IMPORTANCE Identifying early markers of future obesity risk can help target preventive interventions. Several studies have shown that a heartier appetite in infancy is a risk factor for more rapid weight gain, but to date no investigations have been able to rule out familial confounding.

OBJECTIVES To use a sibling design (data from same-sex, dizygotic twin pairs) to test the hypothesis that sibling differences in infant appetite predicted differential weight gain during childhood.

DESIGN, SETTING, AND PARTICIPANTS Gemini is a population-based twin cohort among the general United Kingdom population born between March 1, 2007, and December 15, 2007. Growth trajectories were analyzed from birth to age 15 months. Appetite-discordant pairs were selected from 800 nonidentical, same-sex twin pairs.

EXPOSURES Appetite during the first 3 months of life was assessed with the food responsiveness (FR) and satiety responsiveness (SR) subscales from the Baby Eating Behaviour Questionnaire. Discordance was defined as a within-pair difference of at least 1 SD.

MAIN OUTCOMES AND MEASURES A mean of 11.5 weight measurements per child were available between birth and age 15 months. Multilevel models, adjusted for sex and birth weight, compared growth curves for the higher-appetite vs lower-appetite twins.

RESULTS In total, 172 pairs were discordant for SR and 121 pairs for FR. Within-pair analyses showed that those with higher FR and those with lower SR grew faster than their sibling. At age 6 months, those with higher FR were 654 (95% CI, 395-913) g heavier and at age 15 months were 991 (95% CI, 484-1498) g heavier. For sibling pairs discordant for SR, the weight differences between siblings were 637 (95% CI, 438-836) g at age 6 months and 918 (95% CI, 569-1267) g at age 15 months.

CONCLUSIONS AND RELEVANCE A heartier appetite (indexed with higher FR or lower SR) in early infancy is prospectively associated with more rapid growth up to age 15 months in a design controlling for potential familial confounding, supporting a causal role for appetite in childhood weight gain. Appetite could be an early marker for risk of weight gain in the current obesogenic environment and might be a potential target for preventive interventions.
Obesity is a major concern for children's health and for adults' health because of its persistence. Children of the late 20th century are growing faster and reaching a higher adult body mass index than any previous generation, a phenomenon that is rooted in environments containing easily available, cheap, palatable, energy-dense, and extensively marketed foods. Therefore, modifying the environmental drivers of the obesity epidemic is a key goal for public health policy. However, alongside the broad pattern of population-level weight gain, individual variation remains high, and siblings vary in weight even within families. Identifying the individual-level factors that promote or protect against weight gain, particularly those expressed in early childhood, could help identify potential targets for intervention and prevention.

Studies have implicated appetitive traits in obesity risk, with higher food responsiveness (FR) and lower satiety responsiveness (SR) being associated with greater body mass index. Food responsiveness relates to stimulation of intake by exposure to food cues (eg, smell or sight of palatable food), probably mediated via brain-reward pathways. Satiety responsiveness relates to the sense of satisfaction and fullness experienced after eating, probably mediated via a neuroendocrine feedback loop involving hormones secreted in the gut that interact with control centers in the brain. Satiety responsiveness may be one of the mechanisms through which genetic predisposition leads to weight gain. Longitudinal analyses have demonstrated that higher appetite is prospectively associated with faster growth, and a bidirectional longitudinal analysis showed that the association between infant appetite and subsequent 12-month weight gain was stronger than the association between infant weight and subsequent change in appetite. However, even longitudinal studies cannot rule out confounding by unmeasured differences in the home environments of children with higher and lower appetites, which might be responsible for the differential weight gain.

Sibling designs exploit the fact that siblings share stable aspects of the family and home context. Therefore, comparing longer-term outcomes in siblings who are discordant for an early exposure or a trait provides a more stringent test of causality than studies of individuals reared in different environments. Nonidentical ( dizygotic [DZ] ) twins are a particularly informative sibling comparison group because they not only share on average 50% of their genes and grow up in the same home environment but also are developmentally matched for the timing of family events (eg, loss of a parent or birth of a younger sibling). Using only same-sex DZ pairs further increases control for unmeasured variables related to sex differences. Therefore, the present study used same-sex, DZ twin pairs who were discordant for appetite during the first 3 months of life to test the hypothesis that a heartier appetite in early infancy is associated with faster growth up to age 15 months. Sibling pairs were defined as appetite-discordant if appetite scores differed by at least 1 SD between the siblings; therefore, one of the siblings could be classified as having a higher appetite than the other.

Methods

Participants

Ethical approval was granted by the University College London Committee for the Ethics of Non-National Health Service Human Research. Participants were from the Gemini study, a twin birth cohort set up in 2007 to investigate genetic and environmental influences on growth. Written informed consent was obtained from all participating parents on behalf of themselves and their twins before study entry. From all eligible families in England and Wales with twins born between March 1, 2007, and December 15, 2007 (n = 6754), 2402 parents (35.6% response rate) volunteered for the study and completed a baseline questionnaire when the mean (SD) age of the children was 8.2 (2.2) months.

The baseline sample (n = 2402) included 816 opposite-sex twin pairs and 1586 same-sex twin pairs. Parents of same-sex twins (n = 1586) completed a validated 20-item Zygosity Questionnaire, which was shown to be 100% accurate against DNA results in a random sample of 81 pairs. Based on all available zygosity information, 800 of 1586 same-sex pairs were identified as nonidentical (DZ) and formed the group from which we selected appetite-discordant pairs.

Measures

Appetite Discordance

At baseline, parents completed the Baby Eating Behaviour Questionnaire (BEBQ) for the first 3 months of life when their infants were exclusively milk fed. The following 2 BEBQ subscales were included in the analyses: FR, comprising 6 items (Cronbach α = .79), and SR, comprising 3 items (Cronbach α = .73). Response options (never, rarely, sometimes, often, or always) were scored from 1 to 5. The mean scores were calculated for each subscale, with higher scores indicating greater FR or SR.

Discordance was defined as a within-pair difference of at least 1 SD on FR or SR. The twin from each pair with higher FR or lower SR comprised the higher-appetite group, while their sibling with lower FR or higher SR comprised the lower-appetite group. In total, 228 of 800 same-sex DZ pairs (28.5%) were discordant for FR or SR, and these 456 infants were the subject of the present analyses. They included 121 pairs discordant for FR and 172 pairs discordant for SR. Sixty-five pairs were discordant for both FR and SR.

Infant Weight

Weights from birth onward were based on measurements made by health professionals and recorded in the child’s Personal Health Record. Parents were asked to photocopy the relevant pages of the health records or copy the information into the questionnaire. Where health professional weights were unavailable (3.6% of data collected at baseline), parents were asked to record their children’s weights using weighing scales that were sent to the home. Parents were requested to send in additional weight measurements every 3 months. Exact age at measurement was calculated from the measurement date and date of birth. On average, 11.5 (median, 11; interquartile range, 8-15) weight measurements per sibling were returned by age 15 months.
Sample Characteristics
Information on sex, date of birth, gestational age, and infant feeding method were collected in the baseline questionnaire, as well as the mother’s date of birth and education. Maternal educational level was categorized as high (university education), intermediate (vocational or advanced high school education), or low (no qualifications or basic high school education). Infant feeding method during the first 3 months was categorized as breastfed (entirely or mostly breastfed), bottle fed (mostly, almost entirely, or entirely bottle fed), or mixed (equally breastfed and bottle fed). Birth weight SD scores adjusted for sex and gestational age were calculated based on British 1990 growth reference data using the LMS growth macro (Excel; Microsoft Corporation).26,27

Statistical Analysis
The sample for analysis comprised all same-sex DZ pairs who were discordant for appetite in infancy based on a 1-SD difference on FR or SR (ie, a difference between siblings of ≥0.68 on FR or ≥0.81 on SR). Analyses were run separately for each appetite trait. Weight trajectories were modeled from birth to age 15 months using all available weight measurements with their exact ages. Mixed-model analyses were used to fit trend lines for growth from birth maximizing the use of available weight data. The analyses took into account clustering of siblings within families. Time was represented in the model by linear (age), quadratic (age squared), and cubic (age cubed) terms to allow for nonlinear effects, which improved the fit of the growth models. Birth weight was included as a covariate to adjust for any differences between siblings with lower and higher appetites, and all models included sex. Significant sex × age interactions were also included in the model; however, sex × appetite group interactions were not significant and were not included in the final models.

Each model examined the main effect of appetite group (higher vs lower) and interactions between appetite group and each time parameter (age, age squared, and age cubed), which indicate the mean extra weight gained in those having higher appetite compared with their sibling having lower appetite. The overall contribution of appetite group to the model was assessed by combining all 4 appetite-related parameters (ie, the main effect of appetite group and the 3 interaction effects [between appetite group and each time parameter of age, age squared, and age cubed]). Model parameters were used to estimate the mean weight difference (with 95% CIs) between the higher-appetite sibling and the lower-appetite sibling at 3-month intervals from birth to age 15 months. Analyses were performed with statistical software (SPSS 21 [IBM Corporation] and MLwiN 2.28 [Centre for Multilevel Modeling, University of Bristol]), and P < .05 was considered significant. The effects are shown by presenting weight trajectories by appetite group in graphs.

Results
Sample Characteristics
Characteristics of 228 same-sex DZ twin pairs who were appetite discordant are listed in Table 1, along with all same-sex DZ pairs for comparison. The appetite-discordant sample was similar to the total sample for maternal age at birth (mean, 33 years), maternal educational level (53.5% higher education), infant feeding method (30.0% breastfed), twin sex (51.3% male), gestational age (mean, 36.5 weeks), birth weight (mean, 2.53 kg), and birth weight SD score (mean, −0.57) (typical for twins). The appetite-discordant sample had slightly higher SR than the full sample (2.44 vs 2.4) (t1257 = 3.17, P = .002) but did not differ in FR.

The mean (SD) FR for those with lower appetite was 1.79 (0.54) compared with 3.11 (0.64) for siblings with higher appetite (P < .001). The mean (SD) SR for those with lower appetite was 3.52 (0.62) compared with 1.98 (0.57) for siblings with higher appetite (P < .001).

Modeled Weight Trajectories
Table 2 summarizes the results of modeled trajectories using all available weight measurements. The left column lists the results for FR-discordant sibling pairs, with a total of 2671 weight observations (on average, 11.0 observations per sibling), and the right column lists the results for SR-discordant sibling pairs, with a total of 4045 weight observations (on average, 11.8 observations per sibling). The contribution of FR was highly significant (X2d = 952.97, P < .001), indicating faster growth in the higher-FR member of the pair. Similarly, those with lower SR grew faster than their siblings with higher SR (X2d = 1264.97, P < .001 for the contribution of SR to the model). The weight trajectories are summarized in Figure 1 and Figure 2, with dashed lines showing the 95% CIs.
Differences in Weight at 3-Month Intervals

Table 3 summarizes weight differences at 3-month intervals. At birth, weight differences were not significant between FR-discordant pairs (mean, 0.024 [95% CI, −0.082 to 0.130] kg) or SR-discordant pairs (mean, 0.032 [95% CI, −0.062 to 0.126] kg). By age 3 months, those with higher appetite had started to become heavier than their sibling with lower appetite (mean, 0.370; 95% CI, 0.169-0.571 kg for FR and mean, 0.392; 95% CI, 0.243-0.541 kg for SR). Weight differences were significant at all subsequent ages, increasing at age 15 months to 0.991 (95% CI, 0.484-1.498) kg for FR and 0.918 (95% CI, 0.569-1.267) kg for SR.

Discussion

This study shows that sibling differences in appetite during early infancy are associated with different growth trajectories in the subsequent months. In this sample of sibling pairs discordant for appetite at age 3 months, those with higher appetite (indexed with higher FR or lower SR) in early infancy were on average 918 g (SR) to 991 g (FR) heavier than their sibling with lower appetite by age 15 months. This association cannot be confounded by maternal factors, including weight gain, smoking or food intake in pregnancy, or family-level factors, such as socioeconomic status or the presence of older siblings, because the sibling design ensures that these are exactly matched between groups. In addition, parental feeding practices are similar between twin siblings (eg, breastfeeding prevalence and age at which solid foods are introduced). Therefore, the sibling design also minimizes confounding effects associated with parental feeding behaviors. Any biases in the way individual parents interpret the questionnaire should also be the same for the 2 children within each family.

Weight trajectories differed significantly between appetite-discordant sibling pairs, resulting in weight differences close to 1 kg by 15 months, a substantial difference given that the mean 15-month weight was 10.3 kg. This effect was observed
with comparatively modest differences in appetite, seen in 28.5% of the twins. Therefore, it is likely to resemble differences that occur commonly in the population and is not an effect of extreme cases.

The results were comparable for the 2 aspects of appetite. This is partly due to overlap between the appetite measures because 65 pairs who were discordant for both FR and SR are included in both sets of analyses. However, data using the full Gemini cohort confirm that these appetite measures are only moderately correlated.25

Our findings indicate that within the same family the sibling with the higher appetite grows faster than the sibling with the lower appetite. Similar patterns are to be expected in the wider population; therefore, this study corroborates the hypothesis that a hearty appetite in infancy is a risk factor for faster weight gain.

Our study has several strengths. The present analyses included data from 456 children with more than 5000 weight measurements, allowing detailed and robust modeling of growth trajectories and providing strong evidence that infant appetite is predictive of subsequent weight gain. Limitations of the study should also be noted. Small within-pair differences in birth weight existed, and there could be a residual effect, although birth weight was included as a covariate in all models. Body length is associated with weight and may be relevant when studying weight gain. However, the measurement of length in early infancy is unreliable, is not part of routine medical care in the United Kingdom, and was unavailable in the present data set. The BEBQ is completed by parents; however, collecting objective appetite data on sufficiently large samples is prohibitively expensive, and the questionnaire from which the BEBQ was derived was validated against behavioral observations.28

**Conclusions**

In summary, this study shows that a heartier appetite in early infancy is associated with more rapid growth up to age 15 months in a design controlling for potential familial confounding, suggesting a causal role for appetite in early weight gain. Infants with larger appetites may be at increased risk for rapid weight gain in the current obesogenic environment, and might be targeted in strategies to prevent obesity in susceptible individuals.

<p>| Table 3. Weight Differences at 3-Month Intervals in Appetite-Discordant Pairs |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Interval</th>
<th>Food Responsiveness</th>
<th>Satiety Responsiveness</th>
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<tbody>
<tr>
<td>At birth</td>
<td>0.024 (−0.082 to 0.130)</td>
<td>0.032 (−0.062 to 0.126)</td>
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<tr>
<td>Age, mo</td>
<td></td>
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<tr>
<td>3</td>
<td>0.370 (0.169 to 0.571)</td>
<td>0.392 (0.243 to 0.541)</td>
</tr>
<tr>
<td>6</td>
<td>0.654 (0.395 to 0.913)</td>
<td>0.637 (0.438 to 0.836)</td>
</tr>
<tr>
<td>9</td>
<td>0.843 (0.505 to 1.181)</td>
<td>0.765 (0.511 to 1.020)</td>
</tr>
<tr>
<td>12</td>
<td>0.950 (0.562 to 1.338)</td>
<td>0.839 (0.534 to 1.144)</td>
</tr>
<tr>
<td>15</td>
<td>0.991 (0.484 to 1.498)</td>
<td>0.918 (0.569 to 1.267)</td>
</tr>
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**ARTICLE INFORMATION**

**Accepted for Publication:** November 3, 2013.

**Published Online:** February 17, 2014. doi:10.1001/jamapediatrics.2013.4951.

**Author Contributions:** Dr van Jaarsveld had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: van Jaarsveld, Llewellyn, Wardle. Analysis and interpretation of data: All authors. Drafting of the manuscript: van Jaarsveld, Llewellyn, Wardle. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: van Jaarsveld, Boniface. Obtained funding: Wardle. Study supervision: Wardle.

**Conflicts of Interest Disclosures:** None reported.

**Funding/Support:** Gemini was funded by grant C1418A/9794 from Cancer Research UK (Dr Wardle).

**Role of the Sponsor:** The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** We thank the Gemini families who are participating in the study and the Office of National Statistics for their help in recruiting them.

**REFERENCES**


