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Adiponectin and human eating behaviour: a Mendelian randomization study

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Abstract

Background: Adiponectin plays key roles in regulating appetite and food intake. Altered circulating adiponectin levels have been observed in human eating disorders such as anorexia nervosa, bulimia nervosa or binge eating. In addition, an association between circulating adiponectin levels and human eating behaviour (EB) has been reported. Interestingly, a disturbance in eating behaviour is the defining characteristic of human eating disorders. However, it is unknown whether adiponectin is causally implicated in human EB. We therefore aimed to investigate the causal effect of adiponectin on EB.

Results: Mendelian randomization (MR) analysis estimated the influence of blood adiponectin on EB by combining data on the association of adiponectin gene (*ADIPOQ*) variants with adiponectin levels and with three EB factors involving disinhibition, restraint and hunger. Using inverse-variance weighted (IVW) regression method and other complementary MR techniques (weighted median regression, MR Egger and weighted modal regression), the MR analysis revealed a broadly consistent evidence that higher blood adiponectin concentration was significantly associated with increased EB factor disinhibition (beta coefficient for IVW regression [β_{IVW}], 3.05; 95% confidence interval [CI] 1.10, 5.00) but non-significantly associated with increased EB factor restraint (β_{IVW}, 0.17; 95% CI − 1.85, 2.18), and increased EB factor hunger (β_{IVW}, 1.63; 95% CI − 0.75, 4.01).

Conclusions: Overall, our findings indicate a causal role of adiponectin levels in eating disinhibition but not in eating restraint and hunger.

Keywords: Adiponectin, Eating behaviour factors, Mendelian randomization analysis, Disinhibition, Restraint, Hunger

Background

Human circulating adiponectin is a well-described 30 kDa adipocytokine implicated in a wide range of anti-inflammatory [1], insulin-sensitizing [2] and eating disorder [3] pathways. Serum adiponectin levels are highly heritable [4–7] and, in contrast to adipokines, are inversely correlated with several cardiovascular risk factors such as obesity, type 2 diabetes mellitus, coronary artery disease and stroke [8–13]. Adiponectin serum levels may be influenced by nutritional compounds and probably increased food intake which may in turn serve as a positive feedback process [14]. Besides several other loci such as *ARL15* (ADP-ribosylation factor-like 15 gene locus) [15], *CDH13* (cadherin 13 gene locus) and *KNG* (kininogen gene locus) [16, 17], candidate and genome-wide association studies (GWAS) have shown pronounced associations between common polymorphisms in the adiponectin gene (*ADIPOQ*) and adiponectin levels [18–21]. Interestingly, polymorphisms of the ligand adiponectin gene, *ADIPOQ*, have been linked with a range of important clinical parameters such as body mass index (BMI), insulin resistance, cardiovascular disease and type 2 diabetes [22–24].

A number of observational studies have linked altered adiponectin levels with several eating disorders involving anorexia nervosa, bulimia nervosa and binge eating disorders [3]. In particular, several studies showed that serum adiponectin levels are increased in patients affected with anorexia nervosa [25–27] perhaps due in part to the lack of negative feedback exerted by fat mass in adiponectin production and/or enhanced insulin sensitivity [28]. In addition, studies have shown that serum adiponectin secretion in patients with bulimia nervosa

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could be the same, upregulated or downregulated when compared to those found in healthy controls. Moreover, the studies also indicated that adiponectin levels of bulimia nervosa patients were lower than those found in anorexia nervosa patients (reviewed in, e.g. [3]). Further, binge eating disorder was shown to be accompanied with lower serum adiponectin levels than in normal individuals [29, 30]. Of note, a disturbance in eating behaviour is the hallmark of the above clinical eating disorders. Patients with bulimia nervosa experience recurrent episodes of binge eating [31]. Patients with anorexia nervosa severely resist dietary intake and showed a persistent disturbance in eating behaviour even after restoration of body weight and significant improvements in eating disordered and psychological symptoms [32].

Mendelian randomization is an efficient analytical tool that uses genetic variants as instrumental variables to estimate the causal relationship between an exposure and outcome [33]. This method relies on the random assignment of genetic variants during gametogenesis to reduce the possibility of confounding [34, 35]. In addition, since genetic variant is established at conception (i.e. genotype being a fixed exposure), MR reduces the possibility of reverse causality [33]. Taken together, this confirms MR as an efficient tool that can substantially improve causal inference from observational data [36]. If adiponectin serum levels are altered in eating disorders, the genetic variant associated with adiponectin concentration should be associated with eating behaviour. We investigated this assumption through the use of a number of complementary MR techniques to examine the causal nature of the association between blood adiponectin level and three-factor eating behaviour involving restraint, disinhibition and hunger in Central European (CEU) population.

Methods

Data sources

Summary data on the association between *ADIPOQ* single-nucleotide polymorphisms (SNPs) and the phenotypes of interest were extracted from Rohde et al.'s paper (898 individuals of European ancestry) [37] and public databases of different consortia: ADIPOGen for adiponectin (29,347 individuals of European ancestry) [38] and GIANT (Genetic Investigation of ANthropometric Traits) for BMI (229,735 individuals) [39] and WC (795,447 individuals) [40].

Instrumental variables

All the six but one *ADIPOQ* SNPs (Table 1) for our instrumental variable analyses were selected from 145 SNPs strongly ($P < 5 \times 10^{-8}$) associated with blood adiponectin levels in the European ancestry GWAS meta-analysis from the ADIPOGen consortium [38]. The remaining one SNP also selected from the ADIPOGen consortium was less strongly ($P = 2.3 \times 10^{-7}$) associated with adiponectin levels in the European ancestry GWAS meta-analysis [38]. We assessed correlations (linkage disequilibrium) among these SNPs using the LDlink [41] and found these SNPs to be independent variants.

Table 1 Characteristics of SNPs selected for Mendelian randomization

ADIPOQ SNP	Chr	Position*	EA	NEA	EAF†	C1	S6
rs864265	3	186836503	G	T	0.14		✓
rs16861205	3	186843845	G	A	0.85	✓	✓
rs182052	3	186842993	G	A	0.61		✓
rs17366568	3	186852664	G	A	0.93		✓
rs3821799	3	186853697	T	C	0.54		✓
rs3774261	3	186853770	A	G	0.50		✓

Chr chromosome, *EA* effect allele, *EAF* effect allele frequency, *NEA* non-effect allele, *S6* six SNPs used in MR analyses (all but one SNP were selected on basis of reaching genome-wide significant levels in association with adiponectin, $P < 5 \times 10^{-8}$ in ADIPOGen consortium); and *C1* one SNP had a $P < 2.3 \times 10^{-7}$ in association with adiponectin in the ADIPOGen consortium
*Genome Reference Consortium Human Build 38
†1000 genomes

Data analysis procedure

We performed a two-sample Mendelian randomization analysis using summary data from genome-wide association studies (GWAS). SNPs, previously reported to be associated with blood adiponectin levels, were used as instrumental variables for testing the causal effect of adiponectin on the three eating behaviour factors. Data on the association of *ADIPOQ* SNPs with (1) adiponectin levels (first sample) and (2) eating behaviour factors (second samples) were combined to estimate the influence of blood adiponectin on eating behaviour. First, we selected and obtained the beta coefficients and standard errors of six (6) GWAS significant SNPs that predicted adiponectin levels in the ADIPOGen consortium and were available in the eating behaviour outcome GWAS. Second, we re-analysed the summary data of these six SNPs on eating behaviour using their genotype frequencies, means and standard deviations as available in the Rohde et al.'s paper [37] using allelic model of inheritance to obtain the beta coefficients (β) and standard errors (SE) associated with the SNPs (Additional file 1: Table S1). These six *ADIPOQ* SNPs were then used for MR analysis. We also examined the standardized mean difference (and *P* values) of two eating behaviour risk factors involving BMI-adjusted WC and BMI per allele of the selected *ADIPOQ* SNPs for evidence of an effect of the SNPs on these risk factors. This was to enable us to assess the presence of potential bias (horizontal pleiotropy) or mediation of the effect of *ADIPOQ* SNPs with these eating behaviour risk factors.

Estimation of causal effect

The SNP-exposure and SNP-outcome associations for each of the eating behaviour factors were combined in a random effect meta-analysis using the inverse-variance weighted (IVW) regression method as described by Burgess et al. [42]. The β-coefficient of each eating behaviour factor per one natural log greater adiponectin level and its standard error (SE) were calculated.

Sensitivity analysis

While we considered our MR approach unlikely to be biased by horizontal pleiotropy given the functional relationship of *ADIPOQ* to adiponectin levels, yet, we investigated the presence of potential bias (horizontal pleiotropy), by running a number of sensitivity analyses involving weighted-median regression, MR Egger and weighted modal regression that provide causal estimates under less stringent assumptions than the traditional MR approach. The weighted median regression analyses can provide a consistent estimate for the true causal effect when up to half of the weights in the MR analysis are from *ADIPOQ* variants that exert pleiotropic effects on the eating behaviour factors [43, 44]. MR-Egger regression relaxes the assumption that the effects of our *ADIPOQ* variants on the eating behaviour factors are entirely mediated via the adiponectin concentration. This method allows for each *ADIPOQ* variant to exhibit some pleiotropy but assumes that each gene's association with the adiponectin concentration is independent in magnitude from its pleiotropic effects (the InSIDE assumption) [45]. MR Egger achieved this by allowing an intercept term in the weighted regression analysis. The value of the intercept provides an estimate of the degree of pleiotropy affecting the result, while the beta (slope) coefficient represents the causal effect between adiponectin concentration and eating behaviour adjusted for pleiotropy. Finally, the weighted modal regression analyses relax our instrumental variable assumptions [46]. Analysis of association *ADIPOQ* SNPs with eating behaviour factors using an allelic model of inheritance was done in Statistical Analysis System (SAS) version 9.1.0 (SAS Stat) while MR analyses were implemented using MendelianRandomization package in R statistical software (R version 3.5.0).

Results

Association of genetic instruments with adiponectin, EB and EB risk factors

Figure 1 shows the associations of *ADIPOQ* SNPs, used as instrumental variables with adiponectin levels, EB and EB risk factors. Each adiponectin-increasing allele was associated with decreased EB factor restrain (beta coefficient [β], − 0.04; 95% confidence interval [CI] − 0.15, 0.08), increased EB factor disinhibition (β, 0.21; 95% CI 0.10, 0.33), and increased EB factor hunger (β, 0.13; 95% CI 0.02, 0.25). Of the six SNPs, there was some evidence

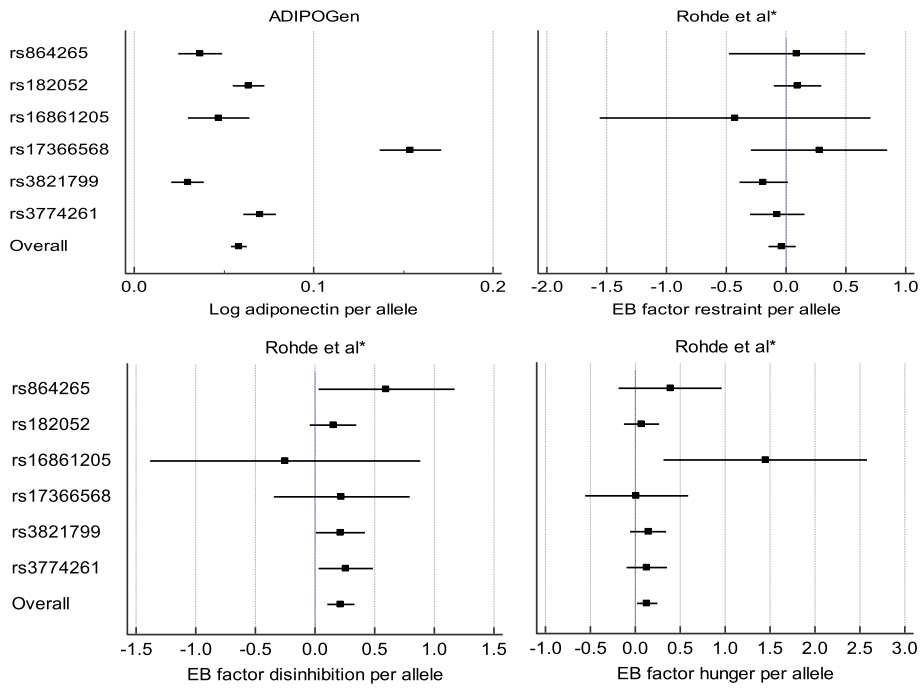

Fig. 1 Forest plots of mean differences in log adiponectin levels and eating behaviour factors per allele of single nucleotide polymorphism (SNP). Analyses including six ADIPOQ SNPs associated with (1) adiponectin at genome-wide significant levels ($P < 5 \times 10^{-8}$) and (2) eating behaviour (EB) factors. Results for log adiponectin included 29,347 individuals from ADIPOGen Consortium and for EB factors included 898 individuals from Rohde et al. 2015*

of heterogeneity ($P < 0.05$) between studies that contributed to ADIPOGen consortium.

None of the six *ADIPOQ* SNPs was associated with EB risk factors involving WC and BMI (Table 2). In addition, pooled effect estimates of these SNPs on these risk factors indicated no significant association with EB factors (Fig. 2). Finally, the adiponectin-increasing *ADIPOQ* variants were not associated with these available EB risk factors (Additional file 2: Table S2)

Effect of blood adiponectin concentration on EB

Table 3 shows the results of all MR analyses assessing the association of genetically predicted adiponectin with the three EB factors. Using IVW regression, higher adiponectin concentration was strongly and significantly associated with increased EB factor disinhibition (β, 3.05; 95% CI 1.10, 5.00). Similarly, using both weighted median MR and weighted modal MR, there was strong evidence of a significant association (weighted median β, 2.66; 95% CI 0.48, 4.84; weighted modal β, 2.63; 95% CI 0.54, 4.73). MR-Egger point estimate (− 0.32) was non-significant and in the opposite direction. The intercept indicated no evidence of pleiotropy (β, 0.23; 95% CI − 0.04, 0.51).

For EB factor restraint, higher adiponectin concentration was weakly and non-significantly associated with an increased likelihood of the EB (IVW β, 0.17; 95% CI − 1.85, 2.18). Results were similar when using weighted median MR (β, 0.98; 95% CI − 1.28, 3.24), MR Egger (β, − 3.85; 95% CI − 0.52, 8.21) and weighted modal estimate (β, 1.07; 95% CI − 1.12, 3.26). The intercept indicated no substantial evidence of pleiotropy (β, − 0.25; 95% CI − 0.53, 0.02).

Finally, there was evidence of an association between higher adiponectin concentration and increased hunger across all but one MR techniques. Inverse-variance weighted MR, weighted median MR and weighted modal MR all produced beta coefficients in the same direction. MR Egger on the other hand had a beta coefficient in the opposite direction. However, we found no statistical evidence of association for all methods (e.g. inverse-variance weighted β, 1.63; 95% CI − 0.75, 4.01). The intercept in the MR-Egger analysis did not indicate any substantial evidence of pleiotropy (β, 0.22; 95% CI − 0.12, 0.55).

Discussion

Using data from ADIPOGen consortium and eating behaviour GWAS study with information for up to 29,347 and 898 participants, respectively, we find evidence for a causal association between adiponectin levels and eating disinhibition but not for eating restraint and hunger. These findings suggest that the observational association between effect allele carriers in the *ADIPOQ* SNPs showing elevated adiponectin serum levels along with the tendency to frequently overeat (eating disinhibition), also confirmed in our datasets, may be causal. This effect was not due to horizontal pleiotropy based on our further investigation of the effect using alternative MR approaches (such as MR Egger, median, and mode estimators) and our assessment of the genetic variants with known and available potential confounders (such as WC and BMI).

The observational study of the role adiponectin in eating behaviour [37] indicated that while some *ADIPOQ* SNPs were related to disinhibition and hunger, none of the associations withstood Bonferroni corrections for multiple testing perhaps due to the relatively small sample size of the study. Taken advantage of the large GWAS consortium data from ADIPOGen, we have undertaken the first MR study of the causal effect of adiponectin on eating behaviour. We applied a rigorous analysis plan to assess the validity and consistency of our findings. This included (1) adopting a conservative approach in selecting SNPs for our instrumental variables, (2) the use of multiple eating behaviour phenotypes, (3) exploring different MR approaches to test the robustness of our results, (4) extensively investigating the presence of bias that may be due to horizontal pleiotropy, and (5) using a two-sample MR to avoid statistical overfitting in comparison to a one-sample MR setting and providing an opportunity to substantially increase our study statistical power.

Our findings reinforce and extend the earlier observation that the minor allele carrier of several *ADIPOQ* loci showed

Table 2 Standardized mean difference, standard errors and *P* values of EB risk factors per allele of SNPs used in Mendelian randomization analyses

SNP	WC				BMI			
	β	SE	*P*	*N*	β	SE	*P*	*N*
rs864265	0.0100	0.0047	0.0330	229,735	0.0013	0.0022	0.5400	795,447
rs16861205	0.0077	0.0084	0.3600	136,176	0.0020	0.0033	0.5400	670,986
rs182052	− 0.0046	0.0045	0.3100	151,881	0.0010	0.0018	0.5700	691,079
rs17366568	0.0073	0.0087	0.4000	125,437	− 0.0006	0.0027	0.8300	659,138
rs3821799	0.0025	0.0045	0.5800	139,525	− 0.0025	0.0018	0.1500	673,736
rs3774261	− 0.0004	0.0035	0.9100	229,363	− 0.0031	0.0017	0.0600	791,528

After Bonferroni correction, only *P* values lower than 4.2×10^{-3} (0.05 ÷6 SNPs ÷2 phenotypes) were considered statistically significant. *BMI* body mass index, *WC* waist circumference, *β* beta coefficient, *SE* standard error, *N* sample size

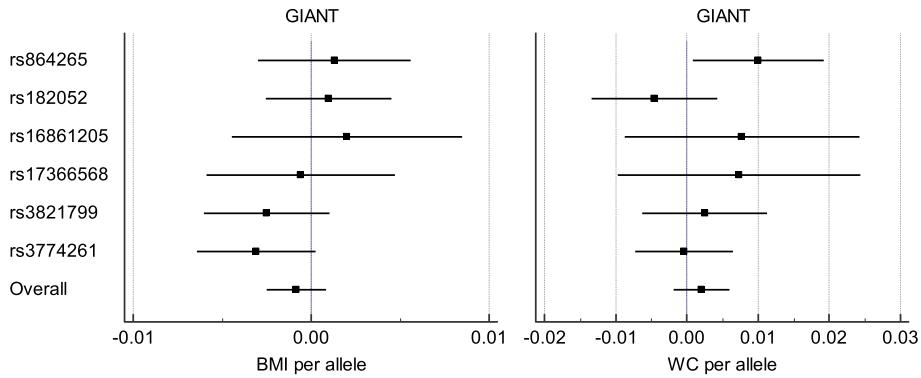

Fig. 2 Forest plots of mean difference in eating behaviour risk factors per allele of single nucleotide polymorphism (SNP). Analysis including six ADIPOQ SNPs associated with adiponectin at genome-wide significant levels ($P < 5 \times 10^{-8}$). Results for BMI and WC included 229,735 and 795,447 individuals, respectively, from GIANT consortium

elevated adiponectin levels along with increased disinhibition [37]. Interestingly, eating disinhibition, correlated with high amount of food intake, was demonstrated to be strongly related to overeating without hunger feelings in certain situational circumstances [47, 48]. It is thus plausible that the increased food intake serves as a positive feedback mechanism. As adiponectin levels are known nutritional compound influencer [14], they can activate adenosine monophosphate-activated protein kinase (AMPK)-mediated signaling through adiponectin receptor binding in the hypothalamus region of animal models [49, 50]. This mechanism seems to alter energy expenditure to cause overeating and ultimately increased body weight [49, 50]. Of note, eating disinhibition has been most consistently reported to be related with increased BMI and obesity [51].

Some limitations of this study should be considered. First, not all the genome-wide significant SNPs that predicted adiponectin levels were available in the outcome GWAS we used. Thus, we were not necessarily capturing the full variance with the included variants. In addition, we were not able to test for effect modification by age and gender because of the use of summary data only. In observational studies, the role of age and gender as modifiable factors of eating behaviour is well recognized [52–54]. Significant differences between male and female adiponectin serum levels have also been reported [37, 55]. Moreover, and surprisingly too, we did not find a positive association between circulating adiponectin and disinhibition in the MR-Egger analysis. This is generally inconsistent with results from other MR techniques and may likely indicate a false-negative finding. Notably, MR-Egger regression analysis yields less precise estimates than other MR methods, owing to a power penalty [36]. Further, we were not able to specifically assess the causal effect of the biologically active and high molecular weight adiponectin in this study. Although we explored the violation of the assumptions of MR, we cannot completely rule out bias due to independence and exclusion restriction assumptions. However, when we tested the association of our genetic instrument with the two available potential EB risk factors (i.e. BMI and WC), the genetic instrument showed no significant association with both. These results strengthen our estimates of the effect of blood adiponectin concentration on EB. Finally, MR studies require large sample sizes partly due to the very small amount of variation in the exposure explained by genetic instruments [33]. Thus, while we believe our study was sufficiently powered to

Table 3 Estimates of standardized mean difference, standard error, *P* values (and 95% confidence interval [CI]) of three eating behaviour factors per 1 U increase in genetically instrumented log adiponectin levels from various Mendelian randomization methods

MR method	EB factor restraint				EB factor disinhibition				EB factor hunger			
	β	SE	95% CI	*P*	*β*	SE	95% CI	*P*	*β*	SE	95% CI	*P*
IVW	0.17	1.03	− 1.85, 2.18	0.87	3.05	1.00	1.10, 5.00	0.002	1.63	1.22	− 0.75, 4.01	0.18
Weighted median	0.98	1.15	− 1.28, 3.24	0.40	2.66	1.11	0.48, 4.84	0.02	1.23	1.09	− 0.90, 3.36	0.26
Weighted modal	1.07	1.12	− 1.12, 3.26	0.34	2.63	1.07	0.54, 4.73	0.01	1.12	1.03	− 0.90, 3.14	0.28
MR Egger	3.85	2.23	− 0.52, 8.21	0.08	− 0.32	2.23	− 4.69, 4.04	0.88	− 1.53	2.74	− 6.89, 3.83	0.58
Constant[†]	− 0.25	0.14	− 0.53, 0.02	0.07	0.23	0.14	− 0.04, 0.51	0.10	0.22	0.17	− 0.12, 0.55	0.20

CI confidence interval, *U* unit, *EB* eating behaviour, *IVW* inverse-variance weighted regression method, *β* beta coefficient, *SE* standard error
[†]MR-Egger intercept

detect relatively small effects, our analysis may have been underpowered to detect, perhaps, very small causal effects operating at the extremes of adiponectin distribution in eating restraint or hunger.

Conclusion

In conclusion, our MR study reported a potential association between circulating adiponectin and eating disinhibition and could have potential implications on pathological disorders which include anorexia nervosa, bulimia nervosa and binge eating.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s43042-019-0022-5.

Additional file 1: Table S1. Estimated Standardized Mean Difference and Standard Errors of EB Factors Per Allele of SNPs Based on Allelic Model of Inheritance on Summary Data from Rohde et al paper [37].

Additional file 2: Table S2. Standardized Mean Difference (and 95% Confidence Interval [CI]) in Eating Behaviour Risk Biomarkers Per 1 U Increase in Genetically Instrumented Log Adiponectin Levels.

Abbreviations

ADIPOQ: Adiponectin gene; AMPK: Adenosine monophosphate-activated protein kinase; ARL15: ADP-ribosylation factor-like 15 gene locus; BMI: Body mass index; CDH13: Cadherin 13 gene locus; CEU: Central European; CI: Confidence interval; EB: Eating behaviour; GIANT: Genetic Investigation of Anthropometric Traits; GWAS: Genome-wide association studies; IVW: Inverse-variance weighted; KNG: Kininogen gene locus; MR: Mendelian randomization; SAS: Statistical analysis system; SE: Standard error; SNP: Single-nucleotide polymorphisms; WC: Waist circumference

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Authors' contributions

AAA conceived the study and the analysis plan, participated in its design and coordination, performed the statistical analyses and drafted the manuscript. OEO participated in the design of the study, assisted in the data acquisition (from public databases) and helped to draft the manuscript. KOA participated in study supervision and coordination, analysis plan and data interpretation. SAO carried out data acquisition and assisted in the statistical analyses. All authors read and approved the final manuscript.

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Availability of data and materials

Data on adiponectin have been contributed by ADIPOGen consortium and have been downloaded from https://www.mcgill.ca/genepi/adipogen-consortium. Data on eating behaviour factors have been contributed by Rohde and colleagues and have been extracted from *Genes Nutr* (2015) 10:1 (see reference [37]). Data on anthropometric traits have been contributed by Genetic Investigation of ANthropometric Traits (GIANT) consortium and have been downloaded from http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. All the data used are publicly available.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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