Common etiological architecture underlying reward responsiveness, externally driven eating behaviors and BMI in childhood: findings from the Gemini twin cohort

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Key words: reward responsiveness, food responsiveness, external eating, BMI, twins

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Running title: Child reward responsiveness, eating behavior and BMI

Abstract

Background: Studies have reported that impulsivity predicts childhood BMI and that the association is mediated by eating behaviors. One aspect of impulsivity – potentially crucial in the obesity context – is reward responsiveness, which may predispose to responsiveness to palatable food cues. The behavioral susceptibility theory hypothesizes that genetic susceptibility to obesity operates partly via genetically determined differences in appetite regulation. Reward responsiveness may therefore be one of the neuro-endophenotypes that mediates genetic susceptibility to obesity.

Objective: To test whether reward responsiveness, eating behaviors and child BMI share common genetic architecture.

Methods: We examined reward responsiveness, eating behaviors and BMI in five-year-old children from Gemini, a UK birth cohort of 2,402 twin pairs born in 2007. All measures were collected by parent report. Reward responsiveness was derived from the Behavioral Approach System. Compulsion to eat and eating for pleasure was measured with the 'food responsiveness' scale of the Child Eating Behavior Questionnaire. Wanting to eat in response to environmental food cues was measured with the 'external eating' scale of the Dutch Eating Behavior Questionnaire. Maximum-likelihood structural equation modelling was used to establish underlying common genetic and environmental influences.

Results: There were significant positive phenotypic correlations between all traits except for reward responsiveness and BMI. Genetic factors explained the majority of the association between food responsiveness and external eating (74%, 95%CI: 61, 87), whereas common shared environmental factors explained the majority of the associations between reward responsiveness with both food responsiveness (55%, 95%CI: 20, 90) and external eating (70%, 95%CI: 39, 100).

Conclusions: Our study demonstrates the importance of common environmental factors in the shared etiology between reward responsiveness and childhood eating behaviors. However, the common etiology underlying both reward responsiveness and BMI is unclear, as there was no phenotypic correlation between reward responsiveness and BMI at this age. Further longitudinal research needs to detangle this complex relationship throughout development.

Background

Over the past four decades there has been an unprecedented global increase in the prevalence of obesity (1) and, despite various public health initiatives, it has remained high (2,3). Major changes to the food environment in industrialized countries, such as advances in farming, production and storage techniques have resulted in food becoming more palatable, energy-dense, readily available and affordable. At the same time, portion sizes have increased, and energy-dense foods are promoted aggressively (4). This has created what is often called an 'obesogenic' environment – one in which the incentive structures encourage us to consume more energy than we expend (5,6). However, not all individuals exposed to the 'obesogenic' environment develop obesity.

Genetic factors explain a large proportion of variation in susceptibility to obesity. Half a century of twin and family studies have estimated that genetic differences between people explain between 50% to 90% of individual differences in human body weight (7). In addition, large-scale genome-wide association studies have identified close to 1,000 common genetic variants (single nucleotide polymorphisms, SNPs) robustly associated with variation in body mass index (BMI) (8). Gene-expression studies have indicated that many of the SNPs associated with BMI are located in or near genes that are predominantly expressed in the brain; including the hypothalamus, hippocampus and limbic system. These findings suggest that neuropsychological processes influencing energy balance may mediate genetic susceptibility to obesity.

The behavioral susceptibility theory of obesity hypothesizes that genetic susceptibility to obesity operates partly via genetically-determined differences in appetite regulation, which encourage overeating in response to the increased opportunity offered by the modern obesogenic environment (9). In this context, food responsiveness (wanting to eat in response to the sight, smell and taste of palatable food) is an appetitive behavior that has received particular attention. Large population studies have shown that BMI-associated SNPs are also associated with food responsiveness in children (10) and adults (11–14), and partly mediates the association between BMI-associated variants and measured BMI (15). Twin studies have also established that variation in food responsiveness is moderately to highly heritable in infancy (16), childhood (17,18) and adulthood (19–21); and individual differences in this behavior are associated with prospective weight gain from infancy to early childhood (22–24).

In addition to eating behaviors such as food responsiveness, other psychological factors such as impulsivity are likely to be involved in obesity susceptibility (25). Impulsivity is a broad psychological

construct encompassing increased behavioral approach, disinhibition, novelty-seeking and reward responsiveness (26). Different aspects of impulsivity are related to variation in BMI in children and adults (25), and share many features with food responsiveness, such as heightened reward responsiveness and disinhibition towards palatable food (27). Food responsiveness might therefore be considered the food-specific expression of the reward-sensitivity component of impulsivity in childhood. Although research into reward and food responsiveness is sparse, a previous cross-sectional study of Dutch children (n=346) reported that impulsivity predicted childhood BMI, and that the association was mediated by a composite of overeating and food responsiveness (28). Food responsiveness and reward responsiveness might be specifically interconnected during childhood. Parents commonly use food to reward behaviour (so-called 'instrumental feeding'), especially if their child is particularly responsive to food cues, potentially strengthening the link between responsiveness to rewards and responsiveness food (29, 30).

Impulsivity has been found to be heritable (31–33); reward responsiveness may be one of the domains of impulsivity that mediates genetic susceptibility to obesity. However, there has been no twin study of reward responsiveness so far, and the extent of the shared genetic etiology underlying reward responsiveness, eating behaviors and BMI has never been examined. Twin studies offer a powerful design for characterizing and quantifying the common genetic and environmental etiology underpinning multiple traits. In this study, we aimed to establish for the first time the extent of common genetic and environmental etiology underlying reward responsiveness, externally driven eating behaviors and BMI in a large sample of British twin children, using twin-based multivariate genetic model-fitting analysis. We hypothesized that reward responsiveness, externally driven eating behaviors and BMI share common genetic architecture, indicated by statistically significant phenotypic and genetic correlations between them.

Methods

We examined reward responsiveness, externally driven eating behaviors and BMI in five-year-old children from Gemini - a large population-based birth cohort of 2,402 twin pairs born in England and Wales in 2007, set up to investigate genetic and environmental contributions to early growth (34). The University College London Committee for the Ethics of non–National Health Service Human Research granted ethical approval for the study.

Participants

The UK Office for National Statistics contacted all eligible families with twins born between March and December 2007 (*n*=6,754) for consent to be contacted by Gemini researchers; 3,435 families consented, of which 2,402 completed the baseline questionnaire and comprise the cohort. Follow-up questionnaires were sent to families when the children were 5 years old. The initial cohort included 749 monozygotic (MZ) twin pairs, 1,616 dizygotic (DZ) pairs, and 37 twin pairs of unknown zygosity (34). Participants included in these analyses were those who had data on zygosity and at least one of the included outcome variables at 5 years of age (n=2,156).

Outcome variables

All behavioral measures were collected by parent report. Participants were included if they had data for the majority of items of subscales (3/4, 3/5 or 4/7 depending on the number of items per scale). For all psychometric tools, internal consistency was evaluated with McDonald's omega. This metric is suitable for ordinal questionnaire items, and seen as superior to the commonly used Cronbach's alpha, with higher values indicating a better internal consistency (35).

We measured generalized reward sensitivity using the parent-reported Reward Responsiveness subscale from the Behavioral Inhibition System/ Behavioral Approach System measure (BIS/BAS) (36). The BIS/BAS measure has 3 BAS subscales and 1 BIS subscale, with the aim of assessing individual differences in trait sensitivity to threats and rewards. The Reward Responsiveness subscale consists of seven items, such as 'My child does things to be praised'. Parents indicate the degree to which they agree with statements applied to their children on a five-point Likert scale ranging from 'extremely untrue' to 'extremely true'. A mean reward responsiveness composite score was generated based on responses to the 7 items (McDonald's omega =0.82).

We measured two eating behaviors that characterize susceptibility to environmental food cues. Food responsiveness (a child's compulsion to eat and eating for pleasure) was measured using the Food Responsiveness subscale from the Child Eating Behavior Questionnaire (CEBQ) (37). The CEBQ is a parent-report questionnaire, aiming to quantify child eating behaviors hypothesized to relate to weight and weight gain in childhood. It has high internal and external reliability and has been validated using laboratory-based objective measures of eating behavior (37). Parents rate how much the statements describe their children's habitual eating behavior using a 5-point frequency Likert scale ranging from 'never' to 'always'. It consists of five items, such as 'Even if my child is full up s/he finds room to eat his/her favorite food'. A mean Food Responsiveness composite score was generated based on these 5 items (McDonald's omega =0.85).

External eating (a child's desire to eat in response to environmental food cues, such as sight, smell and taste) was measured using a modified version of the External Eating subscale from the parent-report version of the Dutch Eating Behavior Questionnaire (DEBQ) (38), which aims to assess psychological aspects of overeating in children (39). We included 4/10 items from the External Eating subscale of the DEBQ-P. We modified the items to ensure they were age-appropriate for 5-year-old children and piloted them extensively before inclusion in this study. The scale included statements such as 'My child wants to eat when s/he sees others eating' and uses the same 5-point frequency Likert scale as the CEBQ. A mean external eating composite score was generated based on these 4 items (McDonald's omega =0.66).

Children's heights and weights were parent-reported in the 5 years questionnaire using electronic weighing scales (Tanita UK Ltd, Yewsley, UK) and a height chart with instructions, sent to all families when the children were two years of age. Body mass index (BMI) was calculated from the parent-reported height and weight in the 5 years questionnaire, as weight/height^2 (kg/m^2). BMI varies considerably with age and sex during childhood, so it was converted to BMI standard deviation scores (BMI-SDS) corrected for age and sex using British 1990 growth reference data (40) with the LMS-Growth Excel (41). A BMI-SDS of 0 indicates an average BMI, >0 indicates a higher BMI and <0 indicates a lower BMI than the mean BMI in the reference data. Child sex was parent-reported at baseline, and child age at the 5-year questionnaire completion was calculated from parent-reported date-of-birth and the date the 5-year questionnaire was completed. The zygosity of same-sex twin pairs was based on a standard self-reported questionnaire measure of similarity (42) that was completed at 8 months (mean= 8.1, range= 4.01-20.3) and again at 29 months (mean = 28.8, range: 22.9-47.6) and validated using DNA (43).

Statistical analysis

All analyses were performed in OpenMx (44), a free and open source package in R. Given that age (and sex for same-sex twins) are exactly correlated for twin pairs, these factors can potentially inflate the estimation of shared environmental influences. We therefore regressed out the effects of age and sex for all phenotypes prior to analyses. Associations between reward responsiveness, food responsiveness, external eating and BMI-SDS were assessed using linear regression analyses.

Genetic twin modelling

Details of the genetic twin modelling can be found in **Supplementary Text 1**. Maximum likelihood structural equation modelling enables the inclusion of all available data and the calculation of

precise estimates of genetic (A), shared environmental (C) and unique environmental (E) influences, with 95% confidence intervals, and goodness-of-fit statistics. A multivariate model (a 'correlated factors model') enables both genetic and environmental influences on each trait to be estimated, along with genetic and environmental contributions to covariance across traits. The multivariate model estimates both the proportion of variance in each individual trait explained by A, C and E (as per the univariate model), and it also partitions the covariation between traits into three types of etiological correlations: i) correlated additive genetic influence (genetic correlation, r_a); ii) correlated shared-environmental influence (shared environmental correlation, r_c); and iii) correlated unique-environmental influence (unique environmental correlation, r_e). These etiological correlations (r_a, r_c and r_e) indicate the extent to which the same genetic, shared environmental and unique environmental influences underlie multiple traits. They range from -1 to 1 and can be interpreted similarly to Pearson's correlations. For example, a high positive genetic correlation indicates that many of the genetic factors that influence high scores on one trait (e.g. reward responsiveness) also influence high scores on another trait (e.g. BMI-SDS); while a high negative genetic correlation indicates that many of the genetic factors that influence high scores on one trait also influence low scores on another trait.

To aid interpretation, the multivariate model also generates bivariate A, C and E estimates. If the bivariate estimates are all in the same direction (positive or negative) they indicate the proportion of each pairwise phenotypic correlation that is explained by common genetic (bivariate A), shared environmental (bivariate C) and non-shared environmental influences (bivariate E). For example, the bivariate A estimate between reward responsiveness and BMI-SDS will quantify the proportion of the phenotypic correlation between these two traits that is explained by shared genetic factors. They are calculated by dividing the covariance of the latent factors (A, C and E) by the phenotypic correlation between the two variables.

The goodness-of-fit of different models of varying parsimony (i.e. dropping A or C parameters, or etiological correlations) is tested in two stages. Firstly, a saturated model is fitted which allows for different means and variances across twin 1 and twin 2, across males and females and across MZ and DZ twins. Secondly, a full ACE model is fitted that is aligned with the assumptions of genetic relatedness and shared environmental effects for MZ and DZ pairs described above. The goodness-of-fit of more parsimonious models are compared to fuller models by assessing both the difference in minus twice the log-likelihood of (−2LL), similar to a $\chi 2$ test, and the Akaike's information criterion (AIC). Lower AIC values indicate a better model fit. When comparing the AIC of two models, a

difference of 4–7 indicates support for one model over the other. An AIC difference of greater than 10 indicates substantial support for the model with the lower AIC value. In the case when the -2LL and AIC do not agree, the AIC will be given precedence as it is considered a superior model fit criterion (45).

Results

Descriptive Statistics

This study included 2,156 individual twin children (362 MZ and 716 DZ twin pairs) with complete data for the measured phenotypes (reward responsiveness, food responsiveness, external eating and BMI-SDS), age at measurement of the phenotypes, sex and zygosity (**Table 1**). The mean age at completion of the 5-year questionnaire was 5.15 years (SD=0.13), and 48.4% were male. The mean BMI was 15.4 kg/m^2 (SD = 1.3) and BMI-SDS was -0.23 kg/m^2 (SD = 1.10), indicating that the sample were slightly leaner that average according to the UK reference data.

Linear regression analysis revealed significant positive phenotypic correlations between: i) reward responsiveness and food responsiveness (0.20; 95% confidence interval (CI): 0.16, 0.25)); ii) reward responsiveness and external eating (0.23; 95% CI: 0.19, 0.27)); iii) food responsiveness and external eating (0.54, 95% CI:0.51, 0.57); iv) food responsiveness and BMI-SDS (0.21; 95%CI: 0.14, 0.27); and v) external eating and BMI-SDS (0.11, 95% CI: 0.04, 0.18) (**Table 2**). The phenotypic correlation between reward responsiveness and BMI-SDS was not statistically significant (0.03 95% CI: -0.04, 0.10). Within-twin and cross-twin correlations for reward responsiveness, food responsiveness, external eating and BMI-SDS are summarized in Table 3. Phenotypic and cross-twin correlations for boys and girls separately can be found in **Supplementary Tables 1 and 2**.

Genetic model fitting

The -2LL suggested a slightly poorer fit of the ACE model compared to the saturated model (difference in -2LL=59.56 (40), *p*=0.02), whereas the AIC value was substantially lower for the ACE than the saturated model, indicating a better fit for the ACE model (difference in AIC=20.44; **Supplementary Table 3**). Based on the ACE model, the heritability estimates (A) ranged from 50% (95% CI: 43%, 58%) for external eating to 79% (95% CI: 62%, 88%) for BMI-SDS, while common environmental contributions (C) ranged from 9% (95% CI: 1%, 26%) for BMI-SDS to 42% (95% CI: 34%, 49%) for external eating (Figure 1). Unique environmental influences (E) accounted for less than 13% of the variance across all traits.

Etiological correlations

The magnitudes of the etiological correlations indicate the extent to which genetic (r_a), common (r_c) or unique environmental (r_e) factors are shared between the traits. There were significant etiological correlations between all factors except for reward responsiveness and BMI-SDS (**Figure 1**). Reward responsiveness shared some genetic influence with both food responsiveness and external eating, indicated by small but significant genetic correlations with both eating behaviors (r_a=0.12; 95% CI: 0.02, 0.22, for both). The genetic correlations between BMI-SDS and the two eating behaviors were moderate (food responsiveness: r_a=0.42; 95% CI: 0.26, 0.54; external eating: r_a=0.31; 95% CI: 0.17, 0.43), indicating considerable overlap in the genetic factors underlying BMI-SDS and these two eating behaviors.

There were moderate shared environmental correlations between reward responsiveness and both eating behaviors (food responsiveness: r_c=0.38; 95% CI: 0.14, 0.62; external eating: r_c=0.45; 95% CI: 0.14, 0.60), indicating some similarity in the shared environmental factors underlying these three traits. The estimates for the shared environmental correlations between BMI-SDS and the two eating behaviors were unreliable (and not statistically significant for BMI-SDS and external eating) due to the very small proportion of variance in BMI-SDS attributable to shared environmental influences.

Unique environmental correlations varied substantially. There was some common unique environmental influence underlying reward responsiveness and food responsiveness, indicated by a small but statistically significant unique environment correlation (r_e=0.09; 95%CI: 0.08, 0.11), and there was considerable common unique environmental influences underlying food responsiveness and external eating (r_e=0.69; 95%CI: 0.63, 0.74), and food responsiveness and BMI-SDS (r_e=0.31; 95%CI: 0.14, 0.44). There were no significant unique environmental correlations detected between reward responsiveness and external eating, or reward responsiveness and BMI-SDS.

Bivariate Estimates

Bivariate estimates indicate the extent to which the phenotypic correlation (r_p) between two traits can be explained by genetic, shared and unique environmental factors (as a proportion of the total phenotypic correlation). Common shared environmental factors contributed the most to the phenotypic associations between reward responsiveness and both eating behaviors; bivariate C explained 55% of the phenotypic correlation between reward responsiveness and food responsiveness (r_p=0.2; 95% CI: 0.16, 0.25; **Table 4**), and 70% of the phenotypic correlation between reward responsiveness and external eating (r_p=0.23; 95% CI: 0.19, 0.27). On the other hand,

common genetic factors explained the greatest proportion (74%) of the phenotypic association between food responsiveness and external eating *(r_p*=0.54, 95%CI: 0.51, 0.57). It was not possible to estimate the contribution of common genetic and environmental factors underlying the phenotypic associations between BMI-SDS and either of the two eating behaviors because the bivariate estimates were in different directions and not statistically significant for bivariate C. There were no statistically significant bivariate estimates for the phenotypic correlation between reward responsiveness and BMI-SDS because the phenotypic correlation itself was not statistically significant.

Discussion

This study aimed to establish, for the first time, the extent of common genetic and environmental etiology underlying impulsivity (reward responsiveness), two externally-driven eating behaviors (food responsiveness and external eating) and BMI-SDS in a large sample of British twin children, using multivariate genetic model-fitting analysis. Our results indicated that all traits are under substantial genetic influence at five years of age. However, contrary to our hypotheses there was not a significant phenotypic association between reward responsiveness and BMI-SDS at this age, as confidence intervals crossed zero, and therefore no evidence of a common genetic architecture. In addition, we found only a small amount of shared genetic influence underlying reward responsiveness and the two eating behaviors, indicated by small but significant genetic correlations (r_g=0.12 for both). Rather, common shared environmental factors were important in shaping both reward responsiveness and externally driven eating behaviors in early childhood, as there were moderate shared environmental correlations between both reward responsiveness and food responsiveness (r_c=0.38) and reward responsiveness and external eating (r_c=0.45). In addition, the bivariate estimates indicated that shared environmental factors explained 55% of the phenotypic association between reward responsiveness and food responsiveness and 70% of the phenotypic association between reward responsiveness and external eating.

A possible common environmental influence on both eating behavior and reward responsiveness is parents' feeding practices. For example, if parents offer children their favorite food as a reward for good behavior or withhold it as a punishment for bad behavior (known as instrumental feeding), children may learn to view that food as having a strong rewarding value (46). In addition, physical aspects of the home environment, such as the availability, accessibility and visibility of highly palatable energy dense foods, is likely to have an impact on the expression of both food responsiveness and external eating, as well as reward responsiveness in early childhood. Together,

these influences may be captured as shared environmental factors in our analyses. Both home and family environment are complex and further studies will be needed to identify which specific components influence both impulsivity and eating behaviors. Our work may signpost potential new targets for interventions that aim to prevent childhood obesity. A previous study using this sample showed that there was a sizeable influence of the shared environment on variation in BMI for children living in healthier homes, which was not detectable for the children living in more 'obesogenic' homes (47). At the same time, for children living in more 'obesogenic' households with greater opportunity for genetic susceptibility to obesity to be expressed, the heritability of BMI was more than twice that observed for children who were reared in healthier homes.

There was considerable genetic overlap between the two externally-driven eating behaviors and BMI-SDS, indicated by moderate genetic correlations (BMI-SDS and food responsiveness: r_a=0.42; BMI-SDS and external eating: r_a=0.31), supporting the hypothesis that genetic susceptibility to obesity operates partly via appetitive processes (13). Our findings are in line with a previous study in adults examining the common genetic factors underlying cognitive and emotional aspects of eating behaviors and BMI, with genetic correlations ranging between 0.16 and 0.51 (48).

Contrary to our hypothesis there was no significant phenotypic association between reward responsiveness and BMI-SDS. There have been very few studies examining reward responsiveness and childhood BMI, with one suggesting that reward responsiveness is indirectly associated with BMI through food responsiveness (combined with a measure of emotional overeating) (29). Although we did not find an association between reward responsiveness and BMI-SDS at the age of 5, it is possible that the association will emerge when children are older and have developed greater autonomy for reward responsiveness to be expressed more freely in eating behavior. For example, as children become more independent, they are able to choose to reward themselves with palatable foods, in line with observations reported in adolescents and adults (49).

The largest phenotypic correlation was between food responsiveness and external eating. This is unsurprising given that both traits are distinct but related facets of appetite avidity - eating for pleasure and responsiveness to external food cues. They are both expressions of the hedonic appetite control system and involve neurologically dissociable processes underpinning wanting and liking. While subjective liking of food involves the mu-opioid and endocannabinoid systems, wanting is primarily regulated by the mesolimbic dopamine system (50). In addition, the association between appetite and childhood BMI is well-documented across childhood. For example, studies have reported that food responsiveness (and other eating behaviors that characterize a larger and more

avid appetite) are positively associated with adiposity in children of 4-5 years (51), 6-7 years (52) and 7-12 years (53) of age.

The heritability of reward responsiveness was moderate in this study (61%), in line with a previous meta-analysis of the heritability of impulsivity (n=41 studies; n=27,147 twin individuals) which found comparable twin-based estimates of genetic influence on this trait at all developmental stages (infants A=53%; children A=59%; adolescents A=54%; adults A=41%) (54). For eating behaviors, our heritability estimates (food responsiveness A=60%; external eating A=50%) were similar to those reported previously in a large sample of children aged 8-11 years of age (*n*=5,435 twin pairs; food responsiveness: A=75%; satiety responsiveness: A=63%) (55). The Quebec Newborn Twin Study also examined traits related to appetite, such as "eating too much", "not eating enough" and "eating too fast", in n=692 twin individuals at 2.5 and 9 years of age, with slightly higher heritability estimates observed for younger children compared to older children (A=71-89% versus 44-56%) (18). For BMI, the Collaborative Project of Development of Anthropometrical measures in Twins study explored genetic and environmental influences on BMI from infancy to the onset of adulthood (*n*=45 studies; *n*=87,782 pairs) and reported BMI heritability estimates to be lowest at 4 years of age (boys: 42%; girls: 41%) and increasing with age until 19 years of age (both sexes: 75%) (56). Our estimate of heritability for BMI-SDS at age 5 (79%) was therefore considerably higher than previous studies of early childhood. A possible explanation of our findings is due to the heterogeneity of studies included in a meta-analysis. Different populations with varying environments might have resulted in a decrease in heritability estimates for BMI, whereas all twin pairs were of very similar age, and born into similar socio-cultural background in our study. In addition, Gemini is a fairly recent cohort, meaning that children grew up in a more obesogenic environment than participants born in previous decades. Further, previous research has suggested that BMI is more heritable in countries with high average GDP, such as the UK (57).

Strengths and Limitations

Only a few studies have examined the complex relationship between reward responsiveness, externally driven eating behaviors and BMI in childhood. Our findings therefore need to be replicated with participants from different populations and age groups to establish their generalizability. However, studying these associations in a twin sample provides unique insights into the underlying genetic and environmental etiology, which would not be possible in a sample of unrelated children. Limitations of the study are the that both reward responsiveness and the two eating behaviors were parent-reported. Studies have demonstrated that the weight status of children can lead to under- and over- reporting of dietary behaviors by parents as a result of social

desirability bias (58)(59)(60). However, objective measures of eating behaviors (such as the 'eating in the absence of hunger' experimental paradigm that indexes food responsiveness (61)) are time-consuming, labor intensive and costly to collect in large sample sizes. The CEBQ has been validated against laboratory-based behavioral measures of food intake, suggesting that children who score high on the food responsiveness scale consume more energy when satiated in comparison to children scoring low on this scale (37). In addition, we focused only on one aspect of impulsivity (reward responsiveness) and rewards are subject to inter-individual variation. A meta-analysis of self-reported and behavioural measures of impulsivity has concluded that impulsivity is a multi-faceted construct (62). Thus, future research needs to explore the complex and subtle relationships between other domains of impulsivity, such as delay of gratification, negative urgency and disinhibition, in relation to eating behaviors and BMI.

Heritability estimates rely on MZ and DZ twins having equal environments. The 'equal environments assumption' has been tested in other twin studies and found to be valid (63). It is also possible that parents rate their twins more similarly if they believe them to be identical, while parents who believe their twins to be non-identical might exaggerate the differences between them. However, in Gemini, we were able to test for this bias directly using measures of eating behavior, by comparing the correlations between MZ pairs whose parents correctly classified them as MZs with the correlations between MZ pairs whose parents incorrectly classified them as DZs. We found no differences in eating behavior correlations between correctly and incorrectly classified MZs, indicating that parents do not rate MZs more similarly than they are, simply because they believe them to be identical, supporting the validity of parent-report measures of children's behaviors for use in twin studies (43). Lastly, because the analyses were cross-sectional it is not possible to make any causal inferences about the direction of the associations between BMI, reward responsiveness, external eating, and food responsiveness. However, the Gemini study is ongoing, and it will be possible to take advantage of prospective data to investigate the directions of associations in the future.

Conclusion

Food responsiveness and external eating may be food-specific behavioral expressions of a broader underlying trait characterized by heightened sensitivity to reward. Although these traits share some common genetic architecture, all three are shaped more importantly by common shared environmental factors in early childhood. Future work is needed to establish which aspects of the early home family environment are involved. Although reward responsiveness is already expressed

by distinct eating behaviors in early childhood, it may not be associated with BMI until children are older and have greater freedom to 'act out' their impulses, which over time lead to weight gain. In addition, food responsiveness, external eating and BMI share a substantial proportion of their genetic architecture, supporting the notion that genetic susceptibility to obesity operates partly via appetite, in line with behavioral susceptibility theory. Together, these findings highlight that eating behaviors in early childhood are promising intervention targets for obesity prevention, but longitudinal studies are needed to understand the direction of associations between reward responsiveness, eating behaviors and BMI throughout development.

Acknowledgement: We thank the Gemini families for participating in the study.

Funder: The Gemini 5-year data collection was supported by a Cancer Research UK program grant (C1418/A7974), awarded to Prof Jane Wardle, who died in 2015. CL was employed on the grant during the time of the study. Gemini is currently funded by an MQ Fellows award to CL (MQ17-4 Llewellyn). CK and JT are part funded by the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. CK is an NIHR clinical lecturer and has also previously received salary support from Novo Nordisk UK Research Foundation and Marie Curie Fellowship. MH is supported by a skills development fellowship from the Medical Research Council UK (MR/T027843/1). The views expressed are those of the authors and not necessarily those of the Wellcome Trust, the NHS, the NIHR, CRUK, MQ, MRC or the Department of Health. The funders did not have a role in the study design, data collection/analysis/interpretation or preparation of this manuscript.

Potential conflict of interest: All authors have indicated they have no conflicts of interest to disclose.

Author contributions: CK, MH, FR, JT and CL designed the research, CK, MH and FR performed the statistical analyses, all authors wrote and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Table 1. Descriptive summary of monozygotic and dizygotic twins in the Gemini twin sample, stratified by sex.

Table 2. Phenotypic correlations (derived from linear regression analysis) between i) reward responsiveness, ii) food responsiveness, iii) external eating and iv) body mass index corrected for age and sex (BMI-SDS).

Table 3. Within-twin and cross-twin correlations for i) reward responsiveness, ii) food responsiveness, iii) external eating and iv) body mass index corrected for age and sex (BMI-SDS), separated by zygosity (MZ: monozygotic; DZ: dizygotic).

Table 4. Phenotypic correlations are partitioned into absolute bivariate estimates of genetic (A), shared environmental (C) and unique environmental (E) factors, as derived from the full ACE twin models for reward responsiveness, food responsiveness, external eating and body mass index corrected for age and sex (BMI-SDS). The sum of the bivariate estimates therefore adds up to the phenotypic correlation. Bivariate estimates indicate the extent to which the phenotypic correlation (rp) between two traits can be explained by common genetic, shared and unique environmental factors.

Figure 1. Parameters estimates from the full ACE twin models for reward responsiveness, food responsiveness, external eating and body mass index (BMI). Rectangular boxes represent the measured phenotypes. Circles represent the latent factors: additive genetic (A), shared environmental (C) and unique environmental (E) effects. Straight single-headed arrows indicate variance explained by each latent factor (including 95% confidence intervals, CI). Curved double-

headed arrows indicate etiological correlations, reflecting the extent of common genetic (r_a), shared environmental (r_c) and unique environmental (r_e) influences across the phenotypes. Asterisks indicate significant pathways. Dotted lines indicate non-significant etiological correlations, with a 95% CI crossing 0.

Table 1. Descriptive summary of monozygotic and dizygotic twins in the Gemini twin sample, stratified by sex.

	Entire Sample	**Monozygotic**		**Dizygotic**		
	n=2,156 individuals	**Male**	**Females**	**Male**	**Females**	**Opposite sex**
Number of paired twins		181	181	172	209	335
Age, mean (SD)	5.2 (0.1)	5.2 (0.1)	5.2 (0.1)	5.2 (0.1)	5.2 (0.1)	5.2 (0.1)
BMI, mean (SD)	15.4 (1.3)	15.3 (1.3)	15.5 (1.4)	15.4 (1.4)	15.3 (1.4)	15.4 (1.4)
BMI-SDS, mean (SD)	-0.23 (1.10)	-0.37 (1.34)	-0.20 (1.07)	-0.20 (1.01)	-0.22 (1.07)	-0.19 (1.03)
Reward responsiveness, mean (SD)	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)	3.5 (0.6)	3.6 (0.6)	3.6 (0.6)
Food responsiveness scores, mean (SD)	2.4 (0.8)	2.4 (0.8)	2.4 (0.8)	2.4 (0.8)	2.3 (0.7)	2.3 (0.7)
External eating scores, mean (SD)	3.4 (0.6)	3.5 (0.6)	3.4 (0.7)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)

SD: Standard Deviation*;* BMI: Body Mass Index; BAS: Behavioral Approach System; CEBQ: Child Eating Behavior Questionnaire.

Table 2. Phenotypic correlations (derived from linear regression analysis) between i) reward responsiveness, ii) food responsiveness, iii) external eating and iv) body mass index corrected for age and sex (BMI-SDS).

	Reward responsiveness	**Food responsiveness**	**External eating**
Reward responsiveness			
Food responsiveness	0.20 (0.16, 0.25)		
External eating	0.23 (0.19, 0.27)	0.54 (0.51, 0.57)	
BMI-SDS	0.03 (-0.04, 0.10)	0.21 (0.14, 0.27)	0.11 (0.04. 0.18)

Table 3. Within-twin and cross-twin correlations for i) reward responsiveness, ii) food responsiveness, iii) external eating and iv) body mass index corrected for age and sex (BMI-SDS), separated by zygosity (MZ: monozygotic; DZ: dizygotic).

Within-twin, within-trait		**Reward responsiveness**	**Food responsiveness**	**External eating**	**BMI-SDS**
MZ		0.91 (0.89, 0.92)	0.89 (0.87, 0.91)	0.92 (0.91, 0.94)	0.88 (0.85, 0.91)
DZ		0.60 (0.56, 0.65)	0.59 (0.54, 0.64)	0.67 (0.63, 0.71)	0.49 (0.39, 0.59)
Cross-twin, cross-trait		**Reward responsiveness**	**Food responsiveness**	**External eating**	**BMI-SDS**
MZ	**Reward responsiveness**				
	Food responsiveness	0.18 (0.13, 0.24)			
	External eating	0.22 (0.17, 0.28)	0.48 (0.44, 0.52)		
	BMI-SDS	0.01 (-0.08, 0.09)	0.16 (0.08. 0.25)	0.08 (-0.01, 0.16)	
DZ	**Reward responsiveness**				
	Food responsiveness	0.15 (0.09, 0.20)			
	External eating	0.19 (0.14, 0.24)	0.28 (0.23, 0.33)		
	BMI-SDS	-0.03 (-0.11, 0.06)	0.02 (-0.08, 0.11)	-0.02 (-0.11, 0.07)	

Table 4. Phenotypic correlations are partitioned into absolute bivariate estimates of genetic (A), shared environmental (C) and unique environmental (E) factors, as derived from the full ACE twin models for reward responsiveness, food responsiveness, external eating and body mass index corrected for age and sex (BMI-SDS). The sum of the bivariate estimates therefore adds up to the phenotypic correlation. Bivariate estimates indicate the extent to which the phenotypic correlation (rp) between two traits can be explained by common genetic, shared and unique environmental factors.

	Phenotypic correlation (95% confidence intervals)	**Bivariate estimates (95% confidence intervals)**		
		A	**C**	**E**
Reward responsiveness: Food responsiveness	0.20 (0.15, 0.25)	0.07 (0.01, 0.14)	0.11 (0.04, 0.18)	0.02 (0.01, 0.03)
Reward responsiveness: External eating	0.23 (0.18, 0.28)	0.07 (0.01, 0.12)	0.16 (0.09, 0.23)	0.01 (0, 0.02)
Reward responsiveness: BMI-SDS	0.01 (-0.07, 0.09)	0.07 (-0.04, 0.17)	-0.06 (-0.17, 0.06)	0 (-0.01, 0.02)
Food responsiveness: External eating	0.54 (0.51, 0.58)	0.40 (0.33, 0.47)	0.08 (0.01, 0.16)	0.06 (0.05, 0.08)
Food responsiveness: BMI-SDS	0.20 (0.11, 0.28)	0.29 (0.17, 0.37)	-0.13 (-0.2, 0)	0.04 (0.02, 0.05)
External eating: BMI-SDS	0.10 (0.02, 0.19)	0.20 (0.10, 0.27)	-0.12 (-0.21, 0)	0.03 (0.01, 0.04)

Figure 1. Parameters estimates from the full ACE twin models for reward responsiveness, food responsiveness, external eating and body mass index (BMI). Rectangular boxes represent the measured phenotypes. Circles represent the latent factors: additive genetic (A), shared environmental (C) and unique environmental (E) effects. Straight single-headed arrows indicate variance explained by each latent factor (including 95% confidence intervals, CI). Curved double-headed arrows indicate etiological correlations, reflecting the extent of common genetic (r_a), shared environmental (r_c) and unique environmental (r_e) influences across the phenotypes. Asterisks indicate significant pathways. Dotted lines indicate non-significant etiological correlations, with a 95% CI crossing 0.