See corresponding editorial on page 429.

# The role of eating behavior traits in mediating genetic susceptibility to obesity

*Raphaëlle Jacob,*[1,2,3] *Vicky Drapeau,*[1,3,4] *Angelo Tremblay,*[1,3,5] *Véronique Provencher,*[1,2] *Claude Bouchard,*[6] *and Louis Pérusse*[1,5]

[1]Institute of Nutrition and Functional Foods (INAF); [2]School of Nutrition; [3]Quebec Heart and Lung Institute Research Center; [4]Department of Physical Education, Faculty of Educational Sciences; and [5]Department of Kinesiology, Faculty of Medicine, Laval University, Quebec, Canada; and [6]Pennington Biomedical Research Center, Baton Rouge, LA

## ABSTRACT

**Background:** Genome-wide association studies (GWASs) have identified several genes associated with obesity. The mechanisms through which these genes affect body weight are not fully characterized. Recent studies suggest that eating behavior (EB) traits could be involved, but only a few EB traits were investigated.

**Objective:** This study aimed to investigate whether genetic susceptibility to obesity is mediated by EB traits (cognitive restraint, disinhibition, hunger) and their subscales. We hypothesized that EB traits, and their subscales, partly mediate this association.

**Design:** Adult individuals ($n = 768$) who participated in the Quebec Family Study were included in this cross-sectional study. A genetic risk score (GRS) of obesity was calculated based on the 97 genetic variants recently identified in a GWAS meta-analysis of body mass index (BMI). EB traits and their subscales were assessed with the use of the Three-Factor Eating Questionnaire. Regression analyses with age and sex as covariates were used to investigate the associations between GRS, EB traits, BMI, and WC and whether the association between GRS and obesity is mediated by EB traits, which represents the indirect effect of GRS on obesity.

**Results:** The GRS of obesity was positively associated with BMI ($\beta = 0.19 \pm 0.04$, $P < 0.0001$) and WC ($\beta = 0.46 \pm 0.10$, $P < 0.0001$). Regression analyses also revealed that the association between GRS of obesity and BMI was partly mediated by disinhibition and susceptibility to hunger ($\beta_{\text{indirect}} = 0.09 \pm 0.03$, $P = 0.0007$, and $\beta_{\text{indirect}} = 0.04 \pm 0.02$, $P = 0.02$, respectively). Habitual and situational susceptibility to disinhibition ($\beta_{\text{indirect}} = 0.08 \pm 0.03$, $P = 0.002$ and $\beta_{\text{indirect}} = 0.05 \pm 0.02$, $P = 0.003$, respectively) as well as internal and external locus of hunger ($\beta_{\text{indirect}} = 0.03 \pm 0.02$, $P = 0.03$ for both) were also found to mediate the association between GRS of obesity and BMI. The same trends were observed with WC.

**Conclusions:** The results of this study indicate that the genetic susceptibility to obesity is partly mediated through undesirable EB traits, which suggests that they could be targeted in obesity treatment and prevention. This trial was registered at clinicaltrials.gov as NCT03355729. *Am J Clin Nutr* 2018;108:445–452.

**Keywords:** obesity, genetic, eating behavior traits, susceptibility to obesity, genetic risk score, cognitive restraint, disinhibition, susceptibility to hunger, adults

## INTRODUCTION

It is estimated that 40–70% of the variability in BMI is explained by genetic factors (1), suggesting a strong inherited component to obesity. Recently, a meta-analysis of genome-wide association studies (GWASs) identified a total of 97 genetic variants associated with BMI (2). The mechanisms through which these obesity-associated genetic variants influence body weight are not well understood, but it has been suggested that they may partly exert their influence on body weight by affecting appetitive, or eating behavior (EB) traits that lead some individuals to eat beyond their needs (3).

Results from the Quebec Family Study (QFS) have shown that EB traits, such as higher levels of disinhibition, which refers to the overconsumption of food associated with a loss of control, and of susceptibility to hunger (i.e., perceived sensation

Supported by the Canadian Institutes of Health Research (CIHR). The Quebec Family Study was supported over the years by multiple grants from the Medical Research Council of Canada and the CIHR (PG-11811, MT-13960, and GR-15187) as well as other agencies. RJ is the recipient of a PhD scholarship from the Fonds de recherche du Québec—Santé (FRQS). AT is the holder of the Canada Research Chair in Environment and Energy Balance. CB is partially funded by the John W Barton, Sr Chair in Genetics and Nutrition.

The CIHR was not involved in designing and conducting the study; in analysis or interpretation of the data; or in preparation and review of the manuscript before submission.

Address correspondence to LP (e-mail: louis.perusse@kin.ulaval.ca).

Abbreviations used: EB, eating behavior; GRS, genetic risk score; GWAS, genome-wide association study; QFS, Quebec Family Study; SNP, single nucleotide polymorphism; TFEQ, Three-Factor Eating Questionnaire; WC, waist circumference.

Received November 28, 2017. Accepted for publication May 18, 2018.

First published online July 5, 2018; doi: https://doi.org/10.1093/ajcn/nqy130.

  

of hunger triggered by internal or external cues) (4), were better predictors of overweight/obesity and weight gain than were more common risk factors such as nonparticipation in high-intensity physical activity and high lipid intake (i.e., ≥40% total energy intake from fat per day) (5). We have also shown that cognitive restraint (i.e., cognitive control over food intake) was not associated with weight gain, whereas its subscale rigid control showed a significant association (6). The heritability of EB traits has been demonstrated among different populations (7, 8), including among participants of the QFS (9). Several genetic variants located in chromosomal regions linked to obesity have been associated with cognitive restraint, disinhibition, and susceptibility to hunger in the QFS (10–12) and other studies (13–16).

The literature thus briefly reviewed suggests that obesity and EB traits are influenced by genetic factors. Considering the links between EB traits and obesity, it is likely that genes influencing obesity may partly exert their effects on body weight through EB traits. Only a few studies have investigated the role of EB traits in mediating the association between genetic susceptibility to obesity, assessed by the contributions of multiple obesity-related genetic variants aggregated into a genetic risk score (GRS), and body weight. Two studies performed in children showed that the association between either a GRS comprised of 32 obesity genetic variants or the fat mass and obesity-associated (*FTO*) gene and BMI was partly mediated by a low satiety responsiveness (17, 18). In another study based on adults, it was observed that the association between a GRS comprised of 90 obesity-related genetic variants and BMI as well as waist circumference (WC) was partly mediated by uncontrolled and emotional eating (19). Similar results have been observed in a recent study among adults (20). In those studies, only a few EB traits were tested, which justifies the need to assess if other dimensions of EB traits mediate genetic susceptibility to obesity. In this regard, the subscales described by Westenhoefer et al. (21) and Bond et al. (22) are of interest because they capture different aspects of EB traits that were not considered in previous studies (19, 20). Addressing whether EB traits and their subscales mediate genetic susceptibility to obesity is of great interest for obesity treatment and prevention.

The aim of this study was to investigate whether EB traits and their subscales, assessed with the full version of the Three-Factor Eating Questionnaire (TFEQ), mediate genetic susceptibility to obesity. We hypothesized that EB traits, and their subscales, partly mediate genetic susceptibility to obesity.

## METHODS

### Participants

The present cross-sectional study included 768 adult subjects (330 men, 438 women) from the QFS (NCT03355729). The general aim of the QFS was to investigate the role of genetic factors in physical fitness, obesity, risk factors for common diseases, and health-related behaviors (23). Participants were recruited through the media and were French Canadians from the greater Quebec City area. Additional details about the QFS have been previously published (23). The inclusion criteria of the present study were to be aged between 18 and 80 y, nonsmokers, not pregnant at the time of the study, have a stable body weight (±5 kg) during the 6 mo preceding testing, be free of any metabolic conditions (e.g., diabetes or hypertension), and not taking medication that could interfere with the study outcomes. Moreover, participants selected for the present study were those for whom genotype data for all the 97 obesity-associated single nucleotide polymorphisms (SNPs) from the recent GWAS meta-analysis of BMI (2) were available. **Figure 1** shows the flowchart diagram of participant selection. Each participant provided written informed consent and the study was approved by the Laval University Research Ethics Committee.

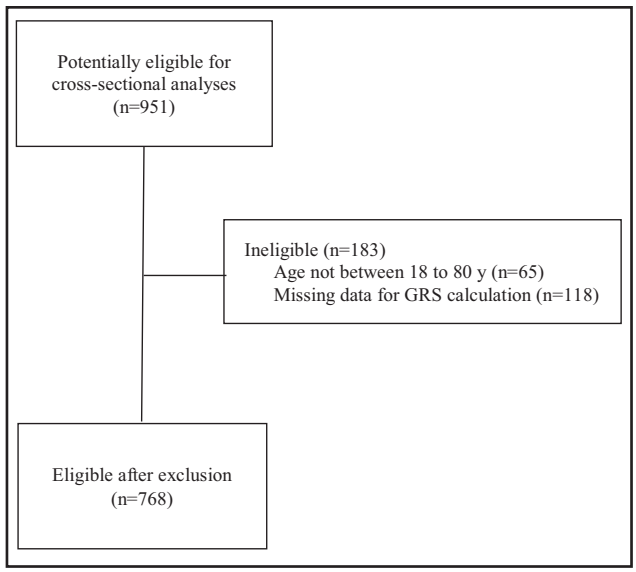


**FIGURE 1** Flowchart diagram of participant selection. The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. GRS, genetic risk score of obesity.

### Measurements

*Anthropometric measurements*

Body weight was taken with a standard beam scale to the nearest 0.1 kg and height was measured to the nearest 0.1 cm with the use of a standard stadiometer. BMI was calculated as kg/m$^2$. WC was measured with a standard tape. All measurements were performed according to standardized laboratory procedures recommended at the Airlie Conference (24).

*EB traits*

EB traits were measured with the use of a French version (25) of the TFEQ (4). This questionnaire is the most widely used to assess the 3 main dimensions of EB traits, namely cognitive restraint, disinhibition, and susceptibility to hunger. This validated questionnaire comprises 51 items, of which 36 items have a true or false format and the remaining 15 items constitute statements answered on a 4-point scale. Each item is scored 0 or 1. Cognitive restraint is defined as the intention to restrain food intake to lose or control body weight and is measured by 21 items. Cognitive restraint has 2 main subscales, i.e., rigid (7 items) and flexible (7 items) control

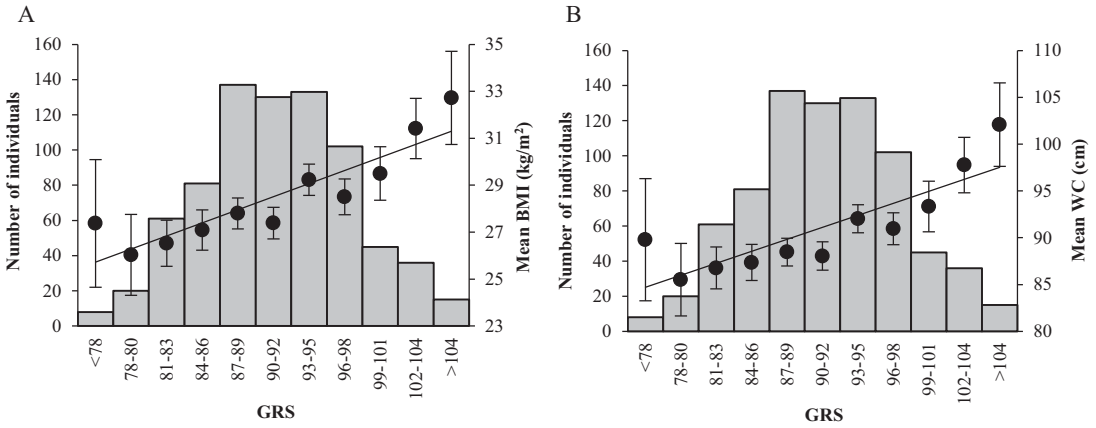


**FIGURE 2** Regression of age- and sex-adjusted mean BMI (A) and WC (B) across obesity (BMI) GRSs. Black dots: age- and sex-adjusted mean BMI ± SEM (A) and age- and sex-adjusted mean WC ± SEM (B) in each obesity (BMI) GRS category ($n = 768$). Black line: the linear regression between GRS and BMI adjusted for age and sex ($\beta = 0.19 \pm 0.04$, $P < 0.0001$, $R^2 = 2.50\%$), $n = 768$ (A) and the linear regression between GRS and WC adjusted for age and sex ($\beta = 0.46 \pm 0.10$, $P < 0.0001$, $R^2 = 2.81\%$), $n = 754$ (B). The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. GRS, genetic risk score; WC, waist circumference.

over food intake (21), and also measures 3 other specific EB traits, which are strategic dieting behavior (4 items), attitude to self-regulation (5 items), and avoidance of fattening foods (4 items) (22). Disinhibition, measured with 16 items, is defined as overconsumption of food associated with a loss of control over eating triggered by habitual (5 items), emotional (3 items), or situational (5 items) cues representing the 3 disinhibition subscales (22). Lastly, 14 items measure susceptibility to hunger as well as internal locus of hunger (7 items) and external locus of hunger (7 items) as its subscales (22). The TFEQ was completed in a total of 602 participants.

### *Genotyping and GRS*

A GWAS was performed in QFS participants with the use of the Illumina Human610 Quad BeadChips (Illumina, Inc.), as described elsewhere (26). The 97 obesity-related SNPs identified in the most recent genome-wide association meta-analysis of BMI (2) were used to calculate a GRS for obesity. More specifically, the GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 SNPs, so that the GRS obtained for each participant may theoretically vary between 0 and 194.

### Statistical analysis

Anthropometric variables and EB traits are expressed as mean ± SD. Differences in anthropometric variables and in EB traits between men and women were assessed via Student's *t* tests. The association between the obesity GRS and obesity, with BMI and WC as dependent variables, was assessed through the use of linear regression analyses after adding sex and age as covariates in the models. To show its distribution, the GRS was separated into 11 categories, each comprised of 3 different values of the GRS, based on its median value (i.e., 91) (**Figure 2**A, B). Mean BMI and WC within each GRS category were assessed with the use of a general linear model and are reported as mean ± SEM. To assess whether EB traits mediate the association between GRS and obesity, partial correlations (with age and sex as covariates) were first computed to identify potential mediation models, according to Baron and Kenny conditions (27). Thereafter, all EB traits significantly associated with both GRS and BMI or WC were tested for mediation, which consisted of a series of linear regressions followed by the Sobel test to assess the significance of the mediation effect (27). A significant mediation effect occurs when the product of "a" [i.e., the $\beta$ coefficient of the association between the independent variable (i.e., GRS) and the mediator (i.e., EB traits)] and "b" [i.e., the $\beta$ coefficient of the association between the mediator (i.e., EB traits) and the dependent variable (i.e., BMI or WC)] reaches significance. The product of "a" and "b" is also referred to as the "indirect effect" through which GRS can affect BMI or WC. In addition, whether or not the direct association "c'" between the GRS and BMI or WC remained significant when the mediator was added as a covariate into the regression model indicates a partial or a full mediation effect, respectively. Because of sex differences in EB traits, we also tested if sex could be a possible moderator in the mediation analyses by adding an interaction term between the independent variable and sex in the regression analyses. The significance level was set to a 2-sided *P* value of <0.05. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

## RESULTS

### Participant characteristics

This study was conducted among 768 men and women with a mean ± SD age of 43.5 ± 15.5 y and a mean ± SD BMI and WC of 28.2 ± 7.8 and 90.0 ± 18.4 cm, respectively (**Table 1**). Based on these anthropometric data, 29% of the participants were obese (BMI ≥ 30.0) and 27% of men and 36% of women had abdominal obesity (WC ≥ 102 cm and ≥88 cm for men and women, respectively). The mean GRS for obesity was 91.4 ± 6.3, with a range between 74 and 114. No sex difference was observed for the GRS of obesity. Cognitive restraint and disinhibition were higher in women compared with men ($P < 0.0001$) and no sex difference was observed for susceptibility to hunger ($P = 0.45$). All cognitive

**TABLE 1**
Participant characteristics and EB traits[1]

| Variables | All | Men | Women | $P$[2] |
|---|---|---|---|---|
| Sex, *n* (%) | — | 330 (43.0) | 438 (57.0) | 0.001 |
| Age, y | 43.5 ± 15.5 | 43.8 ± 15.6 | 43.3 ± 15.3 | 0.70 |
| BMI, kg/m$^2$ | 28.2 ± 7.8 | 27.8 ± 6.6 | 28.5 ± 8.6 | 0.23 |
| Waist circumference, cm | 90.0 ± 18.4 | 95.1 ± 16.8 | 86.1 ± 18.6 | <0.0001 |
| Weight, kg | 77.3 ± 21.9 | 83.2 ± 20.5 | 72.8 ± 21.9 | <0.0001 |
| GRS of obesity | 91.4 ± 6.3 | 91.3 ± 6.2 | 91.4 ± 6.5 | 0.86 |
| Cognitive restraint | 7.3 ± 4.5 | 5.9 ± 3.8 | 8.2 ± 7.8 | <0.0001 |
| Rigid control | 1.9 ± 1.8 | 1.3 ± 1.5 | 2.3 ± 1.8 | <0.0001 |
| Flexible control | 2.6 ± 1.7 | 2.3 ± 1.5 | 2.9 ± 1.6 | <0.0001 |
| Strategic dieting behavior | 0.9 ± 1.2 | 0.7 ± 1.0 | 1.0 ± 1.3 | 0.0003 |
| Avoidance of fattening foods | 1.9 ± 1.2 | 1.5 ± 1.0 | 2.1 ± 1.2 | <0.0001 |
| Attitude to self-regulation | 2.1 ± 1.4 | 1.8 ± 1.3 | 2.2 ± 1.5 | 0.0001 |
| Disinhibition | 5.5 ± 3.4 | 4.6 ± 3.1 | 6.0 ± 3.5 | <0.0001 |
| Habitual susceptibility | 1.0 ± 1.2 | 0.7 ± 1.0 | 1.2 ± 1.3 | <0.0001 |
| Emotional susceptibility | 1.0 ± 1.2 | 0.5 ± 1.0 | 1.3 ± 1.3 | <0.0001 |
| Situational susceptibility | 1.9 ± 1.5 | 1.9 ± 1.5 | 1.9 ± 1.5 | 0.80 |
| Susceptibility to hunger | 4.1 ± 3.3 | 4.2 ± 3.5 | 4.0 ± 2.2 | 0.45 |
| Internal locus of hunger | 1.5 ± 1.8 | 1.6 ± 1.9 | 1.4 ± 1.7 | 0.35 |
| External locus of hunger | 1.7 ± 1.5 | 1.7 ± 1.5 | 1.7 ± 1.5 | 0.92 |

[1] $n = 768$ for sex, age, BMI, weight, and GRS of obesity; $n = 754$ for waist circumference; $n = 595$–$602$ for EB traits. The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. Values are means ± SDs unless otherwise indicated. EB, eating behavior; GRS, genetic risk score.
[2] $P$ values indicate differences between men and women as per Student's $t$ test.

restraint subscales ($P < 0.001$) as well as habitual and emotional susceptibility to disinhibition ($P < 0.0001$) were also higher in women than in men (Table 1).

### Association between GRS of obesity and obesity

Figure 2A, B show a normal distribution of the GRS of obesity. After adjustment for age and sex, the GRS was positively associated with BMI ($\beta = 0.19 \pm 0.04$, $P < 0.0001$) and with WC ($\beta = 0.46 \pm 0.10$, $P < 0.0001$). However, GRS only explained a small percentage of the variance in these anthropometric traits (i.e., 2.50% for BMI and 2.81% for WC).

### Associations among EB traits, genetic susceptibility to obesity, and obesity

Cognitive restraint showed no association with GRS nor with BMI or WC (**Table 2**). No association was also observed for the 5

**TABLE 2**
Associations between EB traits, GRS of obesity, BMI, and WC[1]

| | GRS | | BMI | | WC | |
|---|---|---|---|---|---|---|
| EB traits | $r$ | $P$ | $r$ | $P$ | $r$ | $P$ |
| Cognitive restraint | 0.04 | 0.36 | −0.02 | 0.56 | −0.04 | 0.36 |
| Rigid control | 0.04 | 0.28 | 0.08 | 0.04 | 0.08 | 0.06 |
| Flexible control | 0.03 | 0.53 | −0.09 | 0.03 | −0.12 | 0.003 |
| Strategic dieting behavior | 0.05 | 0.20 | −0.03 | 0.44 | −0.04 | 0.35 |
| Avoidance of fattening foods | −0.003 | 0.94 | −0.01 | 0.72 | −0.02 | 0.63 |
| Attitude to self-regulation | 0.04 | 0.31 | 0.01 | 0.89 | 0.002 | 0.96 |
| Disinhibition | 0.14 | 0.0005 | 0.50 | <0.0001 | 0.51 | <0.0001 |
| Habitual susceptibility | 0.13 | 0.002 | 0.49 | <0.0001 | 0.49 | <0.0001 |
| Emotional susceptibility | 0.04 | 0.36 | 0.37 | <0.0001 | 0.38 | <0.0001 |
| Situational susceptibility | 0.13 | 0.001 | 0.31 | <0.0001 | 0.32 | <0.0001 |
| Susceptibility to hunger | 0.10 | 0.01 | 0.32 | <0.0001 | 0.31 | <0.0001 |
| Internal locus of hunger | 0.10 | 0.02 | 0.28 | <0.0001 | 0.27 | <0.0001 |
| External locus of hunger | 0.09 | 0.03 | 0.31 | <0.0001 | 0.29 | <0.0001 |

[1] Values are Pearson correlation coefficients ($r$), adjusted for age and sex. Correlations between EB traits and GRS: $n = 595$–$601$; correlations between EB traits and BMI: $n = 595$–$602$; correlations between EB traits and WC: $n = 592$–$598$. The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. EB, eating behavior; GRS, genetic risk score; WC, waist circumference.

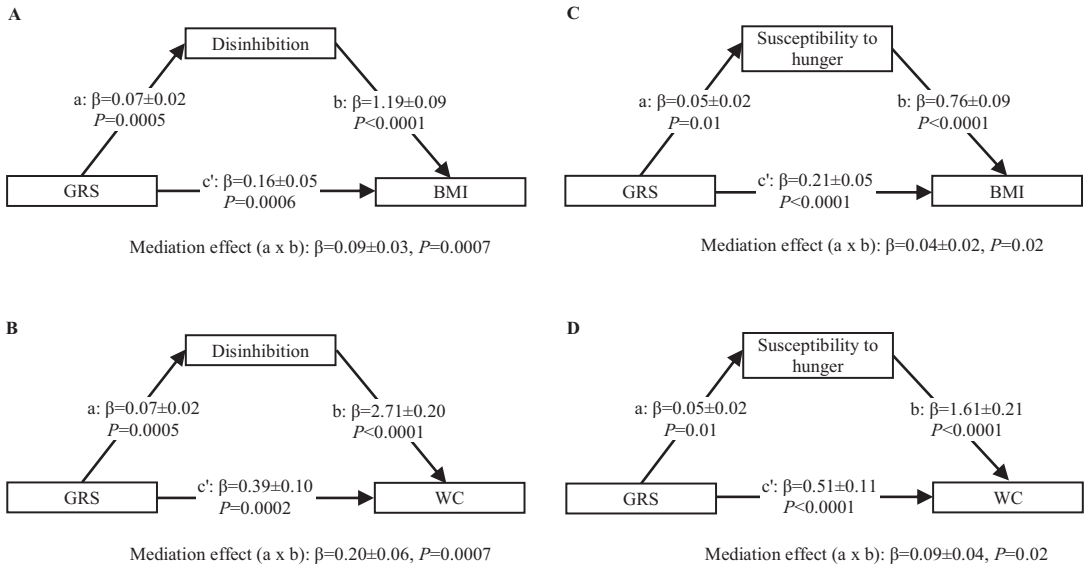


**FIGURE 3** Mediation models of the association between GRS of obesity and BMI or WC. (A) Mediation effect of disinhibition on the association between GRS and BMI, (B) mediation effect of disinhibition on the association between GRS and WC, (C) mediation effect of susceptibility to hunger on the association between GRS and BMI, and (D) mediation effect of susceptibility to hunger on the association between GRS and WC. Mediations are from linear regression models. All regression analyses were adjusted for age and sex. c' represents the association between GRS and BMI (A, C) or WC (B, D) when the mediating variable (i.e., disinhibition or susceptibility to hunger) is in the model. The product of a and b paths (a × b) represents the mediation effect (or the indirect effect) of EB traits on the association between GRS and BMI or WC and the significant mediation effect is assessed by the Sobel test. $n = 598$–$601$. The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. GRS, genetic risk score; WC, waist circumference.

cognitive restraint subscales with GRS. However, flexible control showed a negative association with BMI and WC ($P = 0.03$ and $P = 0.003$, respectively), whereas rigid control was weakly but positively associated with BMI ($P = 0.04$). The 3 remaining cognitive restraint subscales were not associated with adiposity measures. Disinhibition was positively associated with GRS ($P = 0.0005$) and with BMI and WC ($P < 0.0001$). Habitual and situational susceptibility to disinhibition were also both positively associated with GRS ($P = 0.002$ and $P = 0.001$, respectively) and with BMI and WC ($P < 0.0001$). Emotional susceptibility to disinhibition was positively associated with BMI and WC ($P < 0.0001$), but not with GRS. Susceptibility to hunger and its subscales were all positively associated with GRS ($0.03 \geq P \geq 0.01$) and with BMI and WC ($P < 0.0001$).

Based on these results, disinhibition, habitual and situational susceptibility to disinhibition, susceptibility to hunger, and internal and external locus of hunger were tested for mediation between GRS and obesity. Cognitive restraint and all its subscales were not tested for mediation, because none of these EB traits were significantly associated with both the GRS and the adiposity measures (BMI or WC).

### EB traits as mediators of genetic susceptibility to obesity

Disinhibition significantly mediated the association between GRS and BMI ($\beta_{\text{indirect}} = 0.09 \pm 0.03$, $P = 0.0007$, **Figure 3**A) as well as WC ($\beta_{\text{indirect}} = 0.20 \pm 0.06$, $P = 0.0007$, Figure 3B). Because the direct associations between GRS and BMI ($\beta$ (c') $= 0.16 \pm 0.05$, $P = 0.0006$, Figure 3A) and between GRS and WC ($\beta$ (c') $= 0.39 \pm 0.10$, $P = 0.0002$, Figure 3B) remained significant after disinhibition was added as a covariate in the regression models, disinhibition was identified as a partial mediator of these associations. Susceptibility to hunger was also identified as a partial mediator of the association between GRS and BMI ($\beta_{\text{indirect}} = 0.04 \pm 0.02$, $P = 0.02$, Figure 3C) and WC ($\beta_{\text{indirect}} = 0.09 \pm 0.04$, $P = 0.02$, Figure 3D). The subscales habitual and situational susceptibility to disinhibition ($P = 0.003$ or $P = 0.002$, depending on the associations) and internal and external locus of hunger ($P = 0.03$ for each association) were all identified as partial mediators of the associations between GRS and BMI and between GRS and WC (**Table 3**). Sex did not moderate any of the mediations (data not shown).

## DISCUSSION

Understanding how genetic susceptibility to obesity affects body weight is of great relevance from a perspective of obesity treatment and prevention. To the best of our knowledge, this is the first study designed to investigate whether TFEQ-EB traits and their subscales, using the full version of the TFEQ, mediate genetic susceptibility to obesity. The results indicate that genetic susceptibility to obesity is partly mediated by disinhibition, susceptibility to hunger, and the subscales habitual and situational susceptibility to disinhibition and internal and external locus of hunger. These results add further support to the hypothesis that EB traits are one mechanism by which genes are thought to influence body weight.

As mentioned above, Konttinen et al. (19) previously showed that among adults, the association between a GRS of obesity and BMI or WC was partly mediated by uncontrolled eating and emotional eating, and the results for the association between GRS and BMI were recently replicated by de Lauzon-Guillain et al. (20). In the Konttinen et al. study, these 2 EB traits explained a

**TABLE 3**
Mediation models between GRS of obesity, EB traits (subscales), and BMI or WC[1]

| | a | | b | | c′ | | a × b | |
|---|---|---|---|---|---|---|---|---|
| | $\beta \pm$ SE | $P$ | $\beta \pm$ SE | $P$ | $\beta \pm$ SE | $P$ | $\beta \pm$ SE | $P$[2] |
| BMI | | | | | | | | |
| Habitual susceptibility | 0.03 ± 0.01 | 0.002 | 3.20 ± 0.24 | <0.0001 | 0.16 ± 0.05 | 0.0004 | 0.08 ± 0.03 | 0.002 |
| Situational susceptibility | 0.03 ± 0.01 | 0.001 | 1.59 ± 0.21 | <0.0001 | 0.19 ± 0.05 | 0.0002 | 0.05 ± 0.02 | 0.003 |
| Internal locus of hunger | 0.03 ± 0.01 | 0.02 | 1.23 ± 0.18 | <0.0001 | 0.21 ± 0.05 | <0.0001 | 0.03 ± 0.02 | 0.03 |
| External locus of hunger | 0.02 ± 0.01 | 0.03 | 1.56 ± 0.21 | <0.0001 | 0.21 ± 0.05 | <0.0001 | 0.03 ± 0.02 | 0.03 |
| WC | | | | | | | | |
| Habitual susceptibility | 0.03 ± 0.01 | 0.002 | 7.03 ± 0.53 | <0.0001 | 0.41 ± 0.10 | <0.0001 | 0.18 ± 0.06 | 0.002 |
| Situational susceptibility | 0.03 ± 0.01 | 0.001 | 3.67 ± 0.47 | <0.0001 | 0.47 ± 0.11 | <0.0001 | 0.12 ± 0.04 | 0.002 |
| Internal locus of hunger | 0.03 ± 0.01 | 0.02 | 2.55 ± 0.40 | <0.0001 | 0.52 ± 0.11 | <0.0001 | 0.07 ± 0.03 | 0.03 |
| External locus of hunger | 0.02 ± 0.01 | 0.03 | 3.38 ± 0.47 | <0.0001 | 0.51 ± 0.11 | <0.0001 | 0.07 ± 0.03 | 0.03 |

[1]Values are regression coefficients ± SEs from linear regression models adjusted for age and sex. a: association between GRS (independent variable) and EB trait (mediator); b: association between EB trait (mediator) and BMI or WC (dependent variables); c′: association between GRS and BMI or WC controlled for EB trait (mediator); a × b: mediation effect or indirect effect through which GRS influences BMI or WC (product of a and b). $n$ = 597–602. The GRS was calculated by adding up the number of risk alleles (i.e., 0, 1, or 2) at each of the 97 obesity-related single nucleotide polymorphisms identified in the most recent meta-analysis of BMI. EB, eating behavior; GRS, genetic risk score; WC, waist circumference.

[2]Sobel test indicating the mediation effect.

small part of the association between GRS and obesity, because $\beta$ coefficients for the indirect associations observed in this study ranged between 0.01 and 0.03 (19). Uncontrolled eating, as assessed by the TFEQ-R18, reflects a combination of items from the disinhibition and susceptibility to hunger scales from the full TFEQ, and emotional eating is the same EB trait as the subscale emotional susceptibility to disinhibition of the full TFEQ and represents a tendency to eat in response to negative emotions (21, 28). Thus, the results of the present study are in accordance with those of this previous study because disinhibition and susceptibility to hunger were both identified as partial mediators of the association between GRS and BMI and WC. However, these 2 EB traits represent substantially higher indirect effects through which GRS affects BMI or WC in the present study (i.e., $\beta_{\text{indirect}}$ coefficients ranging between 0.04 and 0.20), although these indirect effects are relatively modest considering the low reduction in the direct effects (c' paths) when the mediators were added into the models. A discordant result was observed between the present study and the 2 previous studies based on adults. Indeed, no association was observed between the subscale emotional susceptibility to disinhibition and GRS in the present study, so it could not be tested for mediation, whereas emotional eating was identified as a partial mediator of genetic susceptibility to obesity in the Konttinen et al. and de Lauzon-Guillain et al. studies (19, 20). However, the association between GRS and emotional eating or emotional susceptibility to disinhibition was weak in all studies [e.g., $r = 0.07$, $P < 0.001$ in the Konttinen et al. study (19) and $r = 0.04$, $P = 0.36$ in the present study] and this could explain, at least in part, why no significant correlation was observed in the present sample. More studies are thus needed to investigate this discordant result. Taken together, and in addition with studies among children that showed that genetic susceptibility to obesity was partly explained by a lower satiety responsiveness (17, 18), these findings suggest that genetic susceptibility to obesity may be reflected by the presence of EB traits that favor overeating leading to weight gain and obesity. Whether a low satiety responsiveness (29) or a low satiety efficiency (30) represent behavioral pathways through which genetic susceptibility to obesity affects body weight among adults remains to be investigated in the future.

The genome-wide meta-analysis of BMI from Locke et al. (2) reported that the GRS of obesity based on 97 genetic variants explained 2.7% of the variation in BMI. Using a GRS of obesity based on the same genetic variants, the present study showed that 2.5% and 2.8% of the variance in BMI and WC, respectively, was explained by these genetic variants. Although the GRS used in the present study was based on variants associated with BMI, we used it in the analysis of WC because both traits are highly correlated ($r = 0.95$, $P < 0.0001$). We considered that a GRS based on BMI variants was more relevant than a GRS based on the 49 genetic variants recently identified in a GWAS meta-analysis of waist-to-hip ratio (31) to assess the genetic susceptibility to obesity. Similar results were also observed by Celis-Morales et al. (32) and by de Lauzon-Guillain et al. (20) when using a weighted GRS of obesity comprising respectively 93 and 96 out of the 97 SNPs from the Locke et al. genome-wide meta-analysis. Although the variance explained by the GRS in these anthropometric traits is small, heritability estimates suggest that genetic factors may play a more important role in the etiology of obesity than the percentage of variance yet accounted for by genetic variants (1).

The results pertaining to the associations between GRS of obesity and EB traits are in accordance with previously reported results of the QFS. For instance, it was shown that the heritability estimates of these traits, which included both genetic and shared familial environment factors, were higher for susceptibility to hunger and disinhibition than for cognitive restraint (9). Several loci linked with disinhibition and susceptibility to hunger were also found in the QFS but no loci were associated with cognitive restraint in the same study (10). Moreover, because disinhibition and susceptibility to hunger have been more consistently positively associated with BMI than cognitive restraint (33–35), it is not surprising that the GRS of obesity was more correlated with these EB traits.

This study has several strengths but also some limitations that need to be outlined. First, to the best of our knowledge, this is the first time that the mediating effect of EB traits in the association between genetic susceptibility to obesity and obesity has been tested with the use of the full version of the TFEQ, allowing the capture of more refinement and distinct aspects of EB traits with the 3 main EB traits subscales. Moreover, these mediating effects were tested with the use of a GRS based on all of the 97 obesity-related genetic variants identified so far. The main limitation of the present study is its cross-sectional design that does not allow us to determine directionality between variables. Even though the association between EB traits and obesity may be bidirectional, disinhibition and susceptibility to hunger were previously identified as predictors of weight gain in a longitudinal setting of the QFS (5), which is consistent with the direction of associations tested in the mediation models in the present study. These mediation models need to be tested longitudinally.

In conclusion, the results of this study indicate that disinhibition, susceptibility to hunger, and the subscales habitual and situational susceptibility to disinhibition and internal and external locus of hunger may constitute behavioral pathways through which genetic susceptibility to obesity influences BMI and WC. These results imply that genes may partly influence obesity through undesirable EB traits. Because these variables partly mediated the genetic susceptibility to obesity, other mechanisms or behaviors not investigated in the present study could also represent potential pathways in the association between genetic and obesity. This study highlights the relevance to target EB traits in individuals at risk of overweight and obesity from a perspective of obesity treatment and prevention. Nevertheless, intervention studies are needed to investigate the best approaches to reduce undesirable EB traits or increase the ability to cope with these EB traits, in individuals having a high genetic susceptibility to obesity.

We thank Christian Couture for his help in the statistical analyses.

The authors' contributions were as follows—LP, VD, and AT: designed the research; RJ: performed the statistical analysis and wrote the first draft of the manuscript; LP: had primary responsibility for the final content of the manuscript; and all authors: critically revised the manuscript, contributed intellectually to its development, and provided final approval of the submitted manuscript. The authors declare that they have no conflicts of interest related to the study.

## REFERENCES

1. Pérusse L, Rice TK, Bouchard C. Evidence of a genetic component to obesity from genetic epidemiology. In: G Bray, C Bouchard, editors. Handbook of obesity: epidemiology, etiology, and physiopathology. Boca Raton, FL: CRC Press; 2013. p. 91–104.
2. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206.
3. Llewellyn C, Wardle J. Behavioral susceptibility to obesity: gene-environment interplay in the development of weight. Physiol Behav 2015;152:494–501.
4. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29:71–83.
5. Chaput JP, Leblanc C, Perusse L, Despres JP, Bouchard C, Tremblay A. Risk factors for adult overweight and obesity in the Quebec Family Study: have we been barking up the wrong tree? Obesity (Silver Spring) 2009;17:1964–70.
6. Drapeau V, Provencher V, Lemieux S, Despres JP, Bouchard C, Tremblay A. Do 6-y changes in eating behaviors predict changes in body weight? Results from the Quebec Family Study. Int J Obes Relat Metab Disord 2003;27:808–14.
7. Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H, St Jean PL, Bell CJ, Mitchell BD, Shuldiner AR. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr 2002;75:1098–106.
8. Neale BM, Mazzeo SE, Bulik CM. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (Three Factor Eating Questionnaire). Twin Res 2003;6:471–8.
9. Provencher V, Perusse L, Bouchard L, Drapeau V, Bouchard C, Rice T, Rao DC, Tremblay A, Despres JP, Lemieux S. Familial resemblance in eating behaviors in men and women from the Quebec Family Study. Obes Res 2005;13:1624–9.
10. Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y, Rice T, Rao DC, Vohl MC, Tremblay A, Bouchard C et al. Neuromedin beta: a strong candidate gene linking eating behaviors and susceptibility to obesity. Am J Clin Nutr 2004;80:1478–86.
11. Choquette AC, Bouchard L, Drapeau V, Lemieux S, Tremblay A, Bouchard C, Vohl MC, Perusse L. Association between olfactory receptor genes, eating behavior traits and adiposity: results from the Quebec Family Study. Physiol Behav 2012;105:772–6.
12. Choquette AC, Lemieux S, Tremblay A, Drapeau V, Bouchard C, Vohl MC, Perusse L. GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec Family Study. Physiol Behav 2009;98:505–10.
13. Cornelis MC, Rimm EB, Curhan GC, Kraft P, Hunter DJ, Hu FB, van Dam RM. Obesity susceptibility loci and uncontrolled eating, emotional eating and cognitive restraint behaviors in men and women. Obesity (Silver Spring) 2014;22:E135–41.
14. Harbron J, van der Merwe L, Zaahl MG, Kotze MJ, Senekal M. Fat mass and obesity-associated (FTO) gene polymorphisms are associated with physical activity, food intake, eating behaviors, psychological health, and modeled change in body mass index in overweight/obese Caucasian adults. Nutrients 2014;6:3130–52.
15. Rohde K, Keller M, Horstmann A, Liu X, Eichelmann F, Stumvoll M, Villringer A, Kovacs P, Tonjes A, Bottcher Y. Role of genetic variants in ADIPOQ in human eating behavior. Genes Nutr 2015;10:449.
16. Vega JA, Salazar G, Hodgson MI, Cataldo LR, Valladares M, Obregon AM, Santos JL. Melanocortin-4 receptor gene variation is associated with eating behavior in Chilean adults. Ann Nutr Metab 2016;68:35–41.
17. Llewellyn CH, Trzaskowski M, van Jaarsveld CH, Plomin R, Wardle J. Satiety mechanisms in genetic risk of obesity. JAMA Pediatr 2014;168:338–44.
18. Wardle J, Carnell S, Haworth CM, Farooqi IS, O'Rahilly S, Plomin R. Obesity associated genetic variation in FTO is associated with diminished satiety. J Clin Endocrinol Metab 2008;93:3640–3.
19. Konttinen H, Llewellyn C, Wardle J, Silventoinen K, Joensuu A, Mannisto S, Salomaa V, Jousilahti P, Kaprio J, Perola M et al. Appetitive traits as behavioural pathways in genetic susceptibility to obesity: a population-based cross-sectional study. Sci Rep 2015;5:14726.
20. de Lauzon-Guillain B, Clifton EA, Day FR, Clement K, Brage S, Forouhi NG, Griffin SJ, Koudou YA, Pelloux V, Wareham NJ et al. Mediation and modification of genetic susceptibility to obesity by eating behaviors. Am J Clin Nutr 2017;106:996–1004.
21. Westenhoefer J, Stunkard AJ, Pudel V. Validation of the flexible and rigid control dimensions of dietary restraint. Int J Eat Disord 1999;26:53–64.
22. Bond MJ, McDowell AJ, Wilkinson JY. The measurement of dietary restraint, disinhibition and hunger: an examination of the factor structure of the Three Factor Eating Questionnaire (TFEQ). Int J Obes Relat Metab Disord 2001;25:900–6.
23. Bouchard C. Genetic epidemiology, association, and sib-pair linkage: results from the Québec Family Study. In: G Bray, D Ryan, editors. Molecular and genetic aspects of obesity. Baton Rouge, LA: Louisiana State University Press; 1996. p. 470–81.
24. The Airlie (VA) Consensus Conference. Standardization of anthropometric measurements. Champaign, IL: Human Kinetics; 1988.
25. Llunch A. Identification des conduites alimentaires par approches nutritionnelles et psychomériques: implications thérapeutiques et prévention dans l'obésité humaine [Identification of food intake behaviors by nutritional and psychometric means: implications for

prevention and treatment of human obesity]. Université Nancy 1, Henri Poincaré Nancy, France; 1995.
26. Sung YJ, Perusse L, Sarzynski MA, Fornage M, Sidney S, Sternfeld B, Rice T, Terry JG, Jacobs DR Jr, Katzmarzyk P et al. Genome-wide association studies suggest sex-specific loci associated with abdominal and visceral fat. Int J Obes (Lond) 2016;40:662–74.
27. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173–82.
28. Karlsson J, Persson LO, Sjostrom L, Sullivan M. Psychometric properties and factor structure of the Three-Factor Eating Questionnaire (TFEQ) in obese men and women. Results from the Swedish Obese Subjects (SOS) study. Int J Obes Relat Metab Disord 2000;24: 1715–25.
29. Hunot C, Fildes A, Croker H, Llewellyn CH, Wardle J, Beeken RJ. Appetitive traits and relationships with BMI in adults: development of the Adult Eating Behaviour Questionnaire. Appetite 2016;105: 356–63.
30. Drapeau V, Hetherington M, Tremblay A. Impact of eating and lifestyle behaviors on body weight: beyond energy value. In: Preedy VR, Watson RR, Martin CR, editors. Handbook of behavior, food and nutrition. New York, NY: Springer New York; 2011. p. 693–706.
31. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187–96.
32. Celis-Morales C, Lyall DM, Guo Y, Steell L, Llanas D, Ward J, Mackay DF, Biello SM, Bailey ME, Pell JP et al. Sleep characteristics modify the association of genetic predisposition with obesity and anthropometric measurements in 119,679 UK Biobank participants. Am J Clin Nutr 2017;105:980–90.
33. Provencher V, Drapeau V, Tremblay A, Despres JP, Lemieux S. Eating behaviors and indexes of body composition in men and women from the Quebec Family Study. Obes Res 2003;11:783–92.
34. Bryant EJ, King NA, Blundell JE. Disinhibition: its effects on appetite and weight regulation. Obes Rev 2008;9:409–19.
35. French SA, Mitchell NR, Wolfson J, Finlayson G, Blundell JE, Jeffery RW. Questionnaire and laboratory measures of eating behavior. Associations with energy intake and BMI in a community sample of working adults. Appetite 2014;72:50–8.