

1 Common etiological architecture underlying reward responsiveness, externally driven eating  
2 behaviors and BMI in childhood: findings from the Gemini twin cohort  
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22 Running title: Child reward responsiveness, eating behavior and BMI

23 **Abstract**

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

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

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

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

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

50

51 **Background**

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

60

61 Genetic factors explain a large proportion of variation in susceptibility to obesity. Half a century of  
62 twin and family studies have estimated that genetic differences between people explain between  
63 50% to 90% of individual differences in human body weight (7). In addition, large-scale genome-  
64 wide association studies have identified close to 1,000 common genetic variants (single nucleotide  
65 polymorphisms, SNPs) robustly associated with variation in body mass index (BMI) (8). Gene-  
66 expression studies have indicated that many of the SNPs associated with BMI are located in or near  
67 genes that are predominantly expressed in the brain; including the hypothalamus, hippocampus and  
68 limbic system. These findings suggest that neuropsychological processes influencing energy balance  
69 may mediate genetic susceptibility to obesity.

70

71 The behavioral susceptibility theory of obesity hypothesizes that genetic susceptibility to obesity  
72 operates partly via genetically-determined differences in appetite regulation, which encourage  
73 overeating in response to the increased opportunity offered by the modern obesogenic environment  
74 (9). In this context, food responsiveness (wanting to eat in response to the sight, smell and taste of  
75 palatable food) is an appetitive behavior that has received particular attention. Large population  
76 studies have shown that BMI-associated SNPs are also associated with food responsiveness in  
77 children (10) and adults (11–14), and partly mediates the association between BMI-associated  
78 variants and measured BMI (15). Twin studies have also established that variation in food  
79 responsiveness is moderately to highly heritable in infancy (16), childhood (17,18) and adulthood  
80 (19–21); and individual differences in this behavior are associated with prospective weight gain from  
81 infancy to early childhood (22–24).

82

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

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

97

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

109

## 110 **Methods**

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

116

117 *Participants*

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

125

#### 126 *Outcome variables*

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

132

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

141

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

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

161

162 Children's heights and weights were parent-reported in the 5 years questionnaire using electronic  
163 weighing scales (Tanita UK Ltd, Yewsley, UK) and a height chart with instructions, sent to all families  
164 when the children were two years of age. Body mass index (BMI) was calculated from the parent-  
165 reported height and weight in the 5 years questionnaire, as  $\text{weight/height}^2$  (kg/m<sup>2</sup>). BMI varies  
166 considerably with age and sex during childhood, so it was converted to BMI standard deviation  
167 scores (BMI-SDS) corrected for age and sex using British 1990 growth reference data (40) with the  
168 LMS-Growth Excel (41). A BMI-SDS of 0 indicates an average BMI, >0 indicates a higher BMI and <0  
169 indicates a lower BMI than the mean BMI in the reference data. Child sex was parent-reported at  
170 baseline, and child age at the 5-year questionnaire completion was calculated from parent-reported  
171 date-of-birth and the date the 5-year questionnaire was completed. The zygosity of same-sex twin  
172 pairs was based on a standard self-reported questionnaire measure of similarity (42) that was  
173 completed at 8 months (mean= 8.1, range= 4.01-20.3) and again at 29 months (mean = 28.8, range:  
174 22.9-47.6) and validated using DNA (43).

175

#### 176 *Statistical analysis*

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

182

#### 183 *Genetic twin modelling*

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

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

202

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

211

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

220 difference of 4–7 indicates support for one model over the other. An AIC difference of greater than  
221 10 indicates substantial support for the model with the lower AIC value. In the case when the -2LL  
222 and AIC do not agree, the AIC will be given precedence as it is considered a superior model fit  
223 criterion (45).

224

## 225 **Results**

### 226 *Descriptive Statistics*

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

233

234 Linear regression analysis revealed significant positive phenotypic correlations between: i) reward  
235 responsiveness and food responsiveness (0.20; 95% confidence interval (CI): 0.16, 0.25)); ii) reward  
236 responsiveness and external eating (0.23; 95% CI: 0.19, 0.27)); iii) food responsiveness and external  
237 eating (0.54, 95% CI:0.51, 0.57); iv) food responsiveness and BMI-SDS (0.21; 95%CI: 0.14, 0.27); and  
238 v) external eating and BMI-SDS (0.11, 95% CI: 0.04, 0.18) (**Table 2**). The phenotypic correlation  
239 between reward responsiveness and BMI-SDS was not statistically significant (0.03 95% CI: -0.04,  
240 0.10). Within-twin and cross-twin correlations for reward responsiveness, food responsiveness,  
241 external eating and BMI-SDS are summarized in Table 3. Phenotypic and cross-twin correlations for  
242 boys and girls separately can be found in **Supplementary Tables 1 and 2**.

243

### 244 *Genetic model fitting*

245 The -2LL suggested a slightly poorer fit of the ACE model compared to the saturated model  
246 (difference in -2LL=59.56 (40),  $p=0.02$ ), whereas the AIC value was substantially lower for the ACE  
247 than the saturated model, indicating a better fit for the ACE model (difference in AIC=20.44;  
248 **Supplementary Table 3**). Based on the ACE model, the heritability estimates (A) ranged from 50%  
249 (95% CI: 43%, 58%) for external eating to 79% (95% CI: 62%, 88%) for BMI-SDS, while common  
250 environmental contributions (C) ranged from 9% (95% CI: 1%, 26%) for BMI-SDS to 42% (95% CI:  
251 34%, 49%) for external eating (Figure 1). Unique environmental influences (E) accounted for less  
252 than 13% of the variance across all traits.

253



254 *Etiological correlations*

255 The magnitudes of the etiological correlations indicate the extent to which genetic ( $r_g$ ), common ( $r_c$ )  
256 or unique environmental ( $r_e$ ) factors are shared between the traits. There were significant  
257 etiological correlations between all factors except for reward responsiveness and BMI-SDS (**Figure**  
258 **1**). Reward responsiveness shared some genetic influence with both food responsiveness and  
259 external eating, indicated by small but significant genetic correlations with both eating behaviors  
260 ( $r_g=0.12$ ; 95% CI: 0.02, 0.22, for both). The genetic correlations between BMI-SDS and the two  
261 eating behaviors were moderate (food responsiveness:  $r_g=0.42$ ; 95% CI: 0.26, 0.54; external eating:  
262  $r_g=0.31$ ; 95% CI: 0.17, 0.43), indicating considerable overlap in the genetic factors underlying BMI-  
263 SDS and these two eating behaviors.

264

265 There were moderate shared environmental correlations between reward responsiveness and both  
266 eating behaviors (food responsiveness:  $r_c=0.38$ ; 95% CI: 0.14, 0.62; external eating:  $r_c=0.45$ ; 95% CI:  
267 0.14, 0.60), indicating some similarity in the shared environmental factors underlying these three  
268 traits. The estimates for the shared environmental correlations between BMI-SDS and the two eating  
269 behaviors were unreliable (and not statistically significant for BMI-SDS and external eating) due to  
270 the very small proportion of variance in BMI-SDS attributable to shared environmental influences.

271

272 Unique environmental correlations varied substantially. There was some common unique  
273 environmental influence underlying reward responsiveness and food responsiveness, indicated by a  
274 small but statistically significant unique environment correlation ( $r_e=0.09$ ; 95%CI: 0.08, 0.11), and  
275 there was considerable common unique environmental influences underlying food responsiveness  
276 and external eating ( $r_e=0.69$ ; 95%CI: 0.63, 0.74), and food responsiveness and BMI-SDS ( $r_e=0.31$ ;  
277 95%CI: 0.14, 0.44). There were no significant unique environmental correlations detected between  
278 reward responsiveness and external eating, or reward responsiveness and BMI-SDS.

279

280 *Bivariate Estimates*

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

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

296

## 297 **Discussion**

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

314

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

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

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

337

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

347

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

356 avid appetite) are positively associated with adiposity in children of 4-5 years (51), 6-7 years (52) and  
357 7-12 years (53) of age.

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

380

### 381 **Strengths and Limitations**

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

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

401

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

417

#### 418 **Conclusion**

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

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

432

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434

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446

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448

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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 ( $r_p$ ) 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 ( $r_g$ ), 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.

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

	<b>Reward responsiveness</b>	<b>Food responsiveness</b>	<b>External eating</b>
<b>Reward responsiveness</b>			
<b>Food responsiveness</b>	0.20 (0.16, 0.25)		
<b>External eating</b>	0.23 (0.19, 0.27)	0.54 (0.51, 0.57)	
<b>BMI-SDS</b>	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 ( $r_p$ ) 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
<b>Reward responsiveness: Food responsiveness</b>	0.20 (0.15, 0.25)	0.07 (0.01, 0.14)	0.11 (0.04, 0.18)	0.02 (0.01, 0.03)
<b>Reward responsiveness: External eating</b>	0.23 (0.18, 0.28)	0.07 (0.01, 0.12)	0.16 (0.09, 0.23)	0.01 (0, 0.02)
<b>Reward responsiveness: BMI-SDS</b>	0.01 (-0.07, 0.09)	0.07 (-0.04, 0.17)	-0.06 (-0.17, 0.06)	0 (-0.01, 0.02)
<b>Food responsiveness: External eating</b>	0.54 (0.51, 0.58)	0.40 (0.33, 0.47)	0.08 (0.01, 0.16)	0.06 (0.05, 0.08)
<b>Food responsiveness: BMI-SDS</b>	0.20 (0.11, 0.28)	0.29 (0.17, 0.37)	-0.13 (-0.2, 0)	0.04 (0.02, 0.05)
<b>External eating: BMI-SDS</b>	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.

