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

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

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 weight/height^2 (kg/m^2). 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 χ2 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^2 (SD = 1.3) and BMI-SDS was -0.23 kg/m^2 (SD = 1.10), indicating that the sample

232   were slightly leaner that 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_a), 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_a=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_a=0.42; 95% CI: 0.26, 0.54; external eating:

262 r_a=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,

10

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_a=0.42;

333   BMI-SDS and external eating: r_a=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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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.