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Effects of single genetic variants and polygenic obesity risk scores on disordered eating in adolescents – The HUNT study

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Abstract

Purpose: Improving the understanding of the role of genetic risk on disordered eating (DE). **Methods:** A case-control study including 1,757 (F: 979, M: 778) adolescents (aged 13-19 years) from the Nord-Trøndelag Health Study (HUNT), an ethnically homogenous Norwegian population based study. Cases and controls were defined using a shortened version of the Eating Attitude Test. Logistic regression was employed to test for associations between DE phenotypes and 24 obesity and eating disorder susceptibility SNPs, and the joint effect of a subset of these in a genetic risk score (GRS). **Results:** *COMT* was shown to be associated with poor appetite/undereating (OR: 0.6, CI 95%: 0.43-0.83, p = 0.002). Independent of obesity associations, the weighted GRS was associated to overeating in 13-15 year old females (OR: 2.07, CI 95%: 1.14-3.76, p = 0.017). Additionally, a significant association was observed between the GRS and loss of control over eating in the total sample (OR: 1.62, CI 95%: 1.01-2.61, p = 0.046). **Conclusions:** The *COMT* variant (rs4680) was associated with poor appetite/undereating. Our study further confirms prior findings that obesity risk also confers risk for loss of control over eating; and overeating amongst girls.

Keywords: Disordered eating, EAT-12, obesity polygenic risk score, *COMT*, HUNT, adolescents.

Abbreviations

AN: Anorexia nervosa, *BDNF:* Brain derived neurotropic factor, BN: Bulimia nervosa, BED: Binge eating disorder, *COMT:* Catechol-O-methyl transferase gene, DE: Disordered eating, *DRD2:* Dopamine receptor D2 gene, ED: Eating disorder, *FTO*: Fat mass and obesity associated gene, *GHRL:* Ghrelin, *GNPDA2*: Glucosamine-6-phosphate deaminase 2, *GRB14:* Growth factor Receptor-Bound protein 14 gene, GRS: Genetic risk score, *5-HT2A*: Serotonin 2A receptor, *INSIG2*: Insulin induced gene 2, *KCTD15*: Potassium channel tetramerization domain containing 15 gene, *MC4R:* Melanocortin 4 receptor gene, *MSRA*: Methionine sulfoxide reductase A, *MTCH2:* Mitochondrial carrier 2 gene, *NEGR1*: Neuronal growth regulator 1, OFSED: Other specified feeding and eating disorders, *OPRD1*: Opioid Receptor delta 1 gene, *SEC16B*: Protein transport protein Sec16B, SNP: Single nucleotide polymorphism, *TFAP2B*: Transcription factor AP-2 beta, *TMEM18*: Transmembrane protein 18.

Introduction

Eating disorders pose a significant health risk due to physical and psychological comorbidities (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011) including suicide rates as high as six times that of the healthy population (Arcelus, Mitchell, Wales, & Nielsen, 2011). Prevalence rates of full-threshold eating disorders (EDs), Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED), are relatively low ranging with lifetime prevalence estimates between 0.5-1.0 % for AN and 0.5-3.0 % for BN (Swanson et al., 2011). The combined estimate of AN, BN and BED is ~5% (Stice, Marti, & Rohde, 2013). Compared to full-threshold eating disorders, residual diagnoses are more common with Other Specified or Unspecified Feeding or Eating Disorders (OSFED) estimates of ~11.5% where approximately 13% of adolescents will experience at least one eating disorder by age 20 (Stice et al., 2013).

The term Disordered Eating (DE) is generally used for individuals who show signs and symptoms of ED without reaching the threshold for full blown eating disorders (Treasure, Claudino, & Zucker, 2010). The prevalence of disordered eating is high amongst adolescents (14-22%)(Micali, Solmi, et al., 2015; Treasure et al., 2010) with symptoms prospectively predicting the development of eating disorders (Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004), and etiologic processes may be more closely linked to specific symptoms than to broad diagnoses (Cuthbert, 2005).

Twin and adoption studies have found moderate to high heritability of AN, BN, and BED (h^2 estimates: mean ~50%, range ~28–88%) and disordered eating symptoms (h^2 estimates: mean ~49%, range ~20–85%)(Culbert, Racine, & Klump, 2011) (Trace, Baker, Penas-Lledo, & Bulik, 2013). However, the genetic architecture of ED and DE is far from being fully understood and still little is known concerning their neuropath physiology. There is, nevertheless, growing evidence that neurotransmitter networks that include dopaminergic and opioid systems are highly involved (Kessler, Hutson, Herman, & Potenza, 2016). Linkage studies have not been very successful but have generally suggested several chromosomal regions of interest (Trace et al., 2013). Furthermore, recent genetic studies with special emphasis on AN have failed to identify single genes with large effects (Boraska et al., 2012; Boraska et al., 2014; Pinheiro et al., 2010; Pinheiro, Root, & Bulik, 2009; Root et al., 2011) suggesting the inheritance complexity.

Obesity and eating disorders share a number of risk factors that apply to a broad range of eating- and weight-related problems (Peckmezian & Hay, 2017). Studies indicate that common neurobiological mechanisms of eating disorders and obesity exist which involve regulation of food intake and emotion (Gorwood et al., 2016). Related to this, distortion of the balance between hunger and satiety linked to the rewarding aspect of food are thought to be linked to genetic predisposition. Interestingly, obesity susceptibility genes such as *FTO*, *MC4R*, *BDNF*, (Locke et al., 2015; Speliotes et al., 2010) and *OPRD1* (Kvaloy, Kulle, Romundstad, & Holmen, 2013) have also been associated to disordered eating associated mechanisms (Micali, Field, Treasure, & Evans, 2015; Scherag, Hebebrand, & Hinney, 2010). Through dopaminergic and opioidergic influences on reward-related processes, BED individuals may be prone to elevated food-related hedonic responses (C. A. Davis et al.,

2009). The rs6277 polymorphism of the *DRD2* gene is more common in obese BED individuals than in obese non-BED individuals (C. Davis et al., 2012; C. A. Davis et al., 2009). In addition *DRD2* has been associated to weight gain from normal weight to overweight/obesity longitudinally (Kvaloy, Holmen, Hveem, & Holmen, 2015).

The approach of polygenic risk scores has been successfully used to acquire evidence of genetic effects when no single marker shows effects (Dudbridge, 2013). Obesity genetic risk scores (GRS) based on the GWAS-identified SNP effects have yielded a quantitative measure of inherited predisposition that has also been helpful in understanding obesity related traits and diseases. Furthermore, genetic risk scores have been useful in revealing genetically based mechanisms involved in unhealthy eating and weight gain related to eating behaviors such as appetitive traits (Konttinen et al., 2015; Steinsbekk, Belsky, Guzey, Wardle, & Wichstrom, 2016) and satiety mechanisms (Llewellyn, Trzaskowski, van Jaarsveld, Plomin, & Wardle, 2014).

Disordered eating is highly prevalent at adolescence and is prospectively predicting the development of eating disorders at a later stage in life. Therefore, improved understanding of its etiology which is known to involve both environmental and genetic factors common with obesity susceptibility, is important. Our overall study aims were to investigate whether disordered eating traits such as *uncontrolled appetite/overeating* and *poor appetite/undereating* are associated with genes involved in obesity development, altered reward processing, mood and appetite regulation and that these traits might share a genetic vulnerability in common with obesity. To study this we used 24 single nucleotide polymorphisms previously linked to either obesity, weight measures or eating disorders in an

adolescent sample of 1,757 individuals (13-19 year olds) participating in the Norwegian Young-HUNT1 survey (1995-97). Improved knowledge of the molecular etiology involved seems of particular importance as it enhances the understanding not only about the molecular mechanisms involved, but also of an individual's susceptibility to future eating disorders. More accurately being able to assess the progression of the symptoms earlier will hopefully aid in preventing development to a full-threshold eating disorder.

Material and methods

Study population

The study participants were derived from the HUNT study, a large population based study conducted in three phases in the Nord-Trøndelag County, Norway (Krokstad et al., 2012). The HUNT study has one adult arm with participants aged ≥ 20 years (HUNT1 (1984-86) , HUNT2 (1995-97) and HUNT3 (2006-08) (Krokstad et al., 2013) and one adolescent arm with participants aged 13 to 19 years (Young-HUNT1 (1995-97), Young-HUNT2 (2000-01) and Young-HUNT3 (2006-08)) (Holmen et al., 2013). In all three surveys of the Young-HUNT study, participants completed a comprehensive questionnaire during one school hour. Specially trained nurses visited the schools and performed clinical examinations including anthropometric measures and collection of buccal smears (Young-HUNT3).

Young-HUNT1 recruited a total of 8,983 participants (response rate 88%) who completed the self-report questionnaire. Of the 8,983 individuals, only 8,433 had both anthropometric and

153 self-report data available for analysis. No blood samples were collected at this stage but blood
154 samples were later retrieved from 1,805 participants who, as young adults, took part in the
155 HUNT3 study (2006-08). Successful genotyping data was obtained from 1,801 participants in
156 our study. Characterization of this sub-sample is described elsewhere (Cuypers et al., 2012;
157 Kvaloy et al., 2013).

158

159 **Ethical approvals**

160 All research participants signed a written informed consent. In Norway, legal age for
161 providing consent is 16 years, therefore in the case of participants younger than 16, consents
162 were additionally given by parents or legal guardians. The Young-HUNT study was
163 approved by the Regional Committee for Ethics in Medical Research, the Norwegian Data
164 Inspectorate and Directorate of Health. All procedures followed were in accordance with the
165 ethical standards of the responsible committee on human experimentation (institutional and
166 national) and with the Helsinki Declaration of 1975, as revised in 2000.

167

168 **Eating Attitude Test and case group categorization**

169 The Eating Attitude Test (EAT) originally consisted of 40 items (Garner & Garfinkel, 1979),
170 but has subsequently been shortened to EAT-26 (Mann et al., 1983) and further to 12 items
171 (EAT-12) (Lavik, Clausen, & Pedersen, 1991) consisting of three factors; 1) dieting, 2)
172 bulimia and food preoccupation and 3) oral control. Since the EAT-12 was originally deemed
173 too long to be used in the HUNT study, a shortened 7-item version (EAT-7) missing the

dieting item was instead used to determine disordered eating in Young-HUNT1 (Bjomelv, Mykletun, & Dahl, 2002). The dieting factor was, however, included separately elsewhere in the questionnaire. Bjørnelv et al. validated the 7-item version (EAT-7) towards the 12-item version (EAT-12) (Bjomelv et al., 2002) and reported a two-factor solution robust for age and gender, EAT-A (poor appetite/undereating) and EAT-B (uncontrolled appetite/overeating), when they investigated the psychometric properties of the EAT-7 in comparison with EAT-12. Cronbach's alpha ranged from 0.48 to 0.69 for factor B items and from 0.41 to 0.51 for factor A items (Bjomelv et al., 2002). The internal consistency of EAT-A and EAT-B in a recent study was, 0.512 and 0.695, respectively (Eik-Nes et al., 2015). The EAT-A consists of the following items: 1) When I eat, I cut my food up into small pieces; 2) It takes me longer than it takes others to finish a meal; 3) Other people think I am too thin and 4) I feel that others pressure me to eat. The EAT-B consists of the following items: 1) When I first begin eating, it is difficult to stop (overeating); 2) I spend too much time thinking about food (food preoccupation); 3) I feel that food controls my life (loss of control eating). The four-point Likert scale with answers: "never", "seldom", "often" and "always" was converted to a three-point scale with the response options: never/seldom, often and always coded as 0, 1 and 2, respectively. This gave a maximum score of 8 for EAT-A and 6 for EAT-B where the sum of the individual item scores were calculated separately for EAT-A and EAT-B. Cut-off points were as outlined by Bjørnelv et al, with scores ≥ 3 for EAT-A and ≥ 2 for EAT-B as indicative of DE (Bjomelv et al., 2002). Controls were those who scored less than the cut-offs for both EAT-A and EAT-B.

Anthropometric measurements

Standardized measurements of height and weight were carried out by trained nurses during data collection. Participants wore light clothing and no shoes. Weight was measured to the nearest half kilo and height to the nearest cm. BMI (body mass index) was calculated as weight (kg)/height^2 (m^2). In interpreting BMI in adolescents considerations with regard to age and sex were taken. BMI z-scores (zBMI) were calculated based on mean BMI and SD for each Young-HUNT1 sex and year groups. BMI based weight group characterizations were calculated according to Cole (Cole, Bellizzi, Flegal, & Dietz, 2000; Cole, Flegal, Nicholls, & Jackson, 2007) and a summary and distribution within the EAT-A and EAT-B case groups can be found in Table 1.

Genetic material and candidate gene selection

The following genetic variants for nine of the robustly associated obesity-susceptibility loci at the time of the study design (early 2010) (Loos et al., 2008; Thorleifsson et al., 2009; Willer et al., 2009) was included in our study: rs9939609, rs8050136, rs1121980 (in *FTO*), rs12970134, rs17782313, rs17782313 (near *MC4R*), rs2815752 (near *NEGR1*), rs6548238 (near *TMEM18*), rs10938397 (near *GNPDA2*), rs10838738 (in *MTCH2*), rs4074134, rs925946, rs6265 (near/in *BDNF*), rs987237 (in *TFAP2B*) and rs543874 (near *SEC16B*). Additionally, the following 15 genetic variants previously associated to weight measures or suggested to be implicated in eating disorders (Lindgren et al., 2009; Rask-Andersen, Olszewski, Levine, & Schioth, 2010; Zhao et al., 2009) were added: rs11084753 (near *KCTD15*), rs7566605 (near *INSIG2*), rs545854 (near *MSRA*), rs3734967 (near *5-HT2A*), rs4680 (in *COMT*), rs569356 (near *OPRD1*), rs35683 (in *GHRL*), rs6277 (in *DRD2*), rs10195252 (near *GRB14*). SNPs with lower call rates than 95% were excluded from our

220 study as well as individuals with > 10% genotypes missing. All included SNPs were in
221 Hardy-Weinberg equilibrium. Genotype frequencies were in agreement with previous
222 findings in European populations (NCBI, The National Center for Biotechnology
223 Information). Genotyping procedures and SNP characteristics are described elsewhere
224 (Kvaloy et al., 2013) and summarized in Table 2.

225

226 **Statistical analyses**

227 Descriptive characterizations and file preparations were done using IBM SPSS statistics
228 (version 21). PLINK was used for the genetic analyses (Purcell et al., 2007). In order to study
229 possible associations between single SNPs and outcome phenotypes, logistic regression
230 models were employed testing SNPs in additive models. Analyses were done on the whole
231 study sample and sex stratified samples. BMI was conceptualized as a confounder and z-
232 scores (zBMI) adjusted for in the single SNP conditional models.

233

234 The obesity Genetic Risk Scores (GRSs) was calculated by summing up the number of BMI-
235 increasing risk alleles both using weighted and unweighted GRS exposures. The unweighted
236 GRS (uGRS) was calculated by summing the number of risk alleles across 10 variants and the
237 weighted GRS (wGRS) was calculated by multiplying the number of risk alleles at each locus
238 (0, 1, 2) with the corresponding effect sizes, in kg/m^2 per allele (beta), as reported by
239 Speliotes et al. based on adult BMI associations (Speliotes et al., 2010). In the wGRS the loci
240 in or near *FTO* (rs1121980), *TMEM18* (rs6548238), *MC4R* (rs571312), *NEGR1* (rs2815752),
241 *GNPDA2* (rs10938397), *BDNF* (rs6265), *MTCH2* (rs10838738), *TFAP2B* (rs987237) and

242 *SEC16B* (rs543874) were identical or in high linkage disequilibrium (r^2>0.8, except for
243 rs6265 with r^2= 0.7) to the ones published (Speliotes et al., 2010). In the uGRS, *KCTD15*
244 (rs11084753) which was not in high LD with the proxy analyzed (r^2 = 0.5) by Speliotes et al.
245 (Speliotes et al., 2010), was included. The risk allele effects are outlined in Table 2. GRS
246 analyses were performed using logistic regression models (IBM SPSS statistics, version 22).
247 An additional weighted GRS based on genetic data available through a very recent release
248 from the HUNT study was included in the study comprising all 32 obesity susceptibility
249 variants identified by Speliotes et al., (Speliotes et al., 2010).

250

251 In general, nominal significance was considered at $p < 0.05$. Additionally, a permutation-
252 based test using a basic Max (T) with 1000 permutation specified was used in order to adjust
253 for multiple testing of the SNPs in the single SNP analyses. The Max (T) permutation method
254 employed in PLINK for multiple testing equals stringency of Bonferroni correction when
255 single SNPs are tested. Odds Ratios (ORs) are presented with 95% confidence intervals (CI).

256

257 **Results**

258 **Study subjects**

259 Due to missing genotypes, weight measurements or data on EAT question items, only 1,757
260 (F: 979, M: 778) of the original 1,801 Young-HUNT1 research participants were available for
261 analyses. Among these, 88 cases with poor appetite/undereating (F: 53, M: 35)(EAT-A) and
262 152 cases with uncontrolled appetite/overeating (F: 111, M: 41)(EAT-B) were compared with
263 1,530 controls (see Table 1). Thirteen individuals positive for both EAT-A and EAT-B, were

included in the separate analyses. The mean age was slightly higher among the cases (16.1 – 16.3 years) compared to the controls (15.9 years) and the mean BMI was higher in the uncontrolled appetite/overeating cases (22.18± 3.6) compared to the poor appetite/undereating cases (20.07±2.7). There was a higher percentage of overweight (15.8%) and obese (3.9%) cases with uncontrolled appetite/overeating compared to the cases with poor appetite/undereating (overweight: 4.6%, obese: 1.1%). Furthermore, a higher percentage of underweight amongst cases with poor appetite/undereating (9.2%) compared to cases with uncontrolled appetite/overeating (4.6%) was observed (Table 1).

Associations between individual genetic variants and poor appetite/undereating (EAT-A)

In the minimally adjusted and BMI-conditionally adjusted model the G-allele of rs4680 (*COMT*) was protective towards suffering from poor appetite/undereating (EAT-A) in the total sample even after multiple testing (OR: 0.60, CI 95% 0.43-0.83, p = 0.002 and adjusted p= 0.035) (Table 3). The association was nearly significant after multiple testing in females (OR: 0.54, CI 95% 0.35-0.82, p = 0.004 and adjusted p= 0.074), but not in males.

The following SNPs were significantly associated with poor appetite/undereating at nominal levels: rs11084753 (*KCTD15*) in the minimally adjusted and BMI-adjusted model with an OR: 1.44 (CI: 95% 1.04-1.99, p = 0.027 for the A-allele in the total sample with an even stronger effect in males (OR: 2.09 (CI: 95% 1.24-3.51, p = 0.006), and rs35683 (*GHRL*) in the total sample with an OR: 1.35, CI: 95% 1.00-1.83, p = 0.049 in the conditional model. The G-

allele of rs987237 (*TFAP2B*) was nominally significantly associated in females in the conditionally adjusted model (OR: 1.72, CI: 95% 1.07-2.76, p = 0.025).

Associations between individual genetic variants and uncontrolled appetite/overeating (EAT-B)

Only nominally significant associations were observed with the uncontrolled appetite/overeating (EAT-B) trait as outcome. The G-allele of rs987237 (*TFAP2B*) was positively associated in both minimally adjusted and adjusted models (OR: 1.37 (CI: 95% 1.03-1.84, p = 0.034) (Table 4). This association was only present in females in the stratified analyses (OR: 1.44 (CI: 95% 1.02-2.05, p = 0.040). The C-allele of rs35683 (*GHRL*) was also positively associated (OR: 1.34 (CI: 95% 1.06-1.70, p = 0.015), while the rs10938397 (*GNPDA2*) G-allele had a protective effect (OR: 0.76 (CI: 95% 0.59-0.98, p = 0.035). The T–allele of rs1121980 (*FTO*) conferred risk of uncontrolled appetite/overeating (OR: 1.34 (CI: 95% 1.00-1.78, p = 0.047) in the female only adjusted model.

Effects of the obesity polygenic risk scores (GRSs) on disordered eating

Nine obesity risk loci were included in the weighted and 10 in the unweighted GRSs. Association effects of the unweighted GRS (uGRS) were similar although weaker compared to the weighted GRS (wGRS)(data for uGRS not show). Due to the significant sex interaction identified between the wGRS and uncontrolled appetite/overeating (EAT-B), logistic regression analyses were sex stratified. Overeating (EAT-B Stop) was additionally stratified

by age groups (13-15 and 16-19 years) due to significant wGRS*age interaction identified. There were no significant associations detected between the wGRS and the poor appetite/undereating sub-scale (EAT-A). Supplementary information is shown in Table S1 (Online resource). Independent of obesity associations, wGRS was significantly associated to loss of control eating (EAT-B Cont) in the total sample (OR: 1.62, CI 95%: 1.01-2.61, p = 0.046) and a significant association was additionally observed between the wGRS and overeating (EAT-B Stop) in 13-15 year old females (OR: 2.07, CI 95%: 1.14-3.76, p = 0.017).

Replication of the associations between the wGRS and various EAT-B sub-scale outcomes were performed using an extended wGRS (wGRS-32) consisting of 32 obesity increasing variants (Supplementary table S2 – Online resource). The directions of effects were in agreement with results obtained with the 9-SNP wGRSs although mostly weaker except for an additional significant association between loss of control eating, EAT-B Cont, and wGRS-32 in females (OR: 1.69, CI 95%: 1.06-2.70, p = 0.027). EAT-B Cont was also significantly associated in the total sample (OR: 1.47, CI 95%: 1.02-2.12, p = 0.041) although not after adjustment with BMI. The female-specific association was nearly significant independent of obesity (p = 0.057). The significant association identified between the 9-SNP wGRS and overeating (EAT-B Stop) in 13-15 year old females was nearly significant in the wGRS-32 (p = 0.078).

Discussion

In this study we investigated the effect of 24 genetic variants previously associated with obesity and eating disorders against poor appetite/undereating and uncontrolled appetite/overeating in adolescents (13-19 years). We were able to show that the catechol-O-methyltransferase (*COMT*) gene was associated to poor appetite/undereating (AN like behaviors) while obesity susceptibility variants through genetic risk scores, which quantitatively strengthens the effects compared to single variant effects, were associated to uncontrolled appetite/overeating (BN and BED like behaviors).

The most interesting single variant finding was a protective effect displayed by the G-allele of the *COMT* Val158Met variant rs4680 on poor appetite/undereating independent of BMI both in the total and female only sample. The Val158Met *COMT* is a functional polymorphism with enzyme altering activity. It has been extensively studied in relation to drug dependence, bipolar disorder and schizophrenia (Ioannidis, Serfontein, & Muller, 2014) and seems to influence the reward mechanisms linked to several aspects of aberrant eating (Donofry et al., 2014; Yilmaz, Kaplan, Zai, Levitan, & Kennedy, 2011). In a recent large community sample, the *COMT* Met allele was shown to confer risk both with regards to bulimic symptoms and severe body dissatisfaction (Donofry et al., 2014).

Although not reaching robust significance levels for many of the single variants, the pattern of genetic associations differed between the poor appetite/undereating and uncontrolled appetite/overeating phenotypes. *KCTD15* (Potassium channel tetramerization domain containing 15) and *GHRL* (Ghrelin) were both associated with poor appetite/undereating in

males and in the total sample for *KCTD15*. Previously, *KCTD15* has been associated primarily with obesity (Speliotes et al., 2010) as well as being a gene of interest for eating disorders (Rask-Andersen et al., 2010). Ghrelin, an orexigenic peptide secreted mainly from the stomach, increases appetite and food intake and is found to be low in blood samples of AN patients. However, association studies linking Ghrelin polymorphisms and ED have been somewhat contradictory, with the majority reporting no significant associations with AN (Trace et al., 2013). Deranged Ghrelin response to hedonic eating present in underweight patients with AN has been suggested to be related to reduced motivation toward food intake (Maria Monteleone et al., 2016). Our results give further support to the association between Ghrelin and disordered eating and more specifically anorexic behaviors.

Many confirmed genetic loci for obesity are expressed in regions of the brain that regulate energy intake and reward-seeking behavior. In the single marker testing performed here, *TFAP2B* (Transcription factor AP-2 beta), *GNPDA2* (Glucosamine-6-phosphate deaminase 2) and *FTO* (Fat mass and obesity associated gene) showed evidence of association with the uncontrolled/overeating phenotype. In a recent study by Cornelis and colleagues (Cornelis et al., 2014), the *TFAP2B* was shown to be associated with cognitive restraint which is interesting with regards to DE. Furthermore, *GNPDA2* has previously been associated to obesity (Heid, 2010; Speliotes, 2010), but not directly to eating behavior or eating disorders. *FTO* has been shown to be of particular importance in regulating body weight as well as being implicated in behavioral and cognitive aspects of overeating (Hinney & Volckmar, 2013). Previously, *FTO* has been identified as a gene of interest with regards to AN (Boraska et al., 2014), drive for thinness, bulimia and weight fluctuations (Boraska et al., 2012). In our

sample *FTO* was associated with DE in females at a nominal significance level after adjustments for BMI suggesting a weight independent effect and underlining the notion of *FTO*'s role in disordered eating (Micali, Field, et al., 2015). Whether this observed effect is due to *FTO* affecting appetite and satiety is also interesting to explore. The *FTO* gene has previously been shown to be associated with loss of control over eating (Muller et al., 2012; Tanofsky-Kraff et al., 2009) and Micali and colleagues have very recently found strong associations between binge eating and *FTO* (Micali, Field, et al., 2015) which further supports the evidence of *FTO*'s effect on appetite and food intake. Satiety and hunger have also been linked to eating behavior through *FTO* and *MC4R* (Melanocortin 4 receptor gene) (Stutzmann et al., 2009; Wardle, Carnell, Haworth, & Plomin, 2008).

In our study the use of genetic risk scores enabled us to identify effects asserted by the combined obesity susceptibility SNP-effect on the uncontrolled appetite/overeating trait specified by EAT-B. Furthermore, we more specifically identified single EAT-B items to be of particular interest. The obesity GRS was positively associated with loss of control eating in the total sample, and with overeating in the young adolescent females. Previous findings of Llewellyn and colleagues (Llewellyn et al., 2014) showed that the obesity GRS negatively influenced satiety responsiveness in a sample of 10 year old children and suggested that obesity risk variants influence adiposity via appetite regulatory mechanisms. This is not unexpected as many of the so far identified obesity susceptibility SNPs are within or near genes known to regulate appetite (Locke et al., 2015). Directions of effects were comparable using the two weighted GRSs although weaker associations were in general identified when the extended GRS including 32 obesity risk-variants was used. The discrepancy between the

GRS-analyses could be due to several reasons: 1) that the extended GRS included imputed SNPs in addition to directly analysed ones which makes it less accurate, 2) that the addition of more SNPs makes the distribution within the scores slightly different and 3) that the analyses with the extended GRS included fewer cases compared to the GRS with nine SNPs.

Knowledge of factors influencing disordered eating among males is scarce. The prevalence of eating disorders in males are additionally assumed to be much lower than in females although binge eating disorder (BED), shows a life-time prevalence closer to 1:1 for males and females (1.6% and 2.0%, respectively) (Hudson, Hiripi, Pope, & Kessler, 2007). Both sexes were represented in our study and quite high proportions of DE comparing males to females were identified; 39.8% (n=35 of a total of n=88) reported poor appetite/undereating (EAT-A) and 27.0% (n=41 of a total of n=152) uncontrolled appetite/overeating (EAT-B).

A strength of this study was that anthropometric and clinical measurements were carried out by trained personnel avoiding the pitfall of under- or misreporting weight related measures (Park et al., 2011). Additionally, the HUNT population comprises a very ethnically homogenous sample. The main limitation in our study is the rather low number of cases as expected for rare phenotypes or diseases and thus no statistical significance might be due to lack of power. Also adding more obesity SNPs to the polygenic risk score would probably more precisely capture the genetic predisposition. Furthermore, the effect sizes included in the weighted GRS were based on adult effects which may not fully correlate with the adolescent effects. However, there is evidence for higher heritability of BMI in children compared to

adults (Elks et al., 2012) which would imply larger effect estimates if using an obesity genetic risk score based on adolescent effects.

The genetic data was only retrieved from the individuals who participated both at adolescence in Young-HUNT1 (1995-97) and as young adults in HUNT3 (2006-08). At HUNT3 the lowest participation rate was unfortunately within our target age group (20-39 years). In a non-participant study performed after the HUNT3 survey (Langhammer, Krokstad, Romundstad, Heggland, & Holmen, 2012), the prevalence of cardiovascular diseases, diabetes mellitus and psychiatric disorders were higher in general compared to the participants including all age groups. In the age group of 20-39 years the majority of non-participants report not to have met due to “not receiving an invitation” (14.1%) or “not having the time to meet” (62.6%).We therefore believe that our sample was representative of the Young-HUNT1 participants in general.

Several of the sub-analyses may be underpowered due to lack of cases to include. The sample size required for detecting associations is known to be affected by disease prevalence, disease allele frequency, linkage disequilibrium (LD), inheritance models and effect size of the genetic variant. In our study, the disease prevalence is low and the effect sizes of each genetic variant are probably low. In the case of the *COMT* variant rs4680 which was found to be significantly associated to poor appetite/undereating, we know that the disease/risk allele frequency is high (approximately 0.5). The rs4680 is additionally a functional variant localised within the *COMT* gene, i.e. LD=1. Together these last-mentioned factors will affect

the statistical power positively. According to calculations done by Hong and Park (Hong & Park, 2012) computing the effective sample size and statistical power using a web browser program, Genetic Power Calculator developed by Purcell et al. (Purcell, Cherny, & Sham, 2003)(http://pngu.mgh.harvard.edu/~purcell/gpc/), the smallest sample size in a dominant model to achieve 80% power using a single SNP in a case-control study under the assumptions of 5% disease prevalence, 5% MAF, LD=1 and 1:1 case-control ratio is 90 cases.

Although we found a strong association between rs4680 *COMT* and the poor appetite/undereating, the strength of evidence for many of the other associations were not always backed by multiple testing. To our knowledge, our study is one of very few to study gene associations of DE in a population based sample of European ancestry and our findings show that even in a population based sample, there are indications of associations between the dopaminergic and melanocortin pathways and DE. Our findings need further replication in larger studies.

In conclusion, differential patterns of associations were found between sets of genetic markers for poor appetite/undereating and uncontrolled appetite/overeating. The Val allele of the *COMTVal158Met* variant rs4680 was protective for the poor appetite/undereating trait. The obesity genetic risk score was independent of obesity association, risk-conferring for loss of control eating and overeating, confirming the correlation between obesity susceptibility and disordered eating.

Conflict of interest

Authors have no competing interests.

Aknowledgment

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Table 1. Characteristics of the study sample.

	EAT-A Cases (n=88)	**EAT-B Cases (n=152)**	**Controls (n=1530)**
Gender, females, n (%)	53 (60.2%)	111 (73.0%)	823 (53.8%)
Age,mean (SD)	16.0 (1.8)	16.3 (1.8)	15.9 (1.8)
BMI[1], mean (SD)	20.07 (2.7)	22.18 (3.6)	21.27 (3.2)
wGRS[2], mean (SD)	1.79 (0.04)	1.81 (0.03)	1.79 (0.01)
uGRS[3], mean (SD)	9.48 (0.22)	9.66 (0.16)	9.65 (0.49)
Underweight, n (%)[4]	8 (9.2%)	7 (4.6%)	95 (6.2%)
Normal weight, n (%)[4]	71 (81.6%)	108 (71.1%)	1148 (75.0%)
Overweight, n (%)[4]	4 (4.6%)	24 (15.8%)	192(12.5%)
Obese, n (%)[4]	1 (1.1%)	6 (3.9%)	31 (2.0%)

[1]BMI; Body mass index, [2] wGRS; weighted Genetic Risk Score, [3] uGRS; unweighted Genetic Risk Score [4] Weight categories defined according to IOTF (Cole, Bellizzi, Flegal, & Dietz, 2000; Cole, Flegal, Nicholls, & Jackson, 2007). Less cases in the weight groups due to missing weight data.

Table 2. SNP characteristics.

Nearby gene	CHR	SNP	BP	Call rate (%)	Minor allele	Other allele	MAF	Proxy SNP[1]	Per risk allele change in BMI, beta[2]
OPRD1	1	rs569356	29009273	98.9	G	A	0.129		
NEGR1	1	rs2815752	72585028	99.7	G	A	0.406		0.13
SEC16B	1	rs543874	176156103	99.6	C	T	0.237		0.22
TMEM18	2	rs6548238	624905	99.4	T	C	0.166	rs2867125	0.31
INSIG2	2	rs7566605	118552495	99.0	C	T	0.357		
GRB14	2	rs10195252	165221337	99.4	C	T	0.417		
GHRL	3	rs35683	10303250	99.8	A	C	0.443		
GNPDA2	4	rs10938397	44877284	99.4	G	A	0.389		0.18
TFAP2B	6	rs987237	50911010	98.4	G	A	0.178		0.13
5-HT2A	7	rs3734967	154493441	99.6	G	A	0.292		
MSRA	8	rs545854	9897490	99.8	G	C	0.179		
BDNF	11	rs4074134	27603861	99.7	T	C	0.184		
BDNF	11	rs925946	27623778	99.4	A	C	0.348		
BDNF	11	rs6265	27636492	99.8	A	G	0.182	rs10767664	0.19
MTCH2	11	rs10838738	47619625	99.6	C	T	0.364	rs3817334	0.06
DRD2	11	rs6277	112788669	99.7	C	T	0.466		
FTO	16	rs1121980	52366748	99.7	T	C	0.446	rs1558902	0.39
FTO	16	rs8050136	52373776	99.8	A	C	0.411		
FTO	16	rs9939609	52378028	99.7	A	T	0.412		
MC4R	18	rs571312	55990749	99.1	A	C	0.268		0.23
MC4R	18	rs17782313	56002077	98.4	C	T	0.268		
MC4R	18	rs12970134	56035730	99.7	A	G	0.300		
KCTD15	19	rs11084753	39013977	99.2	A	G	0.307		
COMT	22	rs4680	18331271	99.7	G	A	0.449		

Minor allele is set as reference in the analyses. Effect allele underlined in SNPs used in the weighted GRS. [1] Effect sizes by Speliotes et al., 2010.

[2] Linkage disequilibrium between genotyped SNP and SNP used as reference in the weighted GRS analysis (Speliotes et al., 2010). CHR = Chromosome, SNP = Single nucleotide polymorphism, BP = Base pair, MAF=Minor allele frequency.

Table 3. Association between EAT-A (poor appetite/undereating sub-scale) and genetic variants in the total study sample and sex stratified.

		Minimally adjusted[1] (n=88 cases)			Conditional on zBMI[2] (n=88 cases)			Males conditional on zBMI (n=35 cases)			Females conditional on zBMI (n=53 cases)		
SNP	**Putative gene**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**
rs569356	OPRD1	1.06 (0.69-1.64)	0.791	1	1.06 (0.69-1.64	0.791	1	0.73 (0.33-1.62)	0.446	1	1.29 (0.76-2.18)	0.345	1
rs2815752	NEGR1	1.01 (0.74-0.38)	0.964	1	1.01 (0.74-1.38)	0.964	1	0.89 (0.54-1.44)	0.629	1	1.11 (0.74-1.67)	0.626	1
rs543874	SEC16B	1.10 (0.8-1.55)	0.601	1	1.10 (0.78-1.55)	0.605	1	0.66 (0.35-1.22)	0.185	0.980	1.49 (0.97-2.29)	0.072	0.796
rs6548238	TMEM18	0.90 (0.59-1.38)	0.623	1	0.90 (0.59-1.38)	0.626	1	0.64 (0.30-1.38)	0.258	1	1.07 (0.64-1.79)	0.795	1
rs7566605	INSIG2	1.18 (0.87-1.60)	0.297	0.998	1.18 (0.87-1.60)	0.296	0.997	1.25 (0.78-2.01)	0.348	1	1.13 (0.76-1.69)	0.552	1
rs10195252	GRB14	0.82 (0.60-1.13)	0.225	0.993	0.82 (0.60-1.13)	0.222	0.993	0.87 (0.52-1.45)	0.595	1	0.79 (0.53-1.18)	0.247	0.995
rs35683	GHRL	**1.35 (1.0-1.83)**	**0.050**	0.640	**1.35 (1.00-1.83)**	**0.049**	0.616	1.30 (0.81-2.08)	0.273	1	1.39 (0.94-2.05)	0.100	0.892
rs10938397	GNPDA2	0.92 (0.67-1.25)	0.586	1	0.92 (0.67-1.25)	0.588	1	0.93 (0.56-1.54)	0.786	1	0.91 (0.61-1.36)	0.660	1
rs987237	TFAP2B	1.33 (0.91-1.94)	0.136	0.940	1.33 (0.91-1.94)	0.136	0.952	0.91 (0.48-1.72)	0.769	1	**1.72 (1.07-2.76)**	**0.025**	0.393
rs3734967	5-HT2A	1.05 (0.75-1.47)	0.767	1	1.05 (0.75-1.48)	0.758	1	1.01 (0.59-1.74)	0.963	1	1.09 (0.71-1.68)	0.697	1
rs545854	MSRA	1.20 (0.81-1.76)	0.352	1	1.20 (0.82-1.76)	0.352	0.999	1.63 (0.92-2.88)	0.095	0.857	0.96 (0.57-1.62)	0.870	1
rs4074134	BDNF	1.34 (0.93-1.92)	0.115	0.908	1.34 (0.93-1.92)	0.117	0.918	1.40 (0.81-2.45)	0.231	0.999	1.29 (0.80-2.08)	0.302	0.999
rs925946	BDNF	1.02 (0.74-1.40)	0.929	1	1.02 (0.74-1.40)	0.920	1	0.86 (0.51-1.44)	0.555	1	1.14 (0.76-1.71)	0.535	1
rs6265	BDNF	1.23 (0.84-1.78)	0.284	0.997	1.23 0.84-1.78)	0.287	0.997	1.22 (0.68-2.20)	0.508	1	1.23 (0.75-2.00)	0.409	1
rs10838738	MTCH2	1.00 (0.73-1.36)	0.988	1	1.00 (0.73-1.36)	0.989	1	0.88 (0.53-1.44)	0.609	1	1.09 (0.73-1.63)	0.675	1
rs6277	DRD2	0.99 (0.73-1.34)	0.930	1	0.99 (0.73-1.34)	0.931	1	0.69 (0.42-1.13)	0.140	0.953	1.24 (0.84-1.83)	0.280	0.999
rs1121980	FTO	0.99 (0.73-1.35)	0.960	1	0.99 (0.73-1.35)	0.961	1	0.84 (0.51-1.38)	0.492	1	1.10 (0.74-1.64)	0.629	1
rs8050136	FTO	1.09 (0.80-1.50)	0.572	1	1.09 (0.80-1.50)	0.571	1	0.98 (0.60-1.62)	0.946	1	1.17 (0.79-1.75)	0.438	1
rs9939609	FTO	1.09 (0.80-1.49)	0.588	1	1.09 (0.80-1.49)	0.587	1	0.97 (0.59-1.61)	0.917	1	1.17 (0.79-1.75)	0.438	1
rs571312	MC4R	0.87 (0.61-1.24)	0.436	1	0.87 (0.60-1.24)	0.433	1	0.96 (0.56-1.65)	0.894	1	0.79 (0.49-1.29)	0.346	1
rs17782313	MC4R	0.87 (0.61-1.25)	0.446	1	0.87 (0.61-1.24)	0.444	1	0.97 (0.57-1.66)	0.915	1	0.79 (0.49-1.28)	0.345	1
rs12970134	MC4R	0.84 (0.59-1.19)	0.319	0.999	0.84 (0.59-1.19)	0.318	0.999	0.76 (0.44-1.31)	0.328	1	0.89 (0.57-1.40)	0.627	1
rs11084753	KCTD15	**1.44 (1.04-1.99)**	**0.027**	0.434	**1.44 (1.04-1.99)**	**0.027**	0.407	**2.09 (1.24-3.51)**	**0.006**	0.093	1.14 (0.75-1.74)	0.532	1
rs4680	COMT	**0.60 (0.43-0.84)**	**0.002**	**0.046**	**0.60 (0.43-0.83)**	**0.002**	**0.035**	0.71 (0.42-1.20)	0.204	0.990	**0.54 (0.35-0.82)**	**0.004**	0.074

[1]Minimally adjusted models are adjusted for sex. [2]Conditional models were adjusted for age adjusted z-scores of BMI. Significant results ($P<0.05$) are marked with bold. P^3 - Empirical P-value corrected for multiple testing by 1000 permutations.

Table 4. Association between EAT-B (uncontrolled appetite/overeating sub-scale) and genetic variants in the total study sample and sex stratified.

		Minimally adjusted[1] (n=152 cases)			Conditional on zBMI[2] (n=152 cases)			Males conditional on zBMI (n=41 cases)			Females conditional on zBMI (n=111 cases)		
SNP	**Putative gene**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**	**OR (95% CI)**	**P**	**P[3]**
rs569356	OPRD1	0.80 (0.55-1.61)	0.237	0.994	0.80 (0.55-1.16)	0.238	0.995	0.79 (0.39-1.60)	0.512	1	0.80 (0.51-1.25)	0.324	1
rs2815752	NEGR1	0.91 (0.71-1.17)	0.471	1	0.91 (0.71-1.17)	0.470	1	0.82 (0.52-1.29)	0.382	1	0.96 (0.71-1.29)	0.776	1
rs543874	SEC16B	0.96 (0.73-1.27)	0.792	1	0.96 (0.73-1.27)	0.797	1	0.77 (0.44-1.32)	0.336	1	1.06 (0.76-1.47)	0.743	1
rs6548238	TMEM18	0.89 (0.64-1.24)	0.483	1	0.89 (0.64-1.23)	0.479	1	1.24 (0.70-2.21)	0.463	1	0.77 (0.51-1.15)	0.199	0.994
rs7566605	INSIG2	0.91 (0.71-1.16)	0.442	1	0.91 (0.71-1.16)	0.442	1	0.80 (0.50-1.28)	0.359	1	0.96 (0.71-1.28)	0.769	1
rs10195252	GRB14	1.00 (0.78-1.27)	0.979	1	1.00 (0.78-1.27)	0.975	1	1.06 (0.67-1.68)	0.809	1	0.97 (0.73-1.29)	0.838	1
rs35683	GHRL	**1.34 (1.06-1.70)**	**0.014**	0.257	**1.34 (1.06-1.70)**	**0.015**	0.274	1.43 (0.92-2.22)	0.109	0.916	1.31 (0.99-1.73)	0.059	0.719
rs10938397	GNPDA2	**0.76 (0.59-0.98)**	**0.036**	0.531	**0.76 (0.59-0.98)**	**0.035**	0.517	0.73 (0.45-1.19)	0.204	0.994	0.78 (0.58-1.05)	0.097	0.881
rs987237	TFAP2B	**1.37 (1.03-1.84)**	**0.033**	0.504	**1.37 (1.03-1.84)**	**0.034**	0.503	1.23 (0.72-2.11)	0.443	1	**1.44 (1.02-2.05)**	**0.040**	0.562
rs3734967	5-HT2A	0.97 (0.74-1.26)	0.811	1	0.97 (0.74-1.26)	0.794	1	0.97 (0.59-1.62)	0.922	1	0.97 (0.71-1.32)	0.822	1
rs545854	MSRA	0.91 (0.66-1.26)	0.587	1	0.92 (0.66-1.26)	0.588	1	0.94 (0.51-1.74)	0.844	1	0.91 (0.62-1.32)	0.607	1
rs4074134	BDNF	0.72 (0.52-1.01)	0.060	0.734	0.73 (0.52-1.02)	0.061	0.697	0.62 (0.32-1.21)	0.163	0.978	0.77 (0.52-1.13)	0.181	0.989
rs925946	BDNF	1.05 (0.82-1.35)	0.692	1	1.05 (0.82-1.34)	0.710	1	0.77 (0.47-1.26)	0.291	0.997	1.18 (0.88-1.57)	0.268	1
rs6265	BDNF	0.73 (0.52-1.02)	0.065	0.758	0.73 (0.52-1.02)	0.067	0.733	0.55 (0.27-1.12)	0.100	0.874	0.80 (0.54-1.18)	0.258	1
rs10838738	MTCH2	0.89 (0.70-1.14)	0.370	1	0.89 (0.70-1.14)	0.368	1	0.87 (0.55-1.39)	0.564	1	0.90 (0.67-1.21)	0.489	1
rs6277	DRD2	1.00 (0.79-1.27)	0.987	1	1.00 (0.79-1.27)	0.985	1	1.15 (0.74-1.80)	0.534	1	0.95 (0.71-1.25)	0.694	1
rs1121980	FTO	1.11 (0.87-1.42)	0.387	1	1.11 (0.87-1.42)	0.388	1	0.68 (0.43-1.10)	0.115	0.925	**1.34 (1.00-1.78)**	**0.047**	0.632
rs8050136	FTO	1.09 (0.85-1.39)	0.486	1	1.09 (0.85-1.39)	0.486	1	0.72 (0.44-1.16)	0.173	0.984	1.27 (0.96-1.70)	0.097	0.881
rs9939609	FTO	1.09 (0.85-1.39)	0.499	1	1.09 (0.85-1.39)	0.499	1	0.71 (0.44-1.15)	0.161	0.977	1.27 (0.96-1.70)	0.097	0.881
rs571312	MC4R	0.90 (0.68-1.19)	0.455	1	0.90 (0.68-0.46)	0.463	1	0.84 (0.50-1.40)	0.504	1	0.93 (0.66-1.30)	0.654	1
rs17782313	MC4R	0.91 (0.69-1.20)	0.504	1	0.91 (0.69-1.21)	0.512	1	0.85 (0.51-1.41)	0.520	1	0.94 (0.67-1.32)	0.709	1
rs12970134	MC4R	0.92 (0.70-1.20)	0.530	1	0.92 (0.70-1.20)	0.537	1	0.86 (0.53-1.40)	0.547	1	0.95 (0.69-1.30)	0.729	1
rs11084753	KCTD15	1.18 (0.91-1.52)	0.219	0.991	1.18 (0.91-1.52)	0.219	0.994	1.36 (0.83-2.23)	0.217	0.995	1.11 (0.82-1.50)	0.491	1

rs4680	COMT	0.87 (0.68-1.11)	0.269	0.996	0.87 (0.68-1.12)	0.277	0.998	0.78 (0.48-1.26)	0.313	1	0.91 (0.68-1.21)	0.503	1

[1]Minimally adjusted models are adjusted for sex. [2]Conditional models were adjusted for age adjusted z-scores of BMI. Significant results (P<0.05) are marked with bold. P[3] - Empirical P-value corrected for multiple testing by 1000 permutations. If significant after correction – underlined and marked with bold.

Table 5. Association between EAT-B (uncontrolled appetite/overeating sub-scale) and the weighted genetic risk scores (wGRS) in the total and sex stratified samples.

		Weighted GRS			
		Minimally adjusted		Conditional on BMI	
Outcome	**Sample (case, n)**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
EAT-B	All (n=152)	1.14 (0.77-1.71)	0.514	1.12 (0.74-1.68)	0.602
	Males (n=41)	0.57 (0.27-1.18)	0.131	0.58 (0.27-1.26)	0.170
	Females (n=111)	1.51 (0.93-2.46)	0.093	1.42 (0.87-2.32)	0.166
EAT-B Think	All (n=184)	1.23 (0.85-1.79)	0.270	1.19 (0.82-1.74)	0.362
	Males (n=41)	1.02 (0.49-2.14)	0.951	1.02 (0.48-2.17)	0.962
	Females (n=143)	1.30 (0.84-2.00)	0.238	1.23 (0.79-1.91)	0.357
EAT-B Cont	All (n=108)	**1.66 (1.04-2.65)**	**0.034**	**1.62 (1.01-2.61)**	**0.046**
	Males (n=37)	1.39 (0.64-3.05)	0.407	1.39 (0.61-3.13)	0.434
	Females (n=71)	1.81 (1.00-3.26)	0.050	1.75 (0.97-3.16)	0.063
EAT-B Stop*	All (n=270)	1.20 (0.88-1.64)	0.253	1.11 (0.81-1.53)	0.517
	Males (n=95)	1.06 (0.64-1.74)	0.832	0.95 (0.57-1.61)	0.861
	Females (n=175)	1.29 (0.87-1.92)	0.203	1.20 (0.81-1.80)	0.366
	Females 13-15 year (n=78)	**2.21 (1.23-3.98)**	**0.008**	**2.07 (1.14-3.76)**	**0.017**
	Females 16-19 year (n=97)	0.81 (0.47-1.41)	0.455	0.72 (0.41-1.27)	0.258

The weighted GRS was calculated by multiplying the number of risk alleles at each locus (0, 1, 2) with the corresponding effect sizes per allele, in kg/m^2 (beta), as reported by Speliotes et al. (Speliotes et al., 2010). The minimally adjusted models are adjusted for sex and age in the total sample and age in the sex-stratified samples. The conditional models were adjusted for sex, age and BMI in the total sample and for age and BMI in the sex-stratified samples. Significant results ($P<0.05$) are marked with bold. EAT-B sub-scale includes the following items: “When I first

begin eating, it is difficult to stop" (*overeating*, EAT-B Stop); "I spend too much time thinking about food" (*food preoccupation*, ETA-B Think); "I feel that food controls my life" (*loss of control eating*, EAT-B Cont). * Age group stratification due to significant sex-GRS interaction.

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