that in the plentiful food environment of the 21<sup>st</sup> century, those with a genetic predisposition to be less sensitive to their internal signals of satiety may be more likely to overeat and ultimately to gain excess weight.

### **Environmental influences on early eating behaviour**

A large body of research had examined the impact of environmental factors on the eating behaviour of children of 2 years of age upwards, but little is currently known about their impact on appetite in infancy.

The influential factors for infants are likely to include the intra-uterine environment in terms of under- or over-nourishment, impacting on gestation and birth weight, but parental feeding practices – what, when and how children are fed - will also play a critical role in the development of eating behaviours – both positive and negative. For example, the symbiotic feeding relationship afforded by breastfeeding may help to develop infants' self-regulatory abilities, where the common practice of encouraging a formula-fed infant to finish the bottle may override these. Feeding to soothe rather than only when an infant is hungry, may promote excess intake in those predisposed to food responsiveness [29].

Once solid foods are introduced, rapid exposure to a wide variety of foods is associated with less rejection of novel food and may be especially beneficial for food avoidant children [30]. Parental control over the quantity and type of food eaten has been shown to influence the eating behaviours of older children, and may also be important in infancy. In the Gemini cohort, mothers of infants with a lower birth weight and/or smaller appetite were more likely to pressure their child to eat more and less likely to restrict their intake than mothers of infants with a larger appetite.

In another study, restriction was driven by parental perception of their child's risk of overweight and their belief that infants cannot recognize their own feelings of hunger and satiety [31]. Pressure to eat was associated with concern about their infant's low appetite and risk of underweight. Given that parents typically underestimate their children's weight, there is a danger that normal weight or even overweight children may be pressurized into over-eating resulting in unhealthy weight gain and diminishing self-regulation.



Given that the first years of life are increasingly seen as a critical period for the development of lifelong eating habits, a greater understanding of the environmental influences on infant appetite is an important aim for future research.

### **Conclusions and implications**

It is clear that like weight, appetitive traits are highly heritable. These traits are observable from the earliest stages of life and predict weight gain prospectively. The finding that common genes affect weight partly via appetite explains why some individuals are more susceptible to environmental triggers to over-consume. There is a tendency to assume that if behavioural traits are highly heritable, they are not easily amenable to change. Despite the strong influence of genetic factors in appetite, environmental interventions might reduce the expression of these traits in infants at the high-risk extremes. For example, advising mothers to offer smaller, more frequent feeds might be helpful for infants who become full very quickly and using a slower-flowing teat could reduce eating speed in infants who appear less able to regulate their intake in response to satiety cues. Toddlers who have trouble recognizing when they are full would benefit from smaller portions and a higher proportion of low energy foods in their diet. For those who are particularly food responsive keeping unhealthy foods out of the home environment would pay dividends. In later childhood it might be possible to intervene to teach at-risk children better self-regulation by training them to recognize and act upon their internal feelings of hunger and fullness. This is a relatively unexplored area at present, but is a crucial topic for future research with important implications for obesity prevention.

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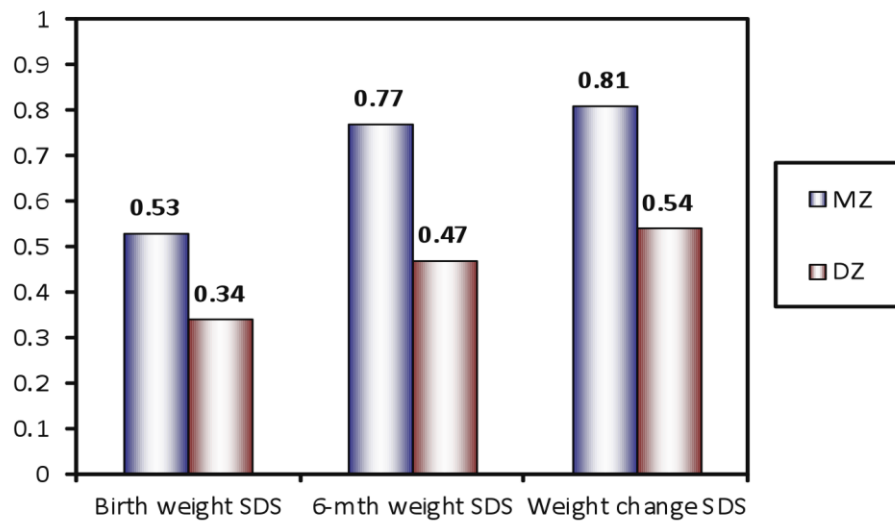
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**Figure 1: Twin correlations for adiposity: birth to 6 months**



**Table 1: Parameter estimates and 95% CI's for ACE model-fitting for the BEBQ subscales**

<b>BEBQ scale</b>	<b>Additive genetic effect (A)</b>	<b>Shared environment effect (C)</b>	<b>Nonshared environment effect (E)</b>
<b>Enjoyment of food (EF)</b>	0.53 (0.43, 0.63)	0.45 (0.35, 0.54)	0.03 (0.02, 0.04)
<b>Food responsiveness (FR)</b>	0.59 (0.52, 0.65)	0.30 (0.24, 0.36)	0.11 (0.10, 0.13)
<b>Slowness in eating (SE)</b>	0.84 (0.79, 0.86)	0.00 (0.00, 0.05)	0.16 (0.14, 0.17)
<b>Satiety responsiveness (SR)</b>	0.72 (0.65, 0.80)	0.12 (0.05, 0.19)	0.16 (0.14, 0.17)