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Relationships between the Planetary Health Diet Index, its food groups, and polygenic risk of obesity in the CARTaGENE cohort

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Abstract

Background The Planetary Health Diet, proposed by the EAT-Lancet Commission, seeks to promote a sustainable and healthy diet for both humans and the environment. However, few studies have investigated relationships between the Planetary Health Diet and the genetic pathway of obesity. The aim of this study was to assess whether adherence to a Planetary Health Diet Index (PHDI) mediated or moderated the genetic susceptibility to obesity.

Methods Participants were 7,037 adults (57% females, aged 55.6 ± 7.7) from the Quebec CARTaGENE Biobank. We constructed a primary polygenic risk score (PRS-Khera) for body mass index (BMI) comprised of ~ 2 million SNPs and utilized a secondary 97 SNPs polygenic risk score (PRS-Locke) for sensitivity analyses. The PHDI was based on 16 food groups. General linear models were conducted to assess main effect associations between the PRSs, the Planetary Health Diet Index (PHDI), and the individual food groups that comprise the PHDI on obesity outcomes. Causal mediation analyses (CMA) were used to evaluate mediation and interaction effects. All models were adjusted for age, sex, genetic ancestry, socio-demographic, and lifestyle variables, including those associated with dietary habits.

Results The overall PHDI was inversely associated with BMI ($\beta = -0.11$, 95% confidence interval (CI): −0.13, −0.09), waist circumference (WC) ($\beta = -0.12$, 95% CI: −0.14, −0.10), and body fat % ($\beta = -0.10$, 95% CI: −0.12, −0.08) for all participants, but did not mediate or moderate obesity polygenic risk. Associations between the PRS-Khera and obesity outcomes in all participants were partly mediated by the intake of red meat (mediation effect BMI: 1.72%, $p = 0.01$; WC: 2.22%, $p = 0.01$; body fat %: 2.14%, $p = 0.01$). Moreover, among males, whole grains intake partly mediated the association between the PRS-Khera and outcomes cross-sectionally (BMI: 1.28%, $p = 0.03$; WC: 1.71%, $p = 0.02$; body fat %: 2.19%, $p = 0.02$) and longitudinally (BMI: 3.80%, $p = 0.02$; WC: 7.38%, $p = 0.04$), but some observations were attenuated upon correction for multiple comparisons.

Conclusions PHDI adherence was associated with a lower BMI, WC, and body fat % and genetic susceptibility to obesity was partly mediated by the intake of red meat and whole grains. Some components of a plant-based diet could be implicated in mechanisms underlying genetic susceptibility to obesity.

Keywords Planetary health diet, Obesity, Polygenic risk, Mediation, Moderation

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Background

Adopting healthy sustainable diets focused on plant-based foods, as opposed to animal-based foods, is crucial for individual health and well-being, as well as for minimizing environmental impacts [1–3]. Plant-based dietary patterns, comprising at least two thirds plant-based food products, have gained popularity [4–6], offering a balanced approach that includes some animal food-products, unlike vegan and vegetarian diets [6]. Shifting towards such sustainable dietary patterns, particularly plant-based ones, is key to reducing greenhouse gas emissions, land use and water use [7]. This is important, given that meat has the major impact on greenhouse gas emissions and land use [8]. Moreover, a growing body of literature recognizes the positive environmental and health effects of plant-based diets [9, 10].

In 2019, the EAT-Lancet Commission proposed the planetary health diet as a healthy and adaptable choice for both people and the planet [11]. This plant-based diet emphasizes whole grains, fruits, vegetables, nuts, and legumes while limiting meat and dairy consumption. It is supported by evidence showing global benefits such as reduced greenhouse gas emissions and a smaller water food footprint [12, 13]. Furthermore, shifting to this diet will not necessarily imply higher costs [14]. However, limited evidence exists regarding its impact on major health outcomes [15], with only two studies indicating an inverse association between adherence to the Planetary Health Diet and obesity [15, 16].

Plant-based diets are generally linked to a lower obesity risk [17]. Diet is recognized as a key obesity risk factor, with emerging evidence suggesting its potential to modify genetic susceptibility [18]. Mediation studies explore mechanisms influencing an observed association, while interaction studies investigate how relationships vary based on a third variable [18]. Specifically, while overall diet quality has been shown to modify (interact with) genetic obesity risk, few studies have explored diet as a mediator of genetic susceptibility [19, 20]. Mediation studies in this area are important because they provide insight into possible dietary mechanisms underlying relationships between genetic risk factors and obesity outcomes. Recent studies have reported evidence of moderation as well as mediation between healthy plant-based dietary and genetic risk of obesity [21, 22], highlighting the complexity of relationships between diet and genetic susceptibility. However, a study that investigated adherence to the Planetary Health Diet specifically did not observe moderation or mediation patterns between diet, polygenic obesity risk, and obesity-related outcomes [23]. Thus, further research is needed to assess plant-based diets' role in the genetic pathway of obesity. In this study, we assessed whether adherence to the Planetary Health Diet, including its food groups, mediated or moderated genetic obesity susceptibility using data from the Quebec CARTaGENE cohort.

Methodology

Study population

The CARTaGENE (CaG) biobank (https://cartagene.qc.ca/) is a population-based cohort of adults residing in Quebec, Canada aimed at investigating environmental, lifestyle and genomic determinants of chronic diseases [24]. The CaG cohort comprises adults aged 40–69 years old from the following regions of the province: Gatineau, Saguenay, Sherbrooke, Québec City, Trois-Rivieres and the Greater Montreal Area. Participants were randomly recruited between 2009 and 2010 and were invited for an in person assessment. Participants provided data via questionnaires, biological samples, and physical measurements at a study centre.

In this analysis, we used a subset of individuals with dietary data collected with a semi-quantitative food frequency questionnaire (FFQ) ($n=9{,}696$). We excluded participants with fewer than half of FFQ items answered, and with implausible energy intakes (females < 500 kcal and > 3500 kcal; males < 800 kcal and > 4200 kcal) [25, 26], implausible or missing values for obesity outcomes, BMI (> 52, $n=140$), waist circumference (WC, < 41 cm, $n=126$), and body fat%, and missing genetic data. The final dataset included 7,037 participants (Fig. 1). Follow-up examinations took place in 2016 (approximately 6 years after baseline) among a sample of $n=14{,}081$ participants who participated in a complementary study. In this analysis, we utilized data from a subsample of $n=2{,}258$ participants who self-reported plausible BMI or WC data collected at follow-up, and had genotype data and dietary information available at baseline. This investigation was approved by the CaG Sample and Data Access Committee and the Research Ethics Board of McGill University's Faculty of Agriculture and Environmental Sciences approved the study in accordance with the Declaration of Helsinki. All participants provided informed consent to participate in the study.

Dietary assessment and calculation of the planetary healthy diet index (PHDI)

Dietary intake was assessed cross-sectionally at baseline with the Canadian adaptation of the US National Institutes of Health Diet History questionnaire (DHQ II). The DHQ II is a validated semi-quantitative FFQ that comprises 164 food and beverage items and evaluates dietary intake over the past 12 months [27]. Respondents are presented with nine frequency options, ranging from "1 time per month or less" to "6 or more times per day," along with varying quantities for each food or drink item,

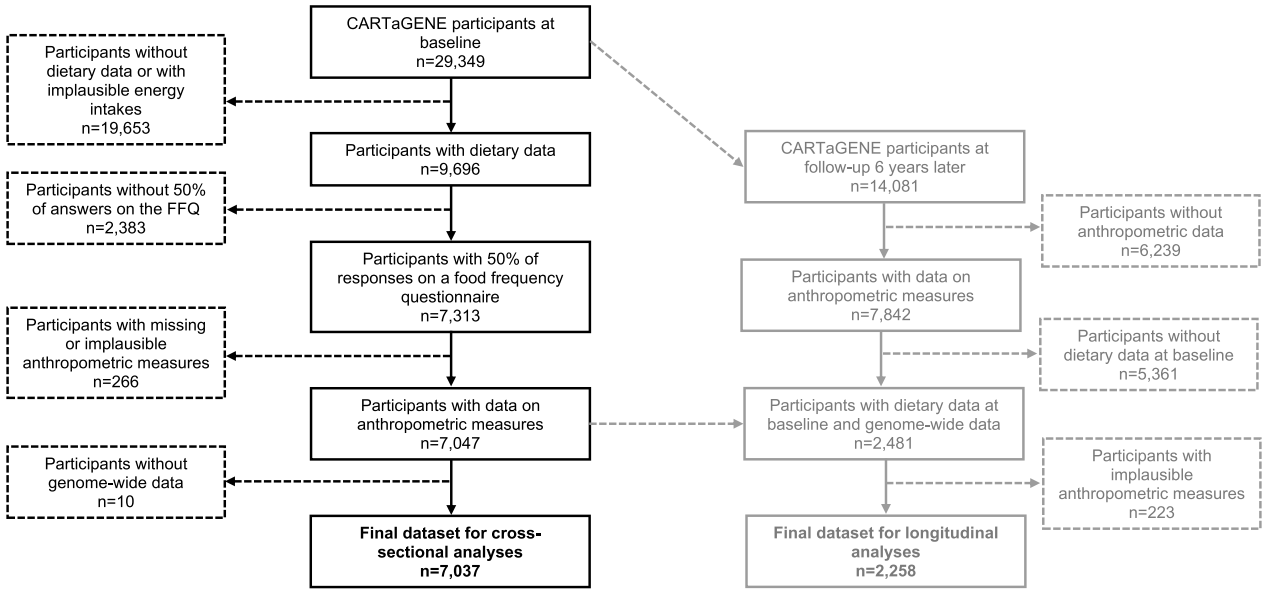

Fig. 1 Participant flowchart

allowing for accurate quantification of food consumption. Energy and nutrient values were calculated using DietCalc software based on the responses provided.

The Planetary Health Diet Index (PHDI) was calculated following the methodology from Cacau et al. [28] that adapted the recommendations from the EAT-Lancet Commission Panel [11] and included intermediate values and interchangeable food groups. The PHDI ranged from 0 to 150 points, with a higher score indicating better adherence. PHDI includes 16 food groups: nuts and peanuts, legumes, fruits, vegetables, whole grains, eggs, fish and seafood, tubers and potatoes, dairy, vegetable oils, red meat, chicken and substitutes, animal fats, added sugars, dark green vegetables ratio, and red and orange vegetables ratio. The FFQ inquired about the consumption of butter and margarine together, thus the food group labelled animal fat, encompassed margarine. The food consumption data for the PHDI components were measured based on daily intake values expressed in grams per day (g/day) and kilocalories per day (kcal/day), as described in Cacau et al. [16].

The PHDI ranged from 0 to 150 points, with a higher score indicating better adherence. For each of the 16 components in the PHDI, a maximum of 10 points could be ascribed, resulting in a total score ranging from 0 to 150 points. All food groups scored from 0 to 10 points, except for the ratios of dark green vegetables and red and orange vegetables, which scored from 0 to 5 points. Table S1 shows information of foods and beverages included in the food groups, cut-off points and scoring system.

Genotyping and polygenic risk scores

DNA was extracted from blood and saliva samples were genotyped using the Illumina Infinitum Global Screening Array. Genotype quality control was applied following the procedure of Anderson et al. (2010), and genetic imputation was performed with Minimac4 software as described elsewhere [29]. We excluded variants with low imputation score (rsq < 0.03) using PLINK 2.0 (www.cog-genomics.org/plink/2.0/). Genetic principal components of ancestry were also calculated using PLINK 2.0.

We constructed two polygenic risk scores (PRS) for BMI, as several GWAS have been conducted on this trait. The PRS utilized in our main analyses (PRS-Khera) was a genome-wide PRS, incorporating all available single nucleotide polymorphisms (SNPs) associated with BMI, regardless of their genome-wide significance. It was constructed as proposed by Khera et al. [30] and comprised over 2 million SNPs, explaining 10% of the BMI variance in this study sample (determined from a multiple linear regression of the association between the PRS and BMI controlling for age, sex, and principal components of ancestry). For sensitivity analyses, we utilized a more conservative and widely studied PRS (PRS-Locke), comprised of 97 SNPs that met genome-wide significance with BMI [31, 32]. In the present study sample, 92 of the 97 PRS-Locke SNPs were available and explained 3% of BMI variance. Additional details regarding the number of SNPs in both PRSs and density plots can be found in Table S2 and Fig. S1, respectively.

Assessment of anthropometric measurements and covariates

At baseline, BMI (kg/m^2) was calculated from measured height and weight. Height was measured using a portable stadiometer (SECA 214) to the nearest 0.1 cm and weight was measured using a digital scale (TANITA) to the nearest 0.1 kg. WC was measured with a tape (SECA 200) between the lowest rib and the iliac crest and reported in cm. Bioelectrical impedance was used to measure body fat percentage (%). Weight, height, WC and bioelectrical impedance at baseline were directly measured at the CaG BioBank assessment centers by trained professionals, ensuring the accuracy and reliability of these measurements. At follow-up, participants self-reported their weight and self-measured their WC. Participants were asked to use a flexible tape measure for WC and they provided the measurement twice. The average of the two measures was used in our analysis.

Socio-demographic and lifestyle characteristics were assessed by questionnaire and included biological sex (male/female), age (in years), ethnicity (Caucasian/Non-Caucasian), alcohol intake (categories of monthly, weekly, or daily consumption), smoking (categories of never, past, occasional, or daily), education (categories of high school or less, college, or university), sleeping time (categories of ≤6 h, 7–8 h, ≥9 h), income (categories of low, low-medium, medium–high, and high), and anxiety (categories of never, several days, more than half of days, almost everyday), as described elsewhere [24]. Anxiety was included as a proxy for mental health, given the relevance for diet and obesity, and was assessed from a standardized anxiety screening questionnaire. It was converted to a binary (yes/no) variable for analyses ("never" preserved and all other categories combined). Principal components of ancestry were derived from genetic data to correct for population stratification [33].

Physical activity level (as a continuous variable) was calculated by dividing the individual's total energy intake (TEI) by their basal metabolic rate (BMR). This approach is commonly used to estimate physical activity level, where TEI represents the total calories consumed, and BMR represents the energy expended at rest. For a subset of participants, BMR and body composition were estimated using bioelectrical impedance (BIA). For participants without BIA data, the Mifflin-St Jeor equation was calculated to estimate their BMR [34]. This method of calculating PAL is supported by previous research, which provided a detailed analysis of predictive equations for estimating energy expenditure [34].

To classify participants as under-, plausible-, or over- reporters, energy misreporter status was calculated based on the percentage of their predicted energy expenditure: < 70% under-reporters; between 70 and 142% plausible-reporters, and > 142% over-reporters [35].

Statistical analyses

Non-normally distributed variables were log-transformed before the analyses. Descriptive characteristics of the study sample were presented as means and standard deviations (SDs) for continuous variables and as numbers and percentages (%) for categorical variables. Differences between males and females were assessed using a *t* test or Pearson's Chi-square test. Differences between quintiles of genetic risk of obesity (PRS-Khera) were calculated using *p* values for trend. For handling missing data on covariates, we utilized the chained random forest imputation. This method assumes that the missing values are random, aiming to minimize the potential bias of missing cases [36]. We utilized the package missRanger (www.CRAN.R-project.org/package=missRanger) for implementing the imputation, which comprised 200 trees. Moreover, we controlled by additional predictors related to those being imputed (BMI, age, and sex) to enhance accuracy.

Main effect associations between the exposures (PHDI and PRSs, evaluated separately) and outcomes were presented as general linear models (GLM) adjusted for age, sex, the top four principal components of ancestry (or ethnicity), income, education, alcohol intake, smoking, physical activity, sleeping time, anxiety, and energy misreporter status. To enhance interpretation and comparability of results, we standardized all exposures and outcomes. Associations with standardized variables are reported in tables to compare effect sizes across results, while regression coefficients reflecting outcome variables in their original scale are included in text for PHDI and PRS main effect associations. Causal mediation analyses (CMA) were performed to identify potential mediation or moderation in the association between the PRS-Khera and obesity outcomes through the PHDI and their food groups (Fig. 2). We utilized the CAUSALMED SAS package to decompose the total effect into: controlled direct effect (total effect of the exposure on the outcome), pure indirect effect (mediation effect), reference interaction (interaction effect), and mediated interaction (effect due to both mediation and interaction). Significant models in the CMA were assessed longitudinally by incorporating an outcome, BMI or WC, measured 6 years later. Longitudinal model 1 was adjusted for the same set of covariates described above. Longitudinal model 2 additionally included the baseline outcome, BMI or WC, as a covariate. Bias corrected estimates and 95% confidence intervals (CIs) were calculated using a bootstrapping approach of 5000 draws.

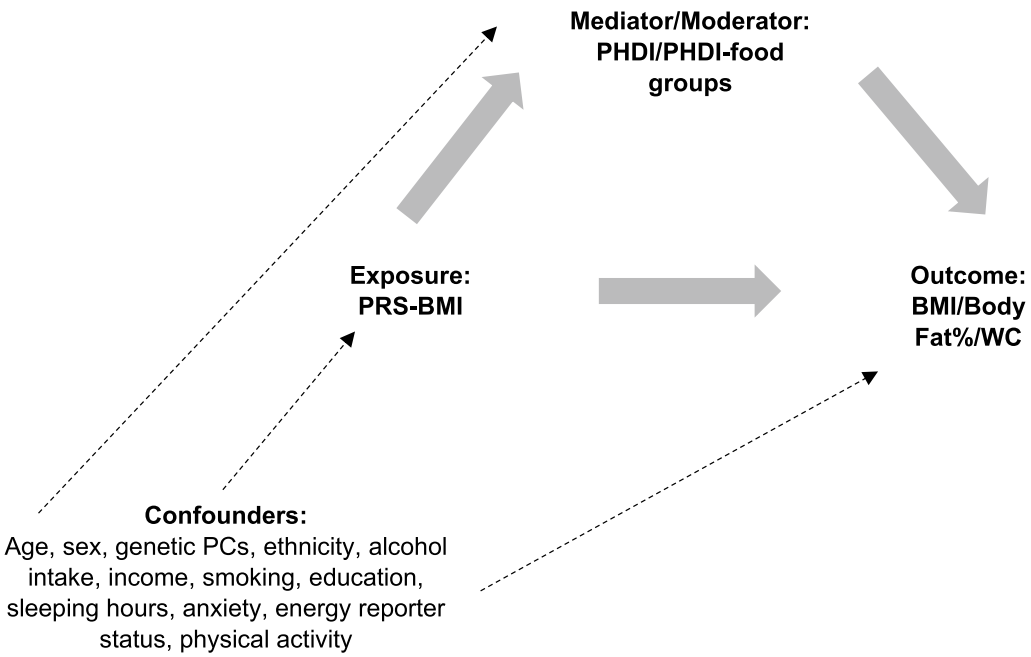

Fig. 2 Directed acyclic graph for the study of the association of a polygenic risk score for BMI on obesity outcomes, body mass index (BMI), body fat % and waist circumference (WC), potentially mediated (or moderated) by the planetary healthy diet index (PHDI) or their food group items. Potential confounders of the associations between exposure, mediator/moderator and outcomes are considered

In mediation analyses, several assumptions must be met: 1) no unmeasured confounder of the exposure-outcome, mediator-outcome, and exposure-mediator relationships; 2) a linear relationship between the exposure and the mediator; and 3) the mediator should be associated with the outcome independent of the exposure. We verified that these assumptions were satisfied and included relevant covariates in our models ensuring absence of collinearity.

Sensitivity analyses were conducted by repeating the same CMA models using the PRS-Locke as exposure. Furthermore, because CMA focuses more on mediation than moderation, we further evaluated gene-diet interactions using GLM with an interaction term in the model. We corrected for multiple testing by applying a false discovery rate (FDR) at $q = 0.10$. An FDR-adjusted p value < 0.10 (unadjusted p value $= 0.01$) was considered as the level of significance. Statistical analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R-Studio statistical software (www.r-project.org).

Results

General characteristics of the study sample

Table 1 shows the descriptive characteristics of the study sample. Approximately 57% of the study sample was female and the sample mean age was 55.6 years old. Females had a higher PHDI adherence, a lower alcohol intake, a lower income, fewer smokers, lower BMI, WC, and body fat %, and were less often under-reporters compared to males. Table S3 shows the descriptive characteristics by quintiles of PRS-Khera.

Main effect associations between the PHDI, food groups, and obesity outcomes cross-sectionally

A higher adherence to the PHDI was inversely associated with BMI ($\beta = -0.55$ kg/m^2 per one SD increase in PHDI), WC ($\beta = -1.67$ cm per one SD increase in PHDI) and body fat % ($\beta = -0.84$% per one SD increase in PHDI) in the overall sample (Table 2). Analyses by sex revealed similar associations in females and males (Table 2). As shown in Table S4, plant-based food items such as nuts, fruits, vegetables, whole grains, and the dark green vegetable ratio were negatively associated with obesity outcomes among the overall sample. However, tubers and potatoes were positively associated with BMI and WC, and body fat %. Eggs, dairy, red meat, chicken and animal fat were positively associated with obesity outcomes, with the strongest association for red meat.

Main effect associations between PRSs, PHDI, and obesity outcomes

Table 3 shows the main effect associations between PRSs, PHDI, and obesity outcomes at baseline, from cross-sectional analyses. All three obesity outcomes, BMI ($\beta = 1.45$ kg/m^2 per one SD increase in PRS), WC ($\beta = 3.20$ cm per one SD increase in PRS), and body fat

Table 1 General characteristics of the study sample

Characteristics	Overall sample *n* = 7,037	Female *n* = 3,981	Male *n* = 3,056	*p* value
Age, y, mean (SD)	55.6 (7.7)	55.3 (7.7)	56.0 (7.8)	0.0002
BMI, kg/^{m2}, mean (SD)*	27.3 (5.0)	26.7 (5.2)	28.0 (4.5)	< 0.0001
BMI follow-up, kg/^{m2}, mean (SD)⁑	26.2 (4.4)	25.4 (4.5)	27.2 (4.1)	< 0.001
Waist circumference, cm, mean (SD)	92.8 (13.9)	87.8 (13.0)	99.3 (12.4)	< 0.0001
Waist circumference follow-up, cm, mean (SD)⁑	92.7 (13.9)	90.1 (41.5)	95.8 (14.0)	< 0.0001
Body fat %, mean (SD)*	31.1 (8.4)	35.3 (7.2)	25.4 (6.3)	< 0.0001
Khera-PRS, mean (SD)	38.8 (0.2)	38.8 (0.2)	38.8 (0.2)	0.005
Locke-PRS, mean (SD)	11.4 (0.8)	11.4 (0.8)	11.4 (0.8)	0.8
PHDI, mean (SD)	60.3 (14.2)	62.0 (13.9)	58.0 (14.2)	< 0.0001
Ethnicity, n (%)				
Caucasian	6,251 (92.7)	3,741 (94.0)	2,780 (91.0)	< 0.0001
Non-Caucasian	414 (5.9)	189 (4.7)	225 (7.3)	
Unsure	102 (1.5)	51 (1.3)	51 (1.7)	
Alcohol, n (%)				
Monthly	2,429 (34.5)	1,526 (38.3)	903 (29.6)	< 0.0001
Weekly	2,555 (36.3)	1,452 (36.5)	1,103 (36.1)	
Daily	1,741 (24.7)	785 (19.7)	956 (31.3)	
Missing	312 (4.4)	218 (5.5)	94 (3.1)	
Income, n (%)				
Low	2,181 (31.0)	1,347 (33.8)	834 (27.3)	< 0.0001
Low–Medium	2,621 (37.2)	1,432 (36.0)	1,189 (38.9)	
Medium–High	1,627 (23.1)	813 (20.4)	814 (26.6)	
High	233 (3.3)	128 (3.2)	105 (3.4)	
Missing	375 (5.3)	261 (6.6)	114 (3.7)	
Smoking, n (%)				
Never	2,921 (41.5)	1,766 (44.4)	1,155 (37.8)	< 0.0001
Past	3,035 (43.1)	1,622 (40.7)	1,413 (46.2)	
Occasional	268 (3.8)	142 (3.6)	126 (4.1)	
Daily	787 (11.2)	434 (10.9)	353 (11.6)	
Missing	26 (0.4)	17 (4.3)	9 (0.3)	
Education, n (%)				
High School or less	1,650 (23.4)	958 (24.1)	692 (22.6)	0.01
College	2,260 (32.1)	1,315 (33.0)	945 (30.9)	
University or higher	3,099 (44.0)	1,691 (42.5)	1,408 (46.1)	
Missing	28 (0.4)	17 (0.4)	11 (0.4)	
Sleep, n (%)				
≤ 6 h	1,352 (19.2)	726 (18.2)	626 (20.5)	< 0.001
7–8 h	4,921 (69.9)	2,774 (69.7)	2,147 (70.3)	
≥ 9 h	730 (10.4)	462 (11.6)	268 (8.8)	
Missing	34 (0.5)	19 (0.5)	15 (9.7)	
Anxiety, n (%)				
Never	6,156 (87.5)	3,408 (85.6)	2,748 (89.9)	< 0.0001
Several days	633 (9.0)	404 (10.1)	229 (7.5)	
More than half of the days	155 (2.2)	107 (2.7)	48 (1.6)	
Almost everyday	70 (1.0)	48 (1.2)	22 (0.7)	
Missing	23 (0.3)	165 (4.1)	9 (0.3)	
Energy reporter status, n (%)				
Under reporter	2,017 (28.7)	920 (23.1)	1,097 (35.9)	< 0.0001
Plausible reporter	4,251 (60.4)	2,522 (63.4)	1,729 (56.6)	

Table 1 (continued)

Characteristics	Overall sample *n* = 7,037	Female *n* = 3,981	Male *n* = 3,056	*p* value
Over reporter	597 (8.5)	374 (9.4)	223 (7.3)	
Missing	172 (2.4)	165 (4.1)	7 (0.2)	
Physical activity level, n (%)				
Sedentary	4,496 (63.9)	2,628 (66.0)	1,868 (61.1)	< 0.0001
Low active	1,110 (15.8)	605 (15.2)	505 (16.5)	
Active	757 (10.8)	376 (9.4)	381 (14.5)	
Very active	503 (11.2)	207 (5.2)	296 (9.7)	
Missing	171 (2.4)	165 (4.1)	6 (0.2)	

Data are presented as numbers (%) and means (and standard deviations), *p* values were determined by *t* test for continuous variables and Pearson's chi-square for categorical variables. *Lower sample size due to missing values, BMI: *n* = 7,022 for the overall sample, *n* = 3,972 for females, *n* = 3,056 for males; body fat %: *n* = 6,651 for the overall sample, *n* = 3,817 for females, *n* = 2,834 for males. ‡Participants at follow-up: *n* = 2,258 for the overall sample, *n* = 1,249 for females and *n* = 1,009 for males. Abbreviations: body mass index (BMI), planetary healthy diet index (PHDI), polygenic risk score (PRS)

Table 2 Main effect of cross-sectional associations between PHDI and obesity outcomes

	PHDI			
Overall	**n**	**β (95% CI)**	***p* value**	**FDR-adjusted *p* value**
Overall sample				
BMI	7,022	−0.11 (−0.13, −0.09)	< 0.0001	0.02
WC	7,037	−0.12 (−0.14, −0.10)	< 0.0001	0.03
Body fat %	6,651	−0.10 (−0.12, −0.08)	< 0.0001	0.02
Females				
BMI	3,972	−0.12 (−0.16, −0.09)	< 0.0001	0.009
WC	3,981	−0.12 (−0.15, −0.09)	< 0.0001	0.01
Body fat %	3,817	−0.10 (−0.13, −0.08)	< 0.0001	0.007
Males				
BMI	3,050	−0.09 (−0.12, −0.06)	< 0.0001	0.005
WC	3,056	−0.12 (−0.15, −0.09)	< 0.0001	0.006
Body fat %	2,834	−0.09 (−0.12, −0.06)	< 0.0001	0.005

Data are standardized beta-coefficients from general linear models with respective 95% confidence intervals. All models were adjusted for: age, sex, ethnicity, alcohol intake, smoking, education, sleeping time, income, anxiety, physical activity, and energy misreporter status. Abbreviations: body mass index (BMI), false discovery rate (FDR), planetary healthy diet index (PHDI), waist circumference (WC)

% ($\beta = 1.76\%$ per one SD increase in PRS), were significantly associated with the PRS-Khera in the overall sample. Similarly, all three obesity outcomes were significantly associated with the PRS-Locke, but associations were weaker (BMI: $\beta = 0.40$ kg/m^2 per one SD increase in PRS, WC: $\beta = 0.83$ cm per one SD increase in PRS, body fat %: $\beta = 0.42\%$ per one SD increase in PRS). The respective PRS associations with the obesity outcomes were similar when analyses were stratified by sex (data not shown). No significant associations were observed between PRSs and the PHDI.

Additionally, associations between PRSs and BMI and WC measured at follow-up (6 years later) in longitudinal analyses, were also evaluated (Table S5). Both PRSs were associated with obesity outcomes in model 1. However, when adjusting for BMI or WC at baseline (model 2), no significant results were observed.

Results from causal mediation analyses

Tables 4, 5 and 6 show the results from CMA on the cross-sectional associations of PRS-Khera with BMI, WC and body fat %, respectively, at baseline. CMA did not indicate mediation or moderation for the PHDI in the genetic susceptibility to obesity. Among food groups, red meat intake mediated the association between the PRS-Khera and BMI (mediation effect 1.72%, $p = 0.01$, $q = 0.09$), WC (mediation effect 2.22%, $p = 0.01$, $q = 0.09$), and body fat % (mediation effect 2.14%, $p = 0.02$, $q < 0.1$). Among females, the results for red meat were borderline significant and mediation was observed for BMI (mediation effect 2.29%, $p = 0.02$, $q = 0.10$) and WC (2.92%, $p = 0.02$, $q = 0.10$), but not for body fat % (mediation effect 2.43% $p = 0.04$, $q = 0.20$). When the analyses were limited to males, the mediation by red meat was not statistically significant, but uncorrected CMA results indicated mediation by whole grains in the association between the PRS-Khera and BMI (mediation effect 1.28%, $p = 0.03$, $q = 0.10$), WC (mediation effect 1.71%, $p = 0.02$, $q = 0.10$), and body fat % (mediation effect, 2.19% $p = 0.02$, $q = 0.10$), though results were borderline significant upon FDR correction. No food group showed statistically significant interactions in CMA.

Since the cross-sectional analyses indicated or suggested mediation through red meat and whole grains

Table 3 Main effect associations between PHDI, PRSs, and obesity outcomes

		PRS-Khera			PRS-Locke		
	n	*β* (95% CI)	*p* value	FDR-adjusted *p* value	*β* (95% CI)	p value	FDR-adjusted *p* value
Overall sample							
BMI	7,022	0.29 (0.27, 0.32)	< 0.0001	0.004	0.08 (0.06, 0.11)	< 0.0001	0.002
WC	7,037	0.23 (0.21, 0.25)	< 0.0001	0.004	0.06 (0.04, 0.08)	< 0.0001	0.002
Body fat %	6,651	0.21 (0.19, 0.23)	< 0.0001	0.004	0.05 (0.04, 0.07)	< 0.0001	0.002
PHDI	7,037	− 0.02 (− 0.04, 0.01)	0.2		0.01 (− 0.02, 0.03)	0.6	
Females							
BMI	3,972	0.32 (0.28, 0.35)	< 0.0001	0.003	0.09 (0.05, 0.12)	< 0.0001	0.002
WC	3,981	0.22 (0.19, 0.25)	< 0.0001	0.003	0.05 (0.02, 0.08)	< 0.001	0.008
Body fat %	3,817	0.22 (0.19, 0.25)	< 0.0001	0.003	0.06 (0.04, 0.09)	< 0.0001	0.002
PHDI	3,981	− 0.01 (− 0.05, 0.02)	0.4		0.02 (− 0.01, 0.05)	0.3	
Males							
BMI	3,050	0.27 (0.23, 0.30)	< 0.0001	0.003	0.08 (0.05, 0.11)	< 0.0001	0.002
WC	3,056	0.24 (0.20, 0.27)	< 0.0001	0.003	0.07 (0.04, 0.10)	< 0.0001	0.002
Body fat %	2,834	0.19 (0.16, 0.22)	< 0.0001	0.002	0.04 (0.02, 0.07)	0.001	0.007
PHDI	3,056	− 0.02 (− 0.06, 0.02)	0.3		0.00 (− 0.04, 0.03)	0.8	

Data are standardized beta-coefficients from general linear models with respective 95% confidence intervals. All models were adjusted for: age, sex, principal components of ancestry, alcohol intake, smoking, education, sleeping time, income, anxiety, physical activity, and energy misreporter status. Abbreviations: body mass index (BMI), false discovery rate (FDR), planetary healthy diet index (PHDI), polygenic risk score (PRS), waist circumference (WC)

on the association of PRS-Khera and obesity outcomes, among the full sample or by sex, we analyzed these food groups in longitudinal models. Results from CMA longitudinal models showed no significant results in the overall sample, but a borderline significant mediation for whole grains in the association between the PRS-Khera and BMI measured 6 years later among males (mediation effect 3.80% $p = 0.02$, $q = 0.10$) in model 1 (Table S6). When the analyses were adjusted for baseline BMI or WC, model 2, no significant mediation was observed (Table S7).

Sensitivity analyses

Table S8 shows results for PRS-diet interactions on obesity outcomes using GLM. No significant interactions were observed between the PRS-Khera and the PHDI or any individual food group on obesity outcomes. CMA models were performed using the PRS-Locke as the genetic exposure (Tables S9, S10 and S11). The PHDI and its food groups did not mediate or moderate the associations between the PRS-Locke and BMI or WC. GLM analyses to test for PRS-diet interactions were also performed using the PRS-Locke (Table S12). No significant interactions were observed between the PRS-Khera and the PHDI or any individual food groups on obesity outcomes (Table S12).

Discussion

This study investigated the complex interrelationships between adherence to PHDI and consumption of its individual food groups, polygenic susceptibility to obesity, and obesity outcomes. Our main findings showed that adherence to the PHDI was inversely associated with obesity outcomes, but PHDI adherence did not mediate or moderate genetic susceptibility to obesity. Further, we demonstrated that the intake of red meat partly mediated the association between a genome-wide PRS-BMI of more than 2 million SNPs and BMI, body fat %, and WC. Our results also suggest that genetic susceptibility to obesity may be partly mediated by whole grains intake among males, both cross-sectionally and longitudinally, extending previous cross-sectional findings of dietary factors as potential mediators of the obesity genetic pathway.

In this study we used a unified approach that assessed both mediation and moderation to understand the interplay between genetic and dietary factors in the development of obesity. Generally, gene-diet interaction studies using PRSs for BMI in samples of European ancestry have reported that healthy diet quality attenuated obesity outcomes among individuals at higher genetic risk [37–41]. Furthermore, recent studies have reported statistical interactions as well as mediation between a PRS for BMI and components of a healthy plant-based dietary index on BMI [21, 22]. However, a separate study that examined

Table 4 Results from the causal mediation models on the association between PRS-Khera and BMI

Mediator	Total effect	Controlled direct effect	Pure indirect effect	Reference interaction	Mediated interaction	% mediated
PHDI	1.402 (1.283, 1.520)***	1.395 (1.276, 1.510)***	0.008 (−0.005, 0.021)	0.000 (−0.001, 0.001)	0.000 (−0.013, 0.009)	
Nuts	1.429 (1.312, 1.547)***	1.425 (1.308, 1.543)***	0.004 (−0.004, 0.014)	0.000 (−0.001, 0.001)	0.000 (−0.013, 0.009)	
Legumes	1.393 (1.275, 1.516)***	1.393 (1.275, 1.515)***	0.000 (−0.004, 0.001)	0.000 (−0.002, 0.002)	0.001 (−0.004, 0.016)	
Fruits	1.401 (1.285, 1.513)***	1.401 (1.284, 1.513)***	0.000 (−0.002, 0.004)	0.000 (−0.001, 0.001)	0.000 (−0.005, 0.012)	
Vegetables	1.401 (1.285, 1.513)***	1.401 (1.284, 1.513)***	0.000 (−0.002, 0.004)	0.000 (−0.001, 0.001)	0.000 (−0.005, 0.012)	
Whole grains	1.409 (1.297, 1.531)***	1.404 (1.292, 1.525)***	0.003 (−0.002, 0.011)	0.000 (−0.002, 0.002)	0.002 (−0.003, 0.022)	
Eggs	1.398 (1.278, 1.525)***	1.390 (1.270, 1.515)***	0.008 (−0.001, 0.018)	0.000 (−0.001, 0.001)	0.000 (−0.013, 0.016)	
Fish	1.427 (1.307, 1.546)***	1.427 (1.308, 1.545)***	0.000 (−0.004, 0.001)	0.000 (−0.002, 0.001)	0.000 (−0.006, 0.011)	
Tubers and potatoes	1.405 (1.290, 1.519)***	1.405 (1.291, 1.519)***	−0.005 (−0.017, 0.005)	0.000 (−0.003, 0.003)	0.006 (−0.004, 0.030)	
Dairy	1.397 (1.279, 1.516)***	1.397 (1.284, 1.515)***	0.000 (−0.008, 0.008)	0.000 (−0.003, 0.002)	0.000 (−0.014, 0.014)	
Vegetable oil	1.384 (1.263, 1.501)***	1.384 (1.265, 1.500)***	0.002 (0.000, 0.007)	0.000 (−0.001, 0.001)	−0.002 (−0.019, 0.010)	
Red meat	1.398 (1.277, 1.518)***	1.374 (1.257, 1.491)***	0.024 (0.005, 0.043)*	0.000 (−0.001, 0.011)	0.000 (−0.014, 0.018)	1.72 (0.40, 1.72)
Chicken	1.395 (1.278, 1.519)***	1.392 (1.278, 1.517)***	0.006 (−0.003, 0.017)	0.000 (−0.001, 0.002)	−0.003 (−0.024, 0.003)	
Animal fat	1.435 (1.319, 1.554)***	1.433 (1.318, 1.550)***	−0.005 (−0.013, 0.001)	0.000 (−0.002, 0.002)	0.007 (−0.002, 0.031)	
Added sugar	1.401 (1.285, 1.515)***	1.401 (1.284, 1.510)***	0.000 (−0.001, 0.005)	0.000 (−0.001, 0.001)	−0.001 (−0.013, 0.004)	
DGV:V	1.414 (1.298, 1.531)***	1.416 (1.302, 1.534)***	0.002 (−0.001, 0.007)	0.000 (−0.002, 0.002)	−0.005 (−0.027, 0.003)	
ROV:V	1.403 (1.285, 1.518)***	1.403 (1.284, 1.517)***	0.000 (−0.003, 0.001)	0.000 (−0.001, 0.001)	0.000 (−0.007, 0.009)	

* FDR-corrected *p* value < 0.10, **FDR-corrected *p* value < 0.05, ***FDR-corrected *p* value < 0.01. Results are presented as beta-coefficients and their respective 95% confidence intervals. All models were adjusted for: age, sex, principal components of ancestry, alcohol intake, smoking, education, sleeping time, income, anxiety, physical activity, and energy misreporter status. Abbreviations: dark green vegetables:total vegetables ratio (DGV:V), false discovery rate (FDR), planetary healthy diet index (PHDI), red and orange vegetables:total vegetables ratio (ROV:V)

adherence to the PHDI reported no observations of moderation or mediation with obesity polygenic risk [23]. Our present study is aligned with those results for overall adherence to the PHDI, though two of its individual food groups were identified as mediators of obesity polygenic risk. Moreover, in the current study, adherence to the PHDI was found to be associated with lower BMI, WC and body fat % when polygenic susceptibility was not considered. This is in agreement with several previous studies that have investigated the relationship between obesity and healthy and sustainable plant-based dietary patterns showing that there is an inverse relationship between the dietary patterns and obesity [15, 16, 42–44]. Thus, following the EAT-Lancet recommendations, or other healthy plant-based dietary patterns, may be beneficial when planning weight loss strategies for adult individuals with the added benefit of helping to reduce global greenhouse gas emissions.

Despite not identifying mediation or moderation effects regarding adherence to PHDI in relation to the genetic susceptibility to obesity, our study revealed that certain food groups in the PHDI, red meat and whole grains, played a mediating role in the association between the genome-wide PRS-BMI and obesity outcomes. This is important because it supports growing evidence that decreasing the intake of red meat and increasing the intake of plant-based alternatives is not only beneficial for human health, but also for the planet. Meat production is

Table 5 Results from the causal mediation models on the association between PRS-Khera and waist circumference

Mediator	Total effect	Controlled direct effect	Pure indirect effect	Reference interaction	Mediated interaction	% mediated
PHDI	1.095 (0.100, 0.121)***	1.086 (0.983, 1.200)***	0.009 (−0.005, 0.023)	0.000 (−0.001, 0.001)	0.000 (−0.008, 0.013)	
Nuts	1.112 (1.000, 1.223)***	1.107 (1.000, 1.217)***	0.005 (−0.004, 0.015)	0.000 (−0.001, 0.001)	0.000 (−0.008, 0.015)	
Legumes	1.090 (0.980, 1.204)***	1.089 (0.975, 1.204)***	−0.001 (−0.005, 0.001)	0.000 (−0.002, 0.002)	0.001 (−0.004, 0.015)	
Fruits	1.094 (0.984, 1.205)***	1.093 (0.982, 1.203)***	0.001 (−0.004, 0.007)	0.000 (−0.001, 0.001)	0.000 (−0.005, 0.010)	
Vegetables	1.094 (0.984, 1.205)***	1.093 (0.982, 1.203)***	0.001 (−0.004, 0.007)	0.000 (−0.001, 0.001)	0.000 (−0.005, 0.010)	
Whole grains	1.104 (0.995, 1.210)***	1.098 (0.990, 1.204)***	0.004 (−0.003, 0.012)	0.000 (−0.002, 0.002)	0.003 (−0.003, 0.022)	
Eggs	1.089 (0.976, 1.207)***	1.077 (0.965, 1.194)***	0.007 (0.000, 0.016)	0.000 (−0.002, 0.002)	0.004 (−0.005, 0.025)	
Fish	1.118 (1.004, 1.231)***	1.118 (1.005, 1.230)***	0.000 (−0.001, 0.003)	0.000 (−0.001, 0.001)	0.000 (−0.011, 0.0049	
Tubers and potatoes	1.098 (0.992, 1.208)***	1.098 (0.992, 1.208)***	−0.005 (−0.017, 0.006)	0.000 (−0.003, 0.003)	0.005 (−0.004, 0.028)	
Dairy	1.092 (0.986, 1.210)***	1.092 (0.987, 1.208)***	0.000 (−0.008, 0.008)	0.000 (−0.002, 0.002)	0.000 (−0.009, 0.010)	
Vegetable oil	1.065 (0.955, 1.178)***	1.068 (0.957, 1.179)***	0.001 (−0.002, 0.004)	0.000 (−0.001, 0.001)	−0.003 (−0.022, 0.006)	
Red meat	1.097 (0.982, 1.212)***	1.070 (0.960, 1.182)***	0.024 (0.005, 0.043)*	0.000 (−0.001, 0.001)	0.002 (−0.010, 0.022)	2.22 (0.49, 3.95)
Chicken	1.090 (0.979, 1.199)***	1.088 (0.979, 1.196)***	0.006 (−0.002, 0.015)	0.000 (−0.002, 0.002)	−0.005 (−0.024, 0.002)	
Animal fat	1.117 (1.005, 1.231)***	1.115 (1.004, 1.227)***	−0.005 (−0.013, 0.001)	0.000 (−0.002, 0.002)	0.007 (−0.002, 0.031)	
Added sugar	1.094 (0.986, 1.205)***	1.095 (0.986, 1.208)***	0.000 (−0.003, 0.001)	0.000 (−0.001, 0.001)	−0.001 (−0.014, 0.004)	
DGV:V	1.094 (0.982, 1.203)***	1.095 (0.985, 1.205)***	0.003 (−0.001, 0.008)	0.000 (−0.002, 0.002)	−0.003 (−0.023, 0.004)	
ROV:V	1.096 (0.988, 1.206)***	1.096 (0.989, 1.206)***	0.000 (−0.001, 0.003)	0.000 (−0.001, 0.001)	0.000 (−0.006, 0.010)	

* FDR-corrected *p* value < 0.10, **FDR-corrected *p* value < 0.05, ***FDR-corrected *p* value < 0.01. Results are presented as beta-coefficients and their respective 95% confidence intervals. All models were adjusted for: age, sex, principal components of ancestry, alcohol intake, smoking, education, sleeping time, income, anxiety, physical activity, and energy misreporter status. Abbreviations: dark green vegetables:total vegetables ratio (DGV:V), false discovery rate (FDR), plant-based diet index (PDI), red and orange vegetables:total vegetables ratio (ROV:V)

responsible for higher greenhouse gas emissions, water overuse, and environmental footprints compared to plant-based alternatives [45]. The food group observations were not present in sensitivity analyses that used the PRS-Locke, a well-established PRS comprised of 97 SNPs associated with BMI [31]. The sensitivity analyses enabled us to assess whether polygenic-diet patterns with BMI varied by type of PRS. The null findings suggest that more comprehensive PRS may better capture relationships between plant-based dietary patterns, polygenic risk, and obesity outcomes.

A previous study from the Quebec Family Study cohort showed that specific food groups characterized by high amounts of fatty acids, sugar and fiber, including sugar-sweetened beverages, high-fat foods, fruits, and vegetables, partly mediated the association between a genome-wide PRS for BMI and the outcomes of BMI and WC among adults [20]. Our results indicated that red meat intake mediated the genetic susceptibility to obesity, but also extended previous findings by revealing possible sex differences in associations. Among females, a borderline significant result suggested that red meat intake partly mediated the association between the PRS-Khera and obesity outcomes. This association was statistically significant among males and females combined. On the other hand, among males, whole grains intake mediated the association, both cross-sectionally and longitudinally.

Table 6 Results from the causal mediation models on the association between PRS-Khera and body fat % ($n = 6,651$)

Mediator	Total effect	Controlled direct effect	Pure indirect effect	Reference interaction	Mediated interaction	% mediated
PHDI	0.982 (0.883, 1.080)***	0.979 (0.880, 1.076)***	0.005 (−0.007, 0.018)	0.000 (−0.001, 0.001)	−0.001 (−0.014, 0.004)	–
Nuts	0.988 (0.885, 1.088)***	0.986 (0.884, 1.087)***	0.003 (−0.004, 0.010)	0.000 (−0.001, 0.001)	0.000 (−0.013, 0.004)	–
Legumes	0.969 (0.869, 1.069)***	0.969 (0.867, 1.069)***	0.000 (−0.003, 0.001)	0.000 (−0.002, 0.002)	0.001 (−0.005, 0.014)	–
Fruits	0.981 (0.885, 1.085)***	0.981 (0.886, 1.085)***	0.000 (−0.004, 0.004)	0.000 (−0.001, 0.001)	0.001 (−0.008, 0.005)	–
Vegetables	0.981 (0.885, 1.085)***	0.981 (0.886, 1.085)***	0.000 (−0.004, 0.004)	0.000 (−0.001, 0.001)	0.001 (−0.008, 0.005)	–
Whole grains	0.987 (0.887, 1.097)***	0.983 (0.885, 1.093)***	0.004 (−0.003, 0.012)	0.000 (−0.001, 0.001)	0.000 (−0.007, 0.012)	–
Eggs	0.963 (0.854, 1.064)***	0.961 (0.853, 1.060)***	0.005 (−0.001, 0.014)	0.000 (−0.002, 0.002)	−0.004 (−0.024, 0.004)	–
Fish	0.997 (0.894, 1.103)***	0.998 (0.896, 1.107)***	0.000 (−0.001, 0.002)	0.000 (−0.001, 0.001)	0.000 (−0.010, 0.005)	–
Tubers and potatoes	0.988 (0.886, 1.086)***	0.989 (0.887, 1.087)***	−0.007 (−0.018, 0.004)	0.000 (−0.002, 0.002)	0.006 (−0.002, 0.027)	–
Dairy	0.978 (0.874, 1.080)***	0.978 (0.878, 1.079)***	0.000 (−0.006, 0.006)	0.000 (−0.002, 0.002)	0.000 (−0.009, 0.009)	–
Vegetable oil	0.969 (0.865, 1.072)***	0.967 (0.863, 1.068)***	0.002 (0.000, 0.007)	0.000 (−0.001, 0.001)	0.000 (−0.009, 0.014)	–
Red meat	0.981 (0.882, 1.080)***	0.961 (0.863, 1.059)***	0.021 (0.004, 0.038)*	0.000 (−0.001, 0.001)	0.000 (−0.014, 0.014)	2.14 (0.41, 2.42)
Chicken	0.972 (0.868, 1.073)***	0.970 (0.868, 1.071)***	0.006 (−0.003, 0.015)	0.000 (−0.002, 0.002)	−0.004 (−0.022, 0.003)	–
Animal fat	1.019 (0.919, 1.122)***	1.015 (0.916, 1.119)***	−0.005 (−0.013, 0.000)	0.000 (−0.002, 0.002)	0.009 (0.000, 0.034)	–
Added sugar	0.981 (0.881, 1.081)***	0.982 (0.883, 1.082)***	0.000 (−0.002, 0.002)	0.000 (−0.001, 0.001)	−0.001 (−0.011, 0.004)	–
DGV:V	0.993 (0.891, 1.097)***	0.992 (0.890, 1.096)***	0.001 (−0.001, 0.007)	0.000 (−0.001, 0.001)	−0.001 (−0.015, 0.004)	–
ROV:V	0.982 (0.882, 1.084)***	0.982 (0.882, 1.083)***	0.000 (−0.001, 0.002)	0.000 (−0.001, 0.001)	0.000 (−0.004, 0.009)	–

* FDR-corrected p value < 0.10, **FDR-corrected p value < 0.05, ***FDR-corrected p value < 0.01. Results are presented as beta-coefficients and their respective 95% confidence intervals. All models were adjusted for: age, sex, principal components of ancestry, alcohol intake, smoking, education, sleeping time, income, anxiety, physical activity, and energy misreporter status. Abbreviations: dark green vegetables:total vegetables ratio (DGV:V), false discovery rate (FDR), plant-based diet index (PDI), red and orange vegetables:total vegetables ratio (ROV:V)

Prior studies have explained that some obesity susceptibility genes are expressed in key brain regions [31], such as the insula or substantia nigra [46], which actively contribute to appetite regulation through the central nervous system [47]. Other investigations have described that obesity genes implicated in controlling energy intake and energy expenditure [48] are more expressed in the adipose tissue [49]. Some of the genes involved in these expression pathways are the *PPARG* gene, which is involved in the adaptive thermogenesis pathway [50], the *MC4R* and the *FTO* genes, which are involved in the appetite pathway [51] and the energy regulation pathway along with the *LEP* gene [52]. The mediation pathways through red meat and whole grains are likely due to their different nutritional properties, as red meat contributes more greatly to saturated fat intake and does not contribute fiber. Obesity genes are known to be involved in lipid metabolism [52] and previous gene-diet interaction studies have shown that fatty acids moderated the genetic susceptibility to obesity, with higher fat intake reported to accentuate genetic risk [53–55]. Indeed, the consumption of plant-based food products is beneficial to reducing weight (or preventing weight gain), as they are typically less energy-dense and contain higher amounts of protective nutrients such as dietary fiber, vitamins, minerals and phytochemicals compared to animal food products [56, 57].

However, the precise mechanisms of expression of all genes implicated in obesity are not fully known, particularly as more genome-wide association studies of obesity are identifying new genetic loci, including in populations of non-European ethnicities [58, 59]. Hence, drawing conclusions regarding the specific pathways through which the intake of certain food groups may explain the genetic susceptibility to obesity is challenging. Nevertheless, a recent study illustrated that genetic variants linked to macronutrient intake are also expressed in the brain [60], making plausible that the intake of certain food groups might exert their influence through genes that regulate the appetite pathway. A recent randomized controlled study by Van Galen et al. [61] demonstrated nutrient-specific neuronal activity after infusing glucose, lipids, and water into the stomach of individuals with normal weight, however, the response was diminished among individuals with obesity. Moreover, after a successful 12-week dietary weight loss intervention, the neuronal response was not repaired among individuals with obesity, suggesting that these damaged signals may be drivers of overeating behaviors and consequently obesity [61].

Another interesting finding is that results from mediation models differed by sex. Body fat and adipose tissue differ among males, who have greater visceral fat mass, while females have greater subcutaneous adipose mass [62, 63]. The mechanisms through which sex chromosomes and gonadal hormones impact food intake, metabolism, and fat accumulation might explain the differences in body fat distribution and body composition among males and females [64]. Moreover, in addition to sex chromosomes, there are also several loci that are more strongly associated or solely associated with obesity phenotypes among females or males specifically [65]. Previous gene-sex interaction studies on obesity did not report interactions between BMI associated loci and biological sex on obesity among samples of European ancestry, but have observed differences in Asian and African samples [65]. Nonetheless, a recent small study of approximately 300 Greek males identified five SNPs related to BMI among males [66]. Hence, further investigations are needed to expand these previous findings and to disentangle whether sex may moderate the genetic susceptibility to obesity. Specifically, it is important to identify sex-specific obesity-loci to further understand the mechanisms by which dietary factors or any other environmental factors may explain the genetic susceptibility to obesity.

Our study is not without limitations. First, the lack of dietary and physical activity data at follow-up did not allow for investigation of prospective associations that assessed the temporal relationship between dietary and activity factors, including energy intake, and obesity outcomes. This limitation was partly addressed by examining CMA longitudinal models using baseline dietary data and follow-up obesity outcomes, which reduced the risk of reverse causation [67]. Additionally, only 32% of the participants from our initial baseline sample provided data at the follow-up survey. This discrepancy in sample size between baseline and follow-up can influence the interpretation of our results. The smaller follow-up sample size may not fully represent the diversity and characteristics of the original cohort, so attrition bias may be present and our longitudinal models may have been underpowered due to a lower sample size. The follow-up anthropometric data were also self-measured/self-reported, which may have resulted in measurement errors.

Moreover, our mediation analyses assume that the PRSs influenced dietary intake, which in turn affected obesity outcomes. While significant mediation effects for red meat and whole grains were found, these results are based on cross-sectional data, limiting causal inferences (68). Additionally, age is a key factor that could influence both dietary habits and obesity outcomes. While we did not explicitly stratify our analyses by age, we adjusted for age in our mediation and moderation models to control for its potential confounding effects. Given that obesity trajectories and dietary habits may differ across the lifespan, future studies should consider age-specific analyses to better understand how age influences gene-diet interactions in the context of obesity.

As is known with epidemiological studies that assess self-reported dietary data, participants with overweight or females tend to underreport their dietary intake and body weight, however at baseline participants anthropometrics were measured by trained professionals providing more accurate and reliable measures [69, 70]. However, the use of FFQs has limitations, such as biases in self-reported food intake and inaccuracies in portion sizes. This may have resulted in some misclassification of adherence to the PHDI, or consumption of its food groups, in the present study. Future studies should include more objective dietary measures, such as biomarkers, to validate FFQ data.

Finally, more studies are needed to replicate these findings, specifically in samples of non-European ancestry, as our study cohort was comprised mainly of French-Canadian individuals of European ancestry. Future studies can also examine PRS-diet relationships using PRSs reflecting other anthropometric traits, such as waist circumference or body composition. Despite these limitations, the strengths of the present study

included the assessment of gene-diet relationships using two different PRSs, a combination of mediation and moderation analyses, and inclusion of longitudinal models that improved the robustness of our results.

Conclusion

This study explored the complex relationship between polygenic susceptibility to obesity, dietary factors, and obesity outcomes. Our findings support that following the Planetary Health Diet may be useful in obesity prevention and management. Moreover, our findings suggest that the consumption of certain food groups included in the PHDI, specifically red meat and whole grains, partly mediate the genetic susceptibility to obesity. Hence, future dietary recommendations promoting components of the PHDI could benefit individuals with higher genetic susceptibility to obesity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00890-0.

Additional file 1.

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Author contributions
GM, DEN: conceptualization; GM, DEN: methodology; GM: formal analysis; GM: data curation; GM, DEN: writing original draft; GM, DEN: draft review and editing; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

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Availability of data and materials
Codebooks for the statistical analyses conducted in this research are available from the authors upon reasonable request. Requests for data access must be submitted to the CARTaGENE Samples and Data Access Committee for review and approval.

Declarations

Ethics approval and consent to participate
We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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