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# Dietary mediators of the genetic susceptibility to obesity - Results from the Quebec Family Study

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**Abbreviations:** BMI, body mass index; CV, coefficient of variation; DV, daily values; FDA, Food and Drug Administration; FFQ, food frequency questionnaire; HEI, Healthy Eating Index; NRF6.3, Nutrient Rich Food Index 6.3; pER, predicted energy requirement; PRS, polygenic risk score; QFS, Quebec Family Study; rEI, reported energy intake; SFAs, saturated fatty acids;

SNPs, single nucleotide polymorphisms; SSBs, sugar-sweetened beverages; TEI, total energy intake; DV, daily values; WC, waist circumference.

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**Abstract**

**Background:** Recent studies showed that eating behaviors such as disinhibition, emotional and external eating, and snacking mediate genetic susceptibility to obesity. It remains unknown if diet quality and intake of specific food groups also mediate the genetic susceptibility to obesity.

**Objective:** This study aimed to assess if diet quality and intakes of specific food groups mediate the association between a polygenic risk score (PRS) for body mass index (BMI) and BMI and waist circumference (WC). We hypothesized that poor diet quality, high intakes of energy-dense food groups and low intakes of nutrient-dense food groups mediate the genetic susceptibility to obesity.

**Methods:** This cross-sectional study included 750 participants (56.3% women, age 41.5±14.9 years, BMI 27.8±7.5 kg/m$^2$) from the Quebec Family Study. A $PRS_{BMI}$ based on >500,000 genetic variants was calculated using LDpred2. Dietary intakes were assessed with a 3-day food record from which a diet quality score (i.e., Nutrient Rich Food Index 6.3) and food groups were derived. Mediation analyses were conducted using a regression-based and bootstrapping approach.

**Results:** The $PRS_{BMI}$ explained 25.7% and 19.8% of the variance in BMI and WC, respectively. The association between $PRS_{BMI}$ and BMI was partly mediated by poor diet quality (β=0.33±0.12; 95% CI: 0.13, 0.60), high intakes of fat and high-fat foods (β=0.46±0.16; 95% CI:

0.19, 0.79) and sugar-sweetened beverages (β=0.25±0.14; 95% CI: 0.05, 0.60), and low intakes of vegetables (β=0.15±0.08; 95% CI: 0.03, 0.32), fruits (β=0.37±0.12; 95% CI: 0.17, 0.64) and dairy products (β=0.17±0.09; 95% CI: 0.02, 0.37). The same trends were observed for WC.

**Conclusions:** The genetic susceptibility to obesity was partly mediated by poor diet quality and intakes of specific food groups. These results suggest that improvement in diet quality may reduce obesity risk among individuals with high genetic susceptibility and emphasize the need to intervene on diet quality among these individuals.

**Keywords:** Genetic susceptibility to obesity; Polygenic risk score; Obesity; Diet quality; Dietary intakes; mediation

## Introduction

Obesity results from a complex interplay between genetic and environmental factors. It is estimated that 40 to 75% of the variation in body mass index (BMI) is explained by genetic factors (1-3) and nearly 1000 single nucleotide polymorphisms (SNPs), explaining approximately 6% of the variance in BMI, have been identified through genome-wide association studies (4).

The study of gene-environment interaction in obesity is traditionally based on the concept of moderation (or effect modification) in which the effects of genes (exposure) on obesity (outcome) is examined in groups of individuals stratified based on an environmental factor. An alternative approach that can be used to characterize the interplay between genetic and environmental factors in obesity is mediation analysis. In contrast to moderation, mediation analysis is used to assess the extent to which the effects of an exposure (genes) on an outcome (obesity) is explained by a given set of mediators (e.g., dietary factors). Although moderation and mediation are interdependent concepts, the assessment of mediation is motivated by understanding the causal

pathways whereby an exposure leads to an outcome with the aim of intervening on the mediator to improve the outcome (5).

Despite extensive evidence supporting the existence of gene-diet interaction in obesity (6-11), relatively few studies used mediation analysis to identify potential mediators of genetic susceptibility to obesity. A previous study by our group using data from the Quebec Family Study (QFS) showed that disinhibition and susceptibility to hunger, both internally or in response to external food cues, mediated the genetic susceptibility to obesity in adults (12). Other studies in adults (13-17) and children (18, 19) provided evidence for the role of eating behavior or appetite-related traits in mediating genetic susceptibility. In addition, a recent study found that disinhibition was a key mediator of the association between genetic susceptibility and weight gain in midlife adults (13). To the best of our knowledge, only one study explored whether diet quality mediated the genetic susceptibility to obesity, assessed with a polygenic risk score (PRS), and found that a score of diet quality based on a short (14-item) Food Frequency Questionnaire (FFQ) did not show any mediating effect (17). However, an eating pattern labeled infrequent and unhealthy eating was found to mediate the genetic susceptibility to obesity (17). Whether diet quality and intakes of specific food groups are potential mediators of the genetic susceptibility to obesity remains to be investigated.

In the present study, we investigated the mediating effect of diet quality and specific food groups, derived from a three-day food record, on the genetic susceptibility to obesity, using BMI and WC as measures of obesity and a PRS for BMI incorporating whole-genome based variants irrespective of their genome-wide significance. This PRS represents a more powerful approach to capture genetic risk (4, 20). We hypothesized that the genetic susceptibility to obesity is mediated

by a poor diet quality, high intakes of energy-dense foods and low intakes of nutrient-dense foods.

## Subjects and Methods

*Study design and Participants*

Participants of this cross-sectional study are from phases 2 (1989-1997) and 3 (1998-2002) of the QFS (NCT03355729). Participants are French-Canadians from the greater Quebec City area recruited from different media. Additional details on the QFS have been previously published (21, 22). The current study excluded participants without genotype data, aged under 18 years, with a diagnosis of type 1 or type 2 diabetes and without BMI data (**Figure 1**). Participants without WC measurement were excluded from WC analyses. The analyses therefore included 750 participants for BMI and 748 participants for WC. For participants with longitudinal data on phases 2 and 3, the sample selection favored the data collection phase with less missing data relevant to the analyses and no exclusion criteria, or favored phase 2 when there were no exclusion criteria and no difference in the number of missing data between the two phases of data collection. The QFS was approved by the Research Ethics Committee of Université Laval and all participants signed an informed consent.

*Anthropometric measurements*

Anthropometric measurements including weight, height and WC were measured following standardized procedures (23). Body mass index was calculated as weight divided by height squared ($kg/m^2$).

*Genotyping and polygenic risk score*

Genome-wide genotyping of participants was performed using the Illumina 610-Quad Chip, as previously described (24). A PRS for BMI, representing an individual's genetic susceptibility to obesity, was derived using LDpred2, a computational algorithm for polygenic scoring that uses genome-wide genotype profile of participants and relevant genome-wide association study (GWAS) data (25). The $PRS_{BMI}$ was calculated using the summary statistics of the most recent GIANT Consortium and UK Biobank meta-analysis of BMI in over 700,000 individuals (4). The LDpred2 tool implemented in R considers the effect size estimates of all variants and accounts for linkage disequilibrium between variants to derive a whole-genome PRS composed of independent variants (25). The PRS used in the present study included 523,101 SNPs.

*Dietary assessment*

Dietary intakes were assessed with a three-day food record on two weekdays and one weekend day (26). All participants received instructions from a registered dietician on how to complete the food record and measure the portions of food consumed. The registered dietician subsequently verified every food record with the participant to ensure its accuracy. Energy and nutrient intakes were assessed based on the 2010 version of the Canadian Nutrient File (27).

Diet quality was assessed with the Nutrient Rich Food (NRF) Index 6.3, which measures the nutritional quality of each food in the diet and can be applied to food, meal and daily diet (28, 29). This index was chosen because the serving size of each food necessary to calculate commonly used diet quality indices such as the Healthy Eating Index (HEI) (30, 31) was not available in the database. The NRF6.3 was also chosen because missing data on vitamin E for

18.3% of food items did not allow the use of the NRF9.3. Although the NRF6.3 performs slightly lower than the NRF9.3 to predict the HEI, the NRF6.3 still explains an adequate proportion (i.e., over 35%) of the variance in HEI (28). For each food, the NRF6.3 is calculated as the sum of the proportion of reference daily values (DV) provided by 100 kcal for 6 nutrients to encourage (i.e., protein, fiber, vitamin A, vitamin C, calcium and iron), minus the sum of the proportion of reference DV provided by 100 kcal for 3 nutrients to limit (i.e, SFAs, sodium and added or total sugars) (28, 29). The 6 nutrients to encourage are based on the US Food and Drug Administration (FDA)'s definition of "healthy" foods, and the 3 nutrients to limit are based on the FDA and other authoritative sources (29). For each food, each nutrient could not exceed 100% of its reference DV to avoid overvaluing foods that provide very large amounts of some specific nutrients. Total sugars were used in the present study because added sugars were not available in the database. Reference DV for total sugars was set to 100 g, as per Health Canada's Table of DV for nutrition labelling (32). To reflect total diet quality, each food's NRF6.3 score was weighted according to their proportion of total energy intake for each day and a mean NRF6.3 score for the three collection days was calculated.

Food items from the food record were classified into food groups mainly based on similarity (e.g., fruits, dairy products) or their macronutrient content (e.g., fat and high-fat foods). Details about food group classification have been presented elsewhere (33). The current analysis included 13 food groups selected based on their positive or negative association with weight gain, obesity or cardiometabolic health (**Supplemental Table 1**) (34, 35). Intakes of food groups are expressed in proportion of total energy intake (%TEI).

*Assessment of covariates*

Information on age, sex (men, 0; women, 1), menopausal status (yes, 1; no, 0), current smoking status (yes, 1; no, 0), and current dieting status (yes, 1; no, 0) were collected through questionnaires. The plausibility of self-reported energy intake was assessed using the method described by Huang et al. (36) where under- and over-reporters of energy intake are defined as those having a ratio of reported energy intake to predicted energy requirements that deviates more than one standard deviation (± 1 SD) calculated from a formula that accounts for measurement error in reported energy intake and predicted energy requirements. In the present study, the within-individual coefficient of variation (CV) for reported energy intake (rEI) was 25.0%, the number of days of dietary assessment was 3 and the CV for predicted energy requirements (pER) was 19.1%. The CV accounting for day-to-day variation and measurement error for objective measurement of total energy expenditure (mTEE) was set at 8.2%, as detailed elsewhere (37). Predicted energy requirements were assessed using equations developed by the National Academy of Medicine (38). As an objective measure of physical activity level was not available for all participants, it was assumed that participants were sedentary, as previously done (39). To account for skewness of energy intake, the ± 1 SD confidence intervals were exponentiated using a multiplicative factor of 1 (40). The resulting confidence intervals were 0.78 to 1.29, meaning that under- and over-reporters of energy intake were defined as those having a ratio of reported energy intake to predicted energy requirements <0.78 and >1.29, respectively. The reporting status (i.e., under-reporters, plausible reporters and over-reporters) was considered in the analyses by creating two indicator variables representing underreporting (yes, 1; no, 0) and overreporting (yes, 1; no, 0) (41).

*Statistical analysis*

Statistical analyses were performed using SAS studio version 3.8. Descriptive statistics were computed and presented as mean ± SD or n and frequency. Sex differences on participant characteristics, anthropometric measurements, $PRS_{BMI}$ and dietary intakes were assessed using Student's T test and Chi-square test. Linear regression models were used to assess the association between the $PRS_{BMI}$ and BMI or WC. Mediation analyses were conducted to assess if diet quality (NRF6.3) and food groups mediate the association between the $PRS_{BMI}$ and BMI or WC. These analyses were conducted with model 4 of the Process macro, version 3.4.1, for SAS (42). The Process macro is an ordinary least square regression path analysis modeling tool that uses percentile bootstrap confidence intervals to assess the mediation or indirect effect (i.e., dietary intakes) through which an independent variable (i.e., $PRS_{BMI}$) influences a dependent variable (i.e., BMI or WC). The present analyses used 5,000 bootstrap samples. The total effect (*c*) is defined as the association between the $PRS_{BMI}$ and BMI or WC and the direct effect (*c'*) represents the association between the $PRS_{BMI}$ and BMI or WC when controlling for the mediator (i.e., dietary intakes). The *a* and *b* paths represent the associations between the independent variable (i.e., $PRS_{BMI}$) and the mediator (i.e., dietary intakes), and between the mediator and the dependent variable (i.e., BMI or WC) while controlling for the independent variable (i.e., $PRS_{BMI}$), respectively. The percentage of mediation was calculated as a ratio of indirect effect to total effect (i.e., (*ab/c*)*100). To support the mediation model, in which the $PRS_{BMI}$ is hypothesized to influence BMI and WC through dietary intakes, we used bivariate genetic analyses to examine the extent to which shared genetic effects and nonshared environmental effects underlie the covariation between BMI and dietary intakes. A positive or negative genetic correlation implies that the effects of genes underlying the two traits are in the same or opposite direction, respectively. These analyses were performed taking into account the family structure of

QFS using SOLAR Eclipse version 8.4.1(43). Mediation analyses and genetic correlations were adjusted for all covariates presented previously, as these variables are known to influence BMI, WC or dietary intakes.

## Results

*Participant characteristics*

The sample of this study included 422 women and 328 men, with a mean age of 41.5 ± 14.9 years (range 18.1 - 75.7 years) and a mean BMI and WC of 27.8 ± 7.5 kg/m$^2$ (range 16.8 - 64.9 kg/m$^2$) and 88.8 ± 18.1 cm (range 57.9 - 164.5 cm), respectively (**Table 1**). Twenty-six percent (26.4%) of the sample had obesity (BMI ≥ 30 kg/m$^2$) and 29.6% of the sample had abdominal obesity defined as a WC ≥ 88 cm for women and ≥ 102 cm for men.

*Associations between $PRS_{BMI}$, BMI and WC*

The $PRS_{BMI}$ explained 25.7% of the variance in BMI (β=10.56 ± 0.66; 95% CI: 9.27, 11.85, *P*<0.0001) and 19.8% of the variance in WC (β=22.53 ± 1.66; 95% CI: 19.27, 25.79, *P*<0.0001), respectively.

*Dietary mediators of the association between $PRS_{BMI}$ and BMI*

Results from the mediation analyses showed that a poor diet quality partly mediated the association between the $PRS_{BMI}$ and BMI (β=0.33 ± 0.12; 95% CI: 0.13, 0.60) (**Figure 2A**). Among food groups, high intakes of SSBs (β=0.25 ± 0.14; 95% CI: 0.05, 0.60) and fat and high-fat foods (β=0.46 ± 0.16; 95% CI: 0.19, 0.79) partly mediated the association between the $PRS_{BMI}$ and BMI (**Table 2**). Low intakes of whole vegetables (β=0.15 ± 0.08; 95% CI: 0.03, 0.32), fruits excluding fruit juices (β=0.37 ± 0.12; 95% CI: 0.17, 0.64) and dairy products (β=0.17 ± 0.09; 95% CI: 0.02, 0.37), particularly milk (β=0.13 ± 0.08; 95% CI: 0.01, 0.30) and

yogurt (β=0.12 ± 0.06; 95% CI: 0.02, 0.25), also partially mediated this association. The total effect (*c*), representing the association between the $PRS_{BMI}$ and BMI (β=10.34 ± 0.64; 95% CI: 9.08, 11.61, *P*<0.0001), was slightly reduced by these mediators, resulting in percentage of mediation varying between 1.2 and 4.4%.

*Dietary mediators of the association between $PRS_{BMI}$ and WC*

Similar results were observed for WC. Accordingly, a poor diet quality partly mediated the association between the $PRS_{BMI}$ and WC (β=0.92 ± 0.31; 95% CI: 0.39, 1.58) (**Figure 2B**). Among food groups, high intakes of SSBs (β=0.58 ± 0.31; 95% CI: 0.12, 1.29) and fat and high-fat foods (β=1.09 ± 0.36; 95% CI: 0.48, 1.92), and low intakes of whole vegetables (β=0.38 ± 0.18; 95% CI: 0.07, 0.77), fruits excluding fruit juices (β=1.04 ± 0.33; 95% CI: 0.47, 1.73) and dairy products (β=0.49 ± 0.23; 95% CI: 0.12, 0.99), particularly milk (β=0.35 ± 0.20; 95% CI: 0.02, 0.79) and yogurt (β=0.33 ± 0.15; 95% CI: 0.07, 0.67), were all partial mediators of the association between the $PRS_{BMI}$ and WC (**Table 3**). Again, the total effect (*c*) (β=22.62 ± 1.51; 95% CI: 19.66, 25.59, *P*<0.0001) was slightly reduced by these mediators, resulting in percentage of mediation varying between 1.5 and 4.8%.

*Genetic correlations between BMI and dietary intakes*

Significant negative genetic correlations were observed between BMI and diet quality ($\rho_g$=-0.46 ± 0.13, *P*=0.001), whole vegetables ($\rho_g$= -0.40 ± 0.17, *P*=0.02), fruits excluding juices ($\rho_g$=-0.56 ± 0.15, *P*=0.002), 100% fruit juices ($\rho_g$=-0.87 ± 0.73, *P*=0.03), dairy products ($\rho_g$=-0.47 ± 0.19, *P*=0.01), milk ($\rho_g$=-0.51 ± 0.17, *P*=0.002), plant-based protein foods ($\rho_g$=-0.37 ± 0.14, *P*=0.01) and nuts and seeds ($\rho_g$=-0.43 ± 0.15, *P*=0.004) (**Table 4**). Positive genetic correlations were observed between BMI and SSBs ($\rho_g$=0.79 ± 0.19, *P*=0.0001), and fat and high-fat foods ($\rho_g$=0.73 ± 0.18, *P*=0.0002).

## Discussion

The mechanisms by which the genetic susceptibility to obesity influences body weight and adiposity are largely unknown. This study aimed to investigate whether diet quality and specific food groups mediate the genetic susceptibility to obesity, using a whole-genome polygenic risk score and BMI and WC as measures of obesity. To our knowledge, only one study has assessed the mediating effect of diet quality (17), and no studies have assessed the mediating effect of specific food groups on the genetic susceptibility to obesity. The results showed that a poor diet quality, as assessed by the NRF6.3, a high proportion of energy from SSBs and fat and high-fat foods and a low proportion of energy from fruits excluding juices, vegetables, total dairy products, and specific dairy products including yogurt and milk, partly mediated the genetic susceptibility to obesity in analyses related to BMI and WC. Although the effect of individual mediator is small, the results suggest that diet quality and intakes of specific food groups explain a part of the genetic susceptibility to obesity. These results also suggest that interventions aimed at improving diet quality and the consumption of specific food groups may have beneficial effects on body weight and WC in individuals with a genetic predisposition to obesity.

In the context of understanding the implication of genes and diet in obesity, both moderation and mediation studies complement each other. Accordingly, moderation highlights the role of diet quality in modifying the genetic association with obesity, while mediation identifies pathways whereby genes influence obesity. Our results thus complement those of Wang et al. (44) who showed, using a gene-diet interaction design in two prospective US cohorts, that improvement in adherence to healthy dietary patterns attenuated the genetic association with weight gain, and this was particularly pronounced among individuals with high genetic susceptibility to obesity. They also complement those of other gene-diet interaction studies which showed that the association

between genetic susceptibility to obesity and BMI was stronger in individuals with low diet quality as well as low intakes of fruits and high intakes of SSBs and fried foods (6-8). In their study investigating the mediating effect of eating patterns on genetic susceptibility to obesity assessed using a $PRS_{BMI}$, Masip et al. (17), observed no mediating effect of diet quality based on a 14-item FFQ (17), but this null finding may be due to the lower accuracy of brief instruments to assess the whole diet and the lack of consideration of systematic errors (i.e., misreporting of energy intake) in dietary assessment (36, 41, 45). However, they found a mediating effect of some eating patterns, such as snacking and infrequent and unhealthy eating, on the association between genetic susceptibility to obesity and measures of BMI and WC (17).

The moderate to large genetic correlations between most statistically significant mediating variables and BMI suggest that dietary intakes and BMI share a common underlying genetic architecture. Several genes associated with obesity have also been associated with dietary intakes (16, 46-48), and unhealthy eating has been recognized as one of the leading causes of obesity (49). This collectively provides support to the hypothesis that dietary intakes may also act as mediators of the genetic susceptibility to obesity. However, because of the cross-sectional design of this study and the fact that individuals with obesity or high WC may modify their food intakes to either control or lose body weight, or to prevent or treat obesity-associated comorbidities, reverse causation between dietary intakes and obesity measures cannot be excluded. Yet, a recent Mendelian randomization study showed that a low proportion of energy from carbohydrates and a high proportion of energy from lipids were causally related to higher BMI and WC, suggesting evidence for a causal effect between dietary intake and measures of BMI and WC (50). This is also supported by studies showing that intakes of vegetables, fruits and yogurt were protective for weight gain, whereas SSBs and high-fat foods, which are mostly fried and ultra-processed, and

similar to foods included in the fat and high-fat food group in the present study, were associated with weight gain (34, 35). Total dairy products and milk appear mostly neutral towards weight gain (34, 35, 51), but have been associated with a lower risk of abdominal obesity (52).

The associations between the $PRS_{BMI}$ and dietary intakes are in line with genetic correlations. Accordingly, all dietary variables negatively associated with the $PRS_{BMI}$, except yogurt, showed a negative genetic correlation with BMI, indicating that shared genetic factors influence BMI and dietary intakes in the opposite direction. Similarly, all dietary variables positively associated with the $PRS_{BMI}$ showed a positive genetic correlation with BMI. Negative genetic correlations between BMI and fruits and vegetables and a positive genetic correlation between soft drinks (soda), a type of SSBs, have also been previously reported (53, 54). The negative association between the $PRS_{BMI}$ and diet quality is consistent with the results of Dashti et al. who showed that a high genetic risk of obesity was associated with purchasing less healthy foods and more food items, as objectively measured over a three-month period at a workplace cafeteria (55). In addition to studies demonstrating an association between genetic susceptibility to obesity and eating behavior traits (12-15, 17, 18, 56, 57), these results collectively suggest that obesity genes may influence dietary intakes. This is also supported by the fact that obesity-related genetic variants are mainly expressed in the central nervous system, in regions involved in appetite regulation, learning, cognition, emotions and memory, such as the hypothalamus, pituitary gland, hippocampus and limbic system (58, 59). It is thus likely that genes affect BMI through behavioral pathways related to food intake (57).

This study has several strengths and limitations. The main strength includes using a whole-genome PRS of BMI which explains a high percentage of variance in BMI and WC (i.e., 25.7% and 19.8%, respectively) compared to genetic risk scores incorporating only genome-wide

significant genetic variants (4, 59). Another strength of this study is the use of a three-day food record with consideration of misreporting (systematic error) (36, 41). This method allows a more comprehensive assessment of dietary intakes compared to a screener or a short FFQ (45) which has been previously used to assess the mediating effect of diet quality on the genetic susceptibility to obesity. However, food records are subjected to day-to-day variation (within-person random error) which may have attenuated estimates of regression models (60). The main limitation of this study is the cross-sectional design that precludes causal inference and that cannot exclude reverse causation between diet and obesity. As such, replication of these results within other cohorts and using longitudinal data is needed. Another limitation is our inability to dissociate single foods from mixed meals that have been entered as such into the food database, which contributed to a mean of 6.3 ± 7.8 % of total energy intake, resulting mainly in the exclusion of these foods from the different food groups. Another limitation of this study is the use of the NRF6.3 to assess diet quality. Despite being a good indicator of the quality of foods in the diet (28, 29), this index focuses on nutrients rather than food patterns and does not reflect adherence to current Canadian dietary guidelines (61). However, the assessment of different food groups as mediators of the genetic susceptibility to obesity overcomes this limit and allows to identify specific foods that could be targeted in obesity prevention and treatment. Future studies should assess if other food groups, such as whole grains and refined grains, are mediators of the genetic susceptibility to obesity.

In conclusion, this study shows that poor diet quality and intakes of specific food groups, including high intakes of high-fat foods and SSBs and low intakes of vegetables, fruits, milk and yogurt, partly mediate the association between genetic susceptibility to obesity and both BMI and WC. To our knowledge, this study is the first to assess the role of specific food groups in

mediating the genetic susceptibility to obesity. These results suggest that improvement in diet quality and in the consumption of specific food groups may reduce obesity risk among individuals with high genetic susceptibility. They also emphasize the relevance of intervening on diet quality to reduce obesity among these individuals.

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**Authors' contributions:** LP, VD, CL, MEL and RJ designed research; CC and RJ analyzed data; RJ wrote the first draft of the manuscript; All authors read, edited and approved the final version of the manuscript; LP had primary responsibility for final content.

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**Table 1.** Characteristics of the 750 participants from the Quebec Family Study[1]

| | Total | Men | Women | $P^2$ |
|---|---|---|---|---|
| Sex, n (%) | | 328 (43.7) | 422 (56.3) | 0.0006 |
| Age, y | 41.5 ± 14.9 | 41.9 ± 15.3 | 41.2 ± 14.6 | 0.53 |
| Body mass index, kg/m$^2$ | 27.8 ± 7.5 | 27.6 ± 6.6 | 27.8 ± 8.1 | 0.71 |
| Waist circumference[3], cm | 88.8 ± 18.1 | 94.4 ± 17.0 | 84.4 ± 17.8 | <0.0001 |
| Menopaused[4], n (%) | 126 (17.1) | - | 126 (30.7) | - |
| Dieting[5], n (%) | 44 (5.9) | 12 (3.7) | 32 (7.6) | 0.02 |
| Smoking[5], n (%) | 157 (21.0) | 64 (19.5) | 93 (22.1) | 0.39 |
| Reporting status[6], n (%) | | | | 0.96 |
| Under-reporters | 86 (11.5) | 37 (11.3) | 49 (11.6) | |
| Plausible reporters | 503 (67.1) | 219 (66.8) | 284 (67.3) | |
| Over-reporters | 161 (21.5) | 72 (22.0) | 89 (21.1) | |
| Polygenic risk score | 0.29 ± 0.36 | 0.29 ± 0.35 | 0.29 ± 0.37 | 0.82 |
| Energy intake, kcal/d | 2346 ± 681 | 2702 ± 685 | 2068 ± 534 | <0.0001 |
| **Diet quality** | | | | |
| Nutrient-Rich Food Index 6.3 | 10.2 ± 6.7 | 9.4 ± 6.3 | 10.7 ± 7.0 | 0.0008 |
| **Food groups, %TEI** | | | | |
| Whole vegetables | 1.9 ± 2.1 | 1.6 ± 2.0 | 2.1 ± 2.1 | 0.002 |
| Fruits[7] | 3.5 ± 3.7 | 2.9 ± 3.4 | 4.1 ± 3.8 | <0.0001 |
| 100% fruit juices | 2.4 ± 3.2 | 2.3 ± 3.0 | 2.4 ± 3.2 | 0.58 |
| Dairy products | 10.4 ± 6.4 | 9.7 ± 6.4 | 10.9 ± 6.4 | 0.008 |
| Milk | 5.2 ± 4.5 | 5.2 ± 4.7 | 5.2 ± 4.4 | 0.97 |
| Yogurt | 0.9 ± 2.0 | 0.6 ± 1.5 | 1.2 ± 2.3 | <0.0001 |
| Cheese | 4.2 ± 4.5 | 3.8 ± 4.5 | 4.5 ± 4.5 | 0.03 |
| Processed meats | 3.3 ± 4.1 | 3.8 ± 4.5 | 3.0 ± 3.7 | 0.01 |
| Plant-based protein foods | 2.1 ± 3.5 | 2.2 ± 3.8 | 2.0 ± 3.1 | 0.44 |
| Nuts and seeds | 1.8 ± 3.1 | 1.9 ± 3.6 | 1.6 ± 2.8 | 0.24 |
| Sugar-sweetened beverages | 2.6 ± 4.5 | 2.7 ± 3.9 | 2.5 ± 4.8 | 0.62 |
| Sugar and sugary foods | 15.7 ± 9.4 | 16.0 ± 9.6 | 15.4 ± 9.3 | 0.38 |
| Fat and high-fat foods | 14.1 ± 9.6 | 14.2 ± 9.8 | 14.0 ± 9.5 | 0.71 |

[1] Data are mean ± standard deviation or n (%); %TEI, percentage or total energy intake. [2] *P* values for sex differences based on Student's T test or Chi-square test. [3]n=748, women n=420. [4]n=738, women n=410. [5]n=749, women n=421. [6]Under-reporters, rEI/pER < 0.78; Plausible reporters, 0.78 ≤ rEI/pER ≤1.29; Over-reporters, rEI/pER > 1.29 (rEI/pER, reported energy intake/predicted energy requirements).

[7]Excluding fruit juices.

**Table 2.** Mediating effect of food groups on the association between genetic susceptibility to obesity ($PRS_{BMI}$) and BMI in the Quebec

| | *a*[3] | | | *b*[4] | | | Direct effect (*c'*)[5] | | | Indirect effect (*ab*)[6] | | % mediation[7] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β ± SE | 95% CI | *P* | β ± SE | 95% CI | *P* | β ± SE | 95% CI | *P* | β ± Boot SE | Boot 95% CI | |
| Whole vegetables | -0.57 ± 0.21 | -0.99, -0.16 | 0.007 | -0.27 ± 0.11 | -0.49, -0.05 | 0.02 | 10.19 ± 0.65 | 8.92, 11.46 | <0.0001 | **0.15 ± 0.08** | **0.03, 0.32** | 1.5 |
| Fruits[2] | -1.54 ± 0.36 | -2.24, -0.85 | <0.0001 | -0.24 ± 0.07 | -0.37, -0.11 | 0.0003 | 9.97 ± 0.65 | 8.70, 11.24 | <0.0001 | **0.37 ± 0.12** | **0.17, 0.64** | 3.6 |
| 100% fruit juices | -0.60 ± 0.32 | -1.23, 0.02 | 0.06 | 0.08 ± 0.07 | -0.06, 0.23 | 0.26 | 10.39 ± 0.65 | 9.13, 11.66 | <0.0001 | -0.05 ± 0.05 | -0.18, 0.04 | - |
| Dairy products | -2.15 ± 0.66 | -3.44, -0.85 | 0.001 | -0.08 ± 0.04 | -0.15, -0.01 | 0.03 | 10.17 ± 0.65 | 8.90, 11.44 | <0.0001 | **0.17 ± 0.09** | **0.02, 0.37** | 1.6 |
| Milk | -0.97 ± 0.47 | -1.89, -0.04 | 0.04 | -0.13 ± 0.05 | -0.23, -0.03 | 0.008 | 10.21 ± 0.64 | 8.95, 11.48 | <0.0001 | **0.13 ± 0.08** | **0.01, 0.30** | 1.2 |
| Yogurt | -0.47 ± 0.20 | -0.86, -0.09 | 0.02 | -0.25 ± 0.12 | -0.49, -0.02 | 0.04 | 10.22 ± 0.65 | 8.96, 11.49 | <0.0001 | **0.12 ± 0.06** | **0.02, 0.25** | 1.2 |
| Cheese | -0.71 ± 0.47 | -1.63, 0.22 | 0.13 | 0.02 ± 0.05 | -0.07, 0.12 | 0.63 | 10.36 ± 0.65 | 9.09, 11.63 | <0.0001 | -0.02 ± 0.04 | -0.10, 0.06 | - |
| Processed meats | 1.34 ± 0.43 | 0.51, 2.18 | 0.002 | 0.08 ± 0.06 | -0.03, 0.19 | 0.17 | 10.24 ± 0.65 | 8.97, 11.51 | <0.0001 | 0.10 ± 0.09 | -0.04, 0.31 | - |
| Plant-based protein foods | -0.80 ± 0.36 | -1.51, -0.08 | 0.03 | -0.09 ± 0.07 | -0.22, 0.04 | 0.17 | 10.27 ± 0.65 | 9.00, 11.54 | <0.0001 | 0.07 ± 0.06 | -0.02, 0.21 | - |
| Nuts and seeds | -0.58 ± 0.33 | -1.23, 0.06 | 0.08 | -0.10 ± 0.07 | -0.24, 0.05 | 0.19 | 10.29 ± 0.65 | 9.02, 11.55 | <0.0001 | 0.06 ± 0.05 | -0.03, 0.18 | - |
| Sugar-sweetened beverages | 1.26 ± 0.45 | 0.38, 2.14 | 0.005 | 0.20 ± 0.05 | 0.09, 0.30 | 0.0002 | 10.10 ± 0.64 | 8.84, 11.36 | <0.0001 | **0.25 ± 0.14** | **0.05, 0.60** | 2.4 |
| Sugar and sugary foods | 0.33 ± 0.97 | -1.57, 2.24 | 0.73 | -0.06 ± 0.02 | -0.10, -0.01 | 0.02 | 10.36 ± 0.64 | 9.10, 11.62 | <0.0001 | -0.02 ± 0.06 | -0.14, 0.10 | - |
| Fat and high-fat foods | 3.88 ± 0.99 | 1.94, 5.82 | 0.0001 | 0.12 ± 0.02 | 0.07, 0.16 | <0.0001 | 9.89 ± 0.64 | 8.63, 11.14 | <0.0001 | **0.46 ± 0.16** | **0.19, 0.79** | 4.4 |

Family Study[1]

[1] n=738, Analyses are performed on complete cases resulting on the exclusion of n=12 participants with missing data on menopausal (n=12), dieting (n=1) or smoking status (n=1) from the analyses Mediation analyses are conducted using the Process Macro v. 3.4.1 for SAS that uses percentile bootstrap confidence intervals to assess the mediating or indirect effect through which the $PRS_{BMI}$ influences BMI. 95% CI for indirect effect are estimated through 5, 000 bootstrap samples. Models are adjusted for age, sex (men, 0; women, 1), current dieting status (yes, 1; no, 0) menopausal status (yes, 1; no, 0), current smoking status (yes, 1; no, 0), misreporting of dietary intakes ([underreporting, yes, 1; no, 0] and [overreporting, yes, 1; no, 0]). Food groups are expressed in percentage of total energy intake. BMI, body mass index; Boot, Bootstrap; CI, confidence interval; PRS, polygenic risk score; SE, standard error; %TEI, percentage or total energy intake. [2] Excluding fruit juices. [3] *a*, association between the $PRS_{BMI}$ and the mediator. [4] *b*, association between the mediator and BMI. [5] direct effect (*c'*), association between the $PRS_{BMI}$ and BMI adjusted for the mediator. [6] indirect effect (*ab*), mediation effect. [7] % mediation calculated as indirect effect ((*ab*)/ total effect

(*c*))*100. Total effect (*c*)= 10.34 ± 0.64; 95% CI: 9.08, 11.61, *P*<0.0001 (association between the $PRS_{BMI}$ and BMI without adjustment for the mediator).

**Table 3.** Mediating effect of food groups on the association between genetic susceptibility to obesity ($PRS_{BMI}$) and WC in the Quebec

| | *a* [3] | | | *b* [4] | | | Direct effect (*c'*) [5] | | | Indirect effect (*ab*) [6] | | % mediation [7] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β ± SE | 95% CI | *P* | β ± SE | 95% CI | *P* | β ± SE | 95% CI | *P* | β ± Boot SE | Boot 95% CI | |
| Whole vegetables | -0.58 ± 0.21 | -0.99, -0.16 | 0.007 | -0.65 ± 0.26 | -1.17, -0.14 | 0.01 | 22.25 ± 1.51 | 19.28, 25.22 | <0.0001 | **0.38 ± 0.18** | **0.07, 0.77** | 1.7 |
| Fruits[2] | -1.55 ± 0.36 | -2.25, -0.85 | <0.0001 | -0.67 ± 0.16 | -0.97, -0.37 | <0.0001 | 21.59 ± 1.51 | 18.62, 24.55 | <0.0001 | **1.04 ± 0.33** | **0.47, 1.73** | 4.6 |
| 100% fruit juices | -0.60 ± 0.32 | -1.22, 0.03 | 0.06 | 0.10 ± 0.18 | -0.24, 0.45 | 0.56 | 22.69 ± 1.51 | 19.71, 25.66 | <0.0001 | -0.06 ± 0.12 | -0.35, 0.15 | - |
| Dairy products | -2.12 ± 0.66 | -3.42, -0.83 | 0.001 | -0.23 ± 0.08 | -0.40, -0.07 | 0.006 | 22.13 ± 1.51 | 19.16, 25.10 | <0.0001 | **0.49 ± 0.23** | **0.12, 0.99** | 2.2 |
| Milk | -0.96 ± 0.47 | -1.89, -0.03 | 0.04 | -0.36 ± 0.12 | -0.60, -0.13 | 0.002 | 22.27 ± 1.51 | 19.32, 25.23 | <0.0001 | **0.35 ± 0.20** | **0.02, 0.79** | 1.6 |
| Yogurt | -0.47 ± 0.20 | -0.86, -0.08 | 0.02 | -0.71 ± 0.28 | -1.26, -0.16 | 0.01 | 22.29 ± 1.51 | 19.33, 25.25 | <0.0001 | **0.33 ± 0.15** | **0.07, 0.67** | 1.5 |
| Cheese | -0.69 ± 0.47 | -1.62, 0.23 | 0.14 | 0.04 ± 0.12 | -0.20, 0.27 | 0.76 | 22.65 ± 1.51 | 19.68, 25.62 | <0.0001 | -0.03 ± 0.09 | -0.21, 0.17 | - |
| Processed meats | 1.34 ± 0.43 | 0.51, 2.18 | 0.002 | 0.17 ± 0.13 | -0.09, 0.42 | 0.21 | 22.40 ± 1.52 | 19.42, 25.38 | <0.0001 | 0.22 ± 0.21 | -0.15, 0.70 | - |
| Plant-based protein foods | -0.79 ± 0.36 | -1.51, -0.08 | 0.03 | -0.22 ± 0.15 | -0.52, 0.08 | 0.15 | 22.45 ± 1.51 | 19.48, 25.42 | <0.0001 | 0.18 ± 0.14 | -0.04, 0.52 | - |
| Nuts and seeds | -0.58 ± 0.33 | -1.23, 0.07 | 0.08 | -0.26 ± 0.17 | -0.59, 0.07 | 0.13 | 22.47 ± 1.51 | 19.51, 25.44 | <0.0001 | 0.15 ± 0.13 | -0.05, 0.47 | - |
| Sugar sweetened beverages | 1.25 ± 0.45 | 0.37, 2.13 | 0.005 | 0.46 ± 0.12 | 0.22, 0.71 | 0.0002 | 22.04 ± 1.50 | 19.09, 25.00 | <0.0001 | **0.58 ± 0.31** | **0.12, 1.29** | 2.6 |
| Sugar and sugary foods | 0.38 ± 0.97 | -1.52, 2.28 | 0.69 | -0.09 ± 0.06 | -0.21, 0.02 | 0.11 | 22.66 ± 1.51 | 19.70, 25.62 | <0.0001 | -0.04 ± 0.10 | -0.27, 0.17 | |
| Fat and high-fat foods | 3.85 ± 0.99 | 1.91, 5.80 | 0.0001 | 0.28 ± 0.06 | 0.18, 0.39 | <0.0001 | 21.53 ± 1.50 | 18.58, 24.47 | <0.0001 | **1.09 ± 0.36** | **0.48, 1.92** | 4.8 |

Family study[1]

[1] n=737, Analyses are performed on complete cases resulting on the exclusion of n=11 participants with missing data on menopausal status from the analyses. Mediation analyses are conducted using the Process Macro v. 3.4.1 for SAS that uses percentile bootstrap confidence intervals to assess the mediating or indirect effect through which the $PRS_{BMI}$ influences WC. 95% CI for indirect effect are estimated through 5, 000 bootstrap samples. Mediation models are adjusted for age, sex (men, 0; women, 1), current dieting (yes, 1; no, 0) menopausal status (yes, 1; no, 0), current smoking status (yes, 1; no, 0), misreporting of dietary intakes ([underreporting, yes, 1; no, 0] and [overreporting, yes, 1; no, 0]). Food groups are expressed in percentage of total energy intake. Boot, Bootstrap; CI, confidence interval, PRS, polygenic risk score; SE, standard error; WC, waist

circumference; %TEI, percentage or total energy intake. [2] Excluding fruit juices. [3] a, association between the $PRS_{BMI}$ and the mediator. [4] *b*, association between the mediator and WC. [5] direct effect (*c'*), association between the $PRS_{BMI}$ and WC adjusted for the mediator. [6] indirect effect (*ab*), mediation effect. [7] % mediation: Percentage of mediation calculated as indirect effect ((*ab*)/ total effect (*c*))*100. Total effect (*c*)= 22.62 ± 1.5; 95% CI: 19.66, 25.59, $P<0.0001$ (association between the $PRS_{BMI}$ and WC without adjustment for the mediator).

| Dietary intakes | $\rho_g \pm$ SE | *P* | $\rho_e \pm$ SE | *P* | $\rho_p \pm$ SE | *P* |
|---|---|---|---|---|---|---|
| **Diet quality** | | | | | | |
| Nutrient-Rich Food Index 6.3 | **-0.46 ± 0.13** | **0.001** | 0.01 ± 0.08 | 0.91 | **-0.18 ± 0.04** | **<0.0001** |
| **Food groups** | | | | | | |
| Whole vegetables | **-0.40 ± 0.17** | **0.02** | 0.03 ± 0.08 | 0.71 | **-0.11 ± 0.04** | **0.004** |
| Fruits[1] | **-0.56 ± 0.15** | **0.002** | -0.08 ± 0.08 | 0.33 | **-0.23 ± 0.04** | **<0.0001** |
| 100% fruit juices | **-0.87 ± 0.73** | **0.03** | **0.15 ± 0.07** | **0.04** | -0.005 ± 0.04 | 0.90 |
| Dairy products | **-0.47 ± 0.19** | **0.01** | 0.01 ± 0.08 | 0.94 | **-0.13 ± 0.04** | **0.0004** |
| Milk | **-0.51 ± 0.17** | **0.002** | 0.07 ± 0.08 | 0.36 | **-0.13 ± 0.04** | **0.0007** |
| Yogurt | -0.04 ± 0.58 | 0.95 | -0.07 ± 0.07 | 0.34 | -0.05 ± 0.04 | 0.15 |
| Cheese | -0.16 ± 0.44 | 0.70 | 0.03 ± 0.08 | 0.67 | 0.002 ± 0.04 | 0.95 |
| Processed meats | -0.03 ± 0.22 | 0.89 | **0.16 ± 0.08** | **0.04** | **0.10 ± 0.04** | **0.007** |
| Plant-based protein foods | **-0.37 ± 0.14** | **0.01** | 0.07 ± 0.08 | 0.38 | **-0.10 ± 0.04** | **0.01** |
| Nuts and seeds | **-0.43 ± 0.15** | **0.004** | 0.14 ± 0.08 | 0.09 | **-0.08 ± 0.04** | **0.047** |
| Sugar-sweetened beverages | **0.79 ± 0.19** | **0.0001** | -0.01 ± 0.08 | 0.90 | **0.21 ± 0.04** | **<0.0001** |
| Sugar and sugary foods | -0.09 ± 0.23 | 0.70 | -0.08 ± 0.08 | 0.32 | **-0.08 ± 0.04** | **0.04** |
| Fat and high-fat foods | **0.73 ± 0.18** | **0.0002** | -0.04 ± 0.08 | 0.60 | **0.19 ± 0.04** | **<0.0001** |

**Table 4.** Genetic, environmental and phenotypic correlations between dietary intakes and BMI in the Quebec Family Study[1]

[1] n families=215, n=738, Analyses are performed on complete cases resulting on the exclusion of n=12 participants with missing data on menopausal (n=12), dieting (n=1) or smoking status (n=1) from the analyses. Bivariate genetic correlation analyses taking into account the family structure of QFS were performed using SOLAR Eclipse version 8.4.1. Food groups are expressed in percentage of total energy intake. Analyses are adjusted for age, sex (men, 0; women, 1), current dieting status (yes, 1; no, 0) menopausal status (yes, 1; no, 0), current smoking status (yes, 1; no, 0), and misreporting of dietary intakes ([underreporting, yes, 1; no, 0] and [overreporting, yes, 1; no, 0]). BMI, body mass index; SE, standard error; $\rho_g$, genotypic correlation; $\rho_e$, environmental correlation; $\rho_p$, phenotypic correlation.

**Figure 1.**

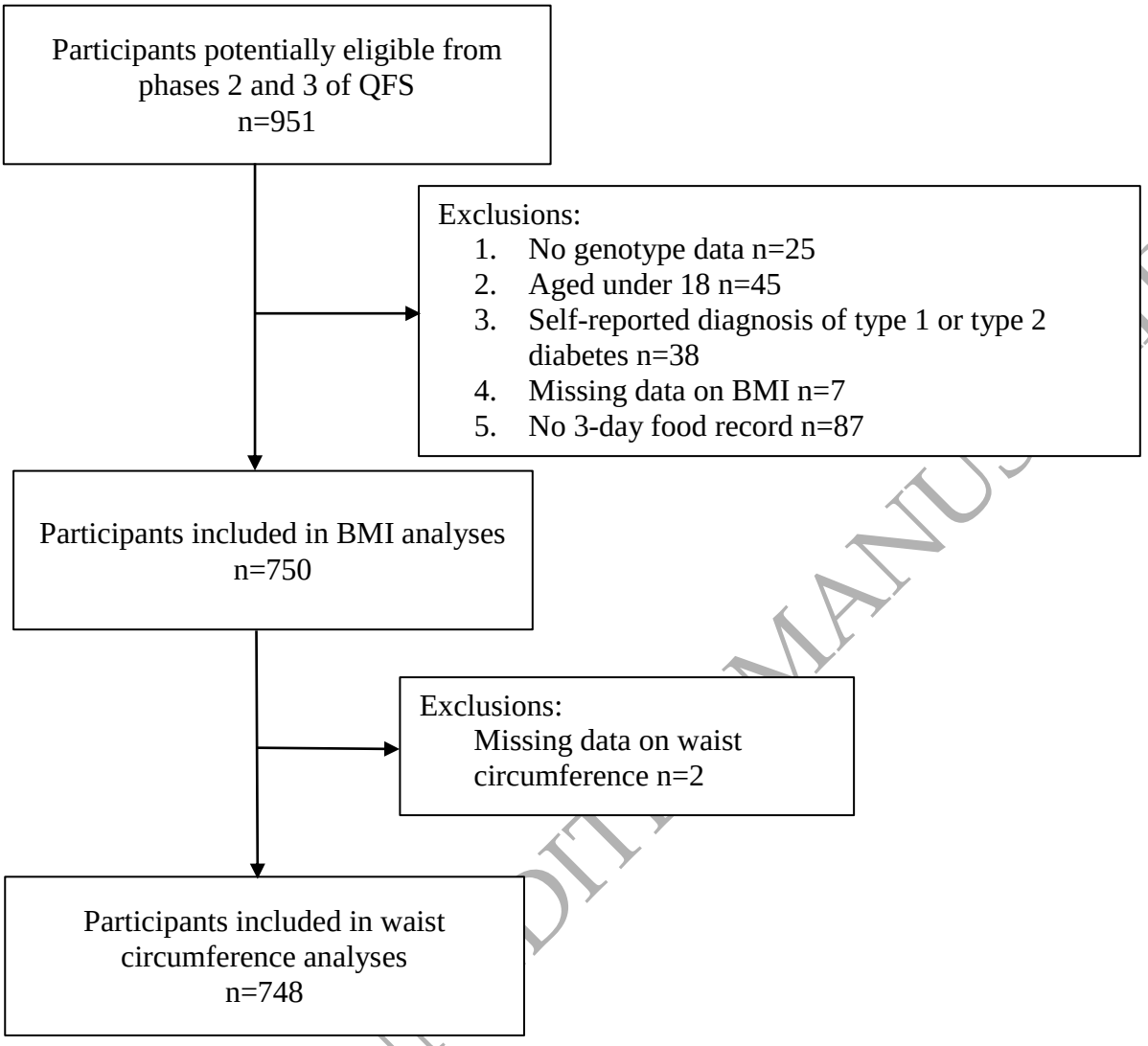


**Figure 1.** Flowchart diagram of participants' selection from the Quebec Family Study[1]

[1] BMI, Body mass index; QFS, Quebec Family Study.

**Figure 2.**

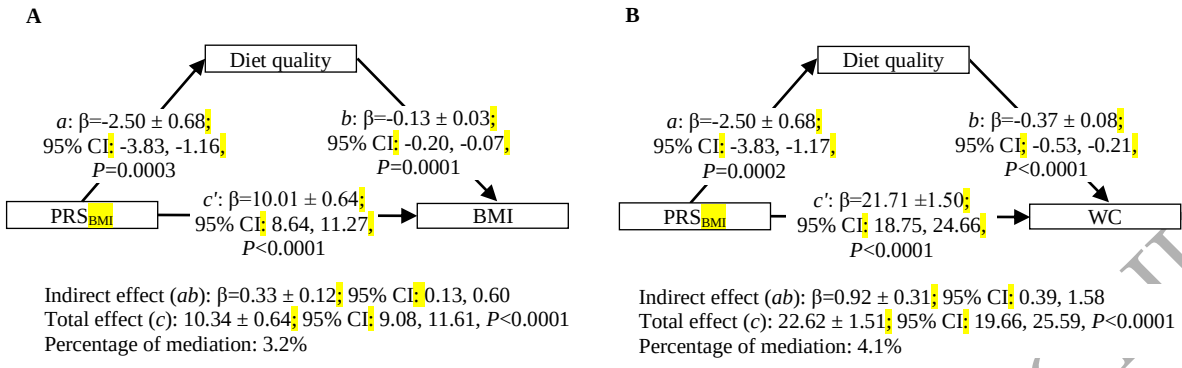


**Figure 2.** Mediating effect of diet quality between genetic susceptibility to obesity ($PRS_{BMI}$) and obesity measures (BMI and WC) in the Quebec Family Study[1]

[1] Values are β coefficients ± standard errors. n=738 for BMI analysis and n=737 for WC analysis. Analyses are performed on complete cases resulting on the exclusion of n=12 participants with missing data on menopausal (n=12), dieting (n=1) or smoking status (n=1) from analysis related to BMI and the exclusion of n=11 participants with missing data on menopausal status from analysis related to WC. Mediation analyses are conducted using the Process Macro v. 3.4.1 for SAS that uses percentile bootstrap confidence intervals to assess the mediating or indirect effect through which the $PRS_{BMI}$ influences BMI (figure 2 A) or WC (figure 2 B). 95% CI for indirect effect are estimated through 5, 000 bootstrap samples. Mediation models are adjusted for age, sex (men, 0; women, 1), current dieting status (yes, 1; no, 0) menopausal status (yes, 1; no, 0), current smoking status (yes, 1; no, 0) and misreporting of dietary intakes ([underreporting, yes, 1; no, 0] and [overreporting, yes, 1; no, 0]). Diet quality assessed by the Nutrient Rich Food Index

6.3 (NRF6.3). *a*, association between the $PRS_{BMI}$ and diet quality (mediator); *b*, association between diet quality (mediator) and BMI or WC; total effect (*c*), association between the $PRS_{BMI}$ and BMI or WC without adjustment for diet quality (mediator); direct effect (*c'*), association between the $PRS_{BMI}$ and BMI or WC adjusted for diet quality (mediator); indirect effect (*ab*), mediation effect; Percentage of mediation: (indirect effect (*ab*)/ total effect (*c*))*100. BMI, Body mass index; CI, confidence intervals; PRS, polygenic risk score; WC, waist circumference.