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Understanding Gene-Lifestyle Interaction in Obesity: The Role of Mediation versus Moderation

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Abstract
Background: Obesity results from complex interactions between genetic susceptibility to weight gain and poor eating and lifestyle behaviors. The approach that has been traditionally used in genetics to investigate gene-environment/lifestyle interaction in obesity is based on the concept of moderation or effect modification. Another approach called mediation analysis can be used to investigate gene-environment interaction in obesity. The objective of this review article is to explain the differences between the concepts of moderation and mediation and summarize the studies that have used mediation analysis to support the role of eating or lifestyle behaviors as putative mediators of genetic susceptibility to obesity. ***Summary:*** Moderation is used to determine whether the effect of an exposure (genes associated with obesity) on an outcome (obesity phenotype) differs in magnitude and/or direction across the spectrum of environmental exposure. Mediation analysis is used to assess the extent to which the effect of the exposure on the outcome is explained by a given set of hypothesized mediators with the aim of understanding how the exposure could lead to the outcome. In comparison with moderation, relatively few studies used mediation analyses to investigate gene-environment interaction in obesity. Most studies found evidence that traits related to appetite or eating behaviors partly mediated genetic susceptibility to obesity in either children or adults. ***Key Messages:*** Moderation and mediation represent two complementary approaches to investigate gene-environment interaction in obesity and address different research questions pertaining to the cause-effect relationship between genetic susceptibility to obesity and various obesity outcomes. More studies relying on mediation are needed to better understand the role of eating and lifestyle habits in mediating genetic susceptibility to obesity.

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Introduction

Recent data on the worldwide trends of body mass index (BMI) indicate that the prevalence of obesity (BMI ≥30 kg/m^2 for adults and more than 2 SD above the median of the WHO growth reference for children and adolescents) has risen considerably in the past 4 decades [1, 2]. In 2016, an estimated 671 million adults and 124 million children and adolescents were living with obesity compared to 100 million and 11 million, respectively, in 1975. Our obesogenic environment characterized by unhealthy eating habits and a sedentary lifestyle is considered a key driver of this rapid increase in the prevalence of obesity. However, the fact that not everybody develops overweight or obesity despite being exposed to the same obesogenic environment suggests that obesity results from a complex interaction between genetic and environmental factors leading to excessive weight gain in genetically susceptible individuals. The approach traditionally used to investigate gene-environment/lifestyle interactions in obesity has been an examination of the effect of genes (exposure) on obesity (outcome) in groups of individuals stratified based on an environmental factor (e.g., active vs. inactive individuals). In this approach, the environment acts as a moderator of the relationship between the exposure and the outcome. An alternative to provide insight into interplay between genetic and environmental factors in obesity is to use mediation analysis, an approach that has not been frequently used in this context. Unlike moderation, mediation analysis is used to assess the extent to which the effect of an exposure (genes associated with obesity) on an outcome (obesity phenotype) is explained by a given set of hypothesized mediators (also called intermediate variables). Despite extensive evidence supporting the existence of gene-environment interaction in obesity [3–7], few studies have used mediation analysis to identify potential mediators of genetic susceptibility to obesity. The aim of this short review is to (1) explain the differences between the concepts of moderation and mediation and (2) provide a brief overview of the studies that have used mediation analysis to support the role of eating or lifestyle behaviors as putative mediators of genetic susceptibility to obesity.

Concepts of Moderation versus Mediation

This section provides a brief overview of moderation and mediation and highlights the differences between the two concepts. In-depth reviews [8–10] and full book-length overviews [11, 12] of these concepts are available elsewhere. Moderation and mediation are used to provide insight into the explanation of causal phenomena, i.e., how exposure affects an outcome [12]. In the context of this review, the exposure (X) represents genetic susceptibility to obesity, while the outcome (Y) represents an obesity phenotype, such as BMI. Although moderation and mediation are interdependent notions and even though researchers tend to use both terms interchangeably, these concepts are different and address different research aims pertaining to the exposure-outcome relationship. The difference between the two concepts is illustrated by the two basic moderation and mediation models illustrated in Figure 1. The concept of moderation is depicted in Figure 1a. The arrow linking W (the moderator) to the effect of X on Y denotes that X's effect on Y varies according to W (effect modification). Moderation analysis is thus used to address the 3 Ws of the relationship between X and Y, i.e., *When*, or under *What* circumstances or for *Who* (what type of people) the effect of X on Y exists or not and in what magnitude [10]. For example, the effect of a genetic variant on BMI may vary by age (*When*), type of diet (*What*), or by sex (*Who*). In the genetic literature, moderation is often referred to as interaction and represents the approach that has been traditionally used to provide

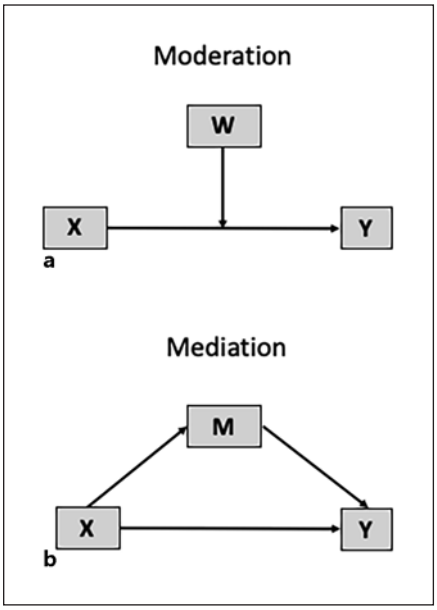

Fig. 1. Basic moderation and mediation models. **a** Moderation model with a single moderator W influencing the effect of X on Y. **b** Mediation model with a single mediator M causally related between X and Y.

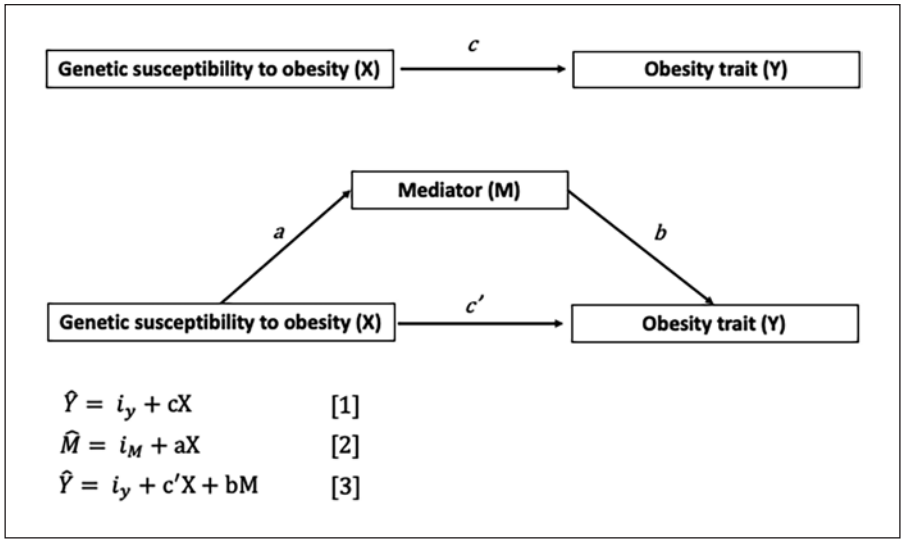

Fig. 2. Simple mediation model of genetic susceptibility to obesity. Illustration of a simple mediation model in which genetic susceptibility to obesity (independent variable *X*) influences an obesity trait (dependent variable *Y*) directly (*c*') or indirectly through a mediator *M*. The direct and indirect effects add to yield the total effect (*c*) of *X* on *Y*. The paths of the model labeled *a*, *b*, *c*, and *c*' are estimated using the three regression equations represented in the figure. The indirect effect or mediated effect of *X* on *Y* through *M* is quantified as the product of *a* and *b* (*ab*).

evidence of gene-environment interaction for obesity in observational studies. For example, several recent studies provided evidence that genetic susceptibility to obesity is modified by various lifestyle characteristics such as alcohol consumption [13, 14], sugar-sweetened beverage [15], dietary fat and total energy intake (EI) [16], healthy diet [17, 18], television viewing [19], physical activity [14, 20, 21], and sleeping habits [22].

Mediation analysis is used when the aim of the research is to determine *How* X exerts its effect on Y. In its simple form, mediation is depicted in Figure 1b where a mediator M (also called an intermediate variable) is located causally between X and Y. In such a model there are two pathways by which X can impact Y. One pathway leads from X to Y without passing through M and is called the direct effect of X on Y. The second pathway from X to Y is the indirect effect of X on Y through M; it first passes from X to M and then from M to Y. The indirect effect represents how Y is influenced by X through a causal sequence in which X influences M, which in turn influences Y. Thus, a mediation model is a set of two or more causal events chained together in a sequence of the form X → M → Y [10, 11]. Although mediation analysis has been around for more than 70 years [10], its use was popularized in the late 1980s by Baron and Kenny [23] using an analytic approach based on regression analyses.

In the context of genetic studies of obesity, the objective of mediation analysis is thus to determine the extent to which the relationship between X (here, single genetic variant or multiple variants associated with obesity) and Y (here, a measure of obesity) is explained by a hypothesized mediator M (or a set of mediators). This objective can be achieved by estimating the regression coefficients of the three regression models represented in the form of the path diagram shown in Figure 2 [10]. The first regression model represents the total effect of X on Y (path *c*, equation [1]). The second regression model represents the effect of X on M (path *a*, equation [2]). The third regression model represents the association between M and Y after adjustment for X (path *b*, equation [3]). The effect of X on Y when M is held constant (path *c*'. equation [3]) is called the direct effect (not via the mediator). The effects represented by the regression coefficients in equations [1–3] can be estimated with any regression analysis or structural equation modeling program [24, 25]. A computational tool for path analysis-based moderation and mediation analyses called PROCESS (for SPSS, SAS, and R) has been developed for estimating direct and indirect effects for various mediation models, allowing for one or multiple mediators simultaneously or for the presence of an interaction between the mediators and the exposure [10, 11]. The indirect effect of X on Y through mediator M quantifies the estimated difference in Y resulting from one-unit change in X through the causal sequence X → M → Y [10]. This indirect effect represents the amount of mediation and is estimated as the product of regression coefficients *a* and *b* in equations [2, 3]. Thus, in a mediation model, the total effect equals the sum of direct and indirect effects ($c = c' + ab$) and the indirect effect equals the reduction of the effect of X on Y when M is controlled versus when it is not ($ab = c - c'$). The indirect effect divided by the total effect (ab/c) can also be

computed to obtain a measure of the proportion of the total effect that is mediated, A rejection of the null hypothesis that the indirect effect is zero ($ab = 0$) is sufficient to support a claim of mediation of the effect of X on Y through M [10]. Various approaches have been proposed to test this null hypothesis. One of the earlier and very popular tests that was used to infer about mediation is the Sobel test [26]. However, the test is considered low in power because it assumes that the sampling distribution of *ab* is normal, which is rarely the case [27]. Therefore, alternative approaches performing better than the Sobel test without making any assumptions about the sampling distribution of *ab* have been proposed [10, 27]. Among these methods, the bootstrap confidence interval (CI) method is considered a good compromise balancing validity and power considerations. Bootstrapping is a nonparametric method of inference based on resampling methods. Briefly, the original sample size *n* is treated as a miniature representation of the population originally sampled. The observations in the sample are then resampled with replacement and the statistic of interest is computed in the new sample constructed through this resampling process. The procedure is repeated multiple times, thousands of times ideally, leading to an empirical sampling distribution of the statistic of interest. In mediation analysis, the method is used to generate a sampling distribution of the indirect effect *ab*, which can be used to derive 95% CIs for the indirect effect. If the 95% CI is entirely above or below zero, this supports a claim of mediation, whereas a CI straddling zero indicates that data are compatible with the absence of mediation. The Sobel test and the bootstrap CI method are both implemented in PROCESS macros for SPSS, SAS, and R.

In summary, moderation and mediation analyses address different research questions pertaining to the exposure-outcome relationship [9, 12] and can be viewed as complementary approaches to investigate gene-environment interaction in obesity. Moderation analysis is used to investigate the role of environment/lifestyle in modifying the association between the genetic susceptibility to obesity (exposure) and a trait associated with obesity (outcome). Mediation analysis is used to identify environmental/lifestyle factors explaining how genetic susceptibility exerts its effects on an obesity outcome. Assessing interaction/moderation may help identify a subgroup of the population who may benefit the most from an intervention. For example, if the impact of genetic susceptibility to obesity on body weight is much greater in a subgroup of the population, e.g., in inactive versus active individuals, then it might be more appropriate to intervene in inactive individuals first instead of intervening on the entire population. Mediation is mainly motivated by the wish to understand the pathways whereby an exposure leads to the outcome with the aim of intervening on the mediator to reduce the risk of disease or improve the outcome. For example, if the effect of genetic susceptibility to obesity on body weight is mainly mediated by eating behavior (EB) traits such as disinhibition (DIS) or satiety responsiveness (SR), then refining the intervention further to target these traits may lead to a more favorable outcome in an intervention trial.

Finally, it is worth noting that both moderation and mediation can occur simultaneously to explain the relationship between the exposure and the outcome. Taking the *FTO* gene as example and considering the evidence showing that the effect of *FTO* on obesity is modified by physical activity level (PAL) [28] and that PAL acts as a mediator of the association between *FTO* and obesity [29], we can postulate that the effect of *FTO* on obesity may operate through both mediation and moderation (interaction). In that context, PAL would act as a mediator of the association between FTO and obesity, but in inactive individuals only, for example. To the best of our knowledge, no studies have investigated the relative impact of mediation versus moderation in explaining the effect of genetic susceptibility to obesity, even though the methodology described above to assess mediation has been extended to allow for the presence of a mediator interacting with the exposure [30, 31]. In that context, the overall effect of the exposure on the outcome can be decomposed into components due to just mediation, to just interaction, to both mediation and interaction, and to neither mediation nor interaction. This four-way decomposition model, which unifies methods to assess effects due to interaction and methods to assess mediation [31], has been implemented in a SAS procedure called CAUSALMED [32]. Future studies based on this unified approach will contribute to improve our understanding of the interplay between genetic and lifestyle factors in the development of obesity.

Role of Eating and Lifestyle Behaviors in Mediating Genetic Susceptibility to Obesity

This section presents an overview of the studies that have used mediation analyses to identify eating or lifestyle behaviors mediating genetic susceptibility to obesity. These studies are summarized in Table 1. Most of the studies were based on the behavioral susceptibility theory of obesity, which proposes that genetic susceptibility to obesity is partly attributable to appetite regulation and

Table 1. Summary of mediation analysis studies supporting the role of eating and lifestyle behaviors as mediators of genetic susceptibility to obesity

Study	*N* (cohort)	Age, years	Genetic instrument (*N* SNPs)	Mediator – tool	Obesity outcome	Mediator (obesity outcome)	*p* value Sobel test or $\beta_{indirect}$ [95% CI] or (% mediation)
Studies in children with eating-related traits as mediators							
Wardle et al. [35]	3,337 (TEDS, UK)	8–11	FTO (rs9939609)	SR; enjoyment of food -CEBQ	BMI	SR (BMI)	<0.05
Llewellyn et al. [36]	2,258 (TEDS, UK)	9.9±0.8	GRS (28)	Satiety Responsiveness (SR) – CEBQ	BMI and WC SDS	SR (BMI-SDS) SR (WC-SDS)	0.006 0.005
Steinsbekk et al. [37]	652 (TESS, Norway)	4–8	GRS (32)	Appetite traits – CEBQ: enjoyment of food, emotional overeating, food responsiveness, satiety responsiveness, slowness in eating	Weight gain from ages 4 to 6 years and 6 to 8 years	No mediating effect	NS
de Lauzon-Guillain et al. [38]	1,142 (EDEN, France)	4 mo–5 yr	GRS (16)	Maternal perception of high appetite (HA)	Weight-for-age, length/ height for age and BMI z scores	HA 2-yr (2-yr BMI z-score) HA 2-yr (3-yr BMI z-score) HA 2-yr (4-yr BMI z-score) HA 2-yr (5-yr BMI z-score)	0.03 (47) 0.03 (35) 0.05 (28) 0.05 (24)
Studies in adults with eating-related traits as mediators							
Konttinen et al. [39]	4,632 (DILGOM, Finland)	25–74	GRS (90)	Uncontrolled Eating (UE); Emotional Eating (EE) – TFEQ-R18	BMI and WC	UE (BMI) UE (WC) EE (BMI) EE(WC)	0.032 [0.021–0.043] 0.030 [0.020–0.040] 0.022 [0.013–0.032] 0.020 [0.011–0.029]
	1,231 (FT12, Finland)	21–26		Cognitive Restrain (CR); Uncontrolled Eating (UE); Emotional Eating (EE) – TFEQ	BMI and WC	EE (BMI) EE (WC)	0.015 [0.000–0.029] 0.013 [0.000–0.026]
de Lauzon-Guillain et al. [40]	2,154 (EDEN, France)	18–56	GRS (27)	Cognitive Restrain (CR); Uncontrolled Eating (UE); Emotional Eating (EE) – TFEQ	BMI	UE (BMI) EE (BMI)	0.04 (6) 0.01 (11)
	3,515 (FENLEND, UK)	35–64	GRS (96)	Uncontrolled Eating (UE); Emotional eating (EE) – TFEQ-R18	BMI	UE (BMI) EE (BMI)	0.0006 (12) 0.02 (10)
Jacob et al. [41]	768 (QFS, Canada)	18–75	GRS (97)	Cognitive restrain; disinhibition (DIS) and subscales habitual (DIS-HAB) and situational (DIS-SITU) susceptibillity to disinhibition; susceptibility to hunger (HUN) and subscales internal (HUN-INT) and external (HUN-EXT) locus of hunger – TFEQ	BMI and WC	DIS (BMI) DIS-(WC) DIS-HAB (BMI) DIS-HAB (WC) DIS-SITU (BMI) DIS-SITU (WC) HUN (BMI) HUN (WC) HUN-INT (BMI) HUN-INT (WC) HUN-EXT (BMI) HUN-EXT (WC)	0.0007 0.0007 0.002 0.002 0.003 0.002 0.02 0.02 0.03 0.03 0.03 0.03

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Table 1 (continued)

Study	*N* (cohort)	Age, years	Genetic instrument (*N* SNPs)	Mediator – tool	Obesity outcome	Mediator (obesity outcome)	*p* value Sobel test or $\beta_{indirect}$ [95% CI] or (% mediation)
Brunner et al. [42]	2,464 (Whitehall II study, UK)	45–65	GRS (92)	Disinhibition (DIS); Hunger (HUN) – TFEQ	BMI trajectories (average BMI from 4 measures at 5-yr interval between 1997–1999 and 2012–2013	DIS (BMI) HUN (BMI)	(33.7) (9.9)
Masip et al. [43]	949 (FT16, Finland)	31–37	PRS obesity (692,758)	4 EB patterns: Snacking (SNACK); Infrequent and Unhealthy Eating (IUE); avoidant eating; Emotional and External Eating (EEA)	BMI and WC	SNACK (BMI) SNACK (WC) IUE (BMI) IUE (WC) EEA (BMI)	0.06 [0.02–0.09] (21) 0.05 [0.02–0.08] (21) 0.01 [0.00–0.02] (3) 0.01 [0.00–0.02] (4) 0.03 [0.00–0.05] (10)
Jacob et al. [44]	750 (QFS, Canada)	18–75	PRS obesity (523,101)	Diet quality – NRF6.3 Intake of 13 specific food groups: Vegetables (VEG) Fruits (FRUIT) Fruit juices Dairy products (DAIRY) Milk (MILK) Yogourt (YOGOURT) Cheese Processed meat Plant-based protein foods Nuts and seeds Sugar-sweetened beverages (SSB) Sugar and sugary foods Fat and high-fat foods (FHFF)	BMI and WC	NRF6.3 (BMI) NRF6.3 (WC) VEG (BMI) VEG (WC) FRUIT (BMI) FRUIT (WC) DAIRY (BMI) DAIRY (WC) MILK (BMI) MILK (WC) YOGURT (BMI) YOGURT (WC) SSB (BMI) SSB (WC) FHFF (BMI) FHFF (WC)	0.33 [0.13–0.60] (3.2) 0.92 [0.39–1.58] (4.1) 0.15 [0.03–0.32] (1.5) 0.38 [0.07–0.77] (1.7) 0.37 [0.17–0.64] (3.6) 1.04 [0.47–1.73] (4.6) 0.17 [0.02–0.37] (1.6) 0.49 [0.12–0.99] (2.2) 0.13 [0.01–0.30] (1.2) 0.35 [0.02–0.79] (1.5) 0.12 [0.02–0.25] (1.2) 0.33 [0.07–0.67] (1.5) 0.25 [0.05–0.60] (2.4) 0.58 [0.12–1.29] (2.6) 0.46 [0.19–0.79] (4.4) 1.09 [0.48–1.92] (4.8)
Studies in adults with physical activity-related traits as mediators							
Klimentidis et al. [45]	3,430 (FHS offspring, USA)	45.4±10.9	FTO (rs9939609)	Physical Activity Level; Time Spent Sitting (TSS)	BMI	TSS (BMI)	0.013 [0.001–0.033] (3.1)
	3,888 (FHS 3rd generation, USA)			Physical Activity Level; Time Spent Sitting (TSS)	BMI	TSS (BMI)	0.021 [0.003–0.43] (4.4)
Oyeyemi et al. [29]	201 (Nigeria)	22.6±3.6	FTO (rs9939609)	Physical Activity Level (PAL); Time Spent Sitting (TSS) – IPAQ-SF Energy Intake (EI) – FFQ	BMI	PAL-TSS-EI (BMI) PAL (BMI) TSS (BMI) EI (BMI)	0.39 [0.30–0.50] 0.13 [0.08–0.20] 0.28 [0.20–0.38] 0.18 [0.11–0.27]

TEDS, Twin Early Development Study; TESS, Trondheim Early Secure Study; EDEN, Étude des déterminants pré et postnatals de la santé et du développement de l'enfant; DILGOM, DIetary, Lifestyle and Genetic determinants of Obesity and Metabolic syndrome; FT12, FinnTwin12; FENLEND, cohort from Cambridgeshire region, UK; QFS, Quebec Family Study; FT16, FinnTwin16; FHS, Framingham Heart Study; CEBQ, Child Eating Behavior Questionnaire; IPAQ-SF, International Physical Activity Questionnaire – Short Form; FFQ, Food Frequency Questionnaire; TFEQ-R18, Three-Factors Eating Questionnaire-Revised shorter 18-item; TFEQ, Three-Factor Eating Questionnaire (51 items).

that EB traits are the behavioral expression of genetic risk of obesity [33]. Several studies reviewed elsewhere [34] investigated the role of EB traits in genetic susceptibility to obesity. Most of the mediation studies summarized in Table 1 investigated the role of eating-related traits as putative mediators of genetic susceptibility to obesity in children or adults and provided support to the behavioral susceptibility theory. The first study was conducted on a sample of 3,337 children aged 8–11 years from the Twin's Early Development Study (TEDS) [35]. The role of two appetite-related traits, SR, a parent-report measure of child appetite, and enjoyment of food, a measure of the extent to which presentation of palatable foods provokes eating, as mediators of the effect of *FTO* rs9939609 single nucleotide polymorphism (SNP) on measures of BMI and waist circumference taken by the parents was investigated. Results indicated that the effect of the *FTO* genotype on BMI was partially mediated by SR. A follow-up of this first study undertaken in 2,258 ten-year-old children showed that SR mediated the association between a genetic risk score (GRS) of obesity comprising 28-BMI SNPs and standardized scores (SDS) of BMI ($p = 0.006$) and waist circumference ($p = 0.005$) [36]. Two other studies investigated the mediating role of appetite-related traits on the genetic susceptibility to obesity assessed in children. The first one examined the association between a GRS of obesity based on 32 SNPs and 5 EB traits measured with the Child EB Questionnaire in 652 children aged 4–8 years [37]. Although results indicated that children with a higher GRS gained weight more rapidly and have a faster eating rate, none of the EB traits significantly mediated the association with weight gain. In the second study, the association between a BMI-GRS of obesity based on 16 SNPs associated with childhood BMI *z*-scores and mother-reported EB in children up to 5 years of age was examined in 1,142 children from the Étude des Déterminants pré et postnatals de la santé de l'Enfant (EDEN) birth cohort [38]. High maternal perception of their child's appetite at 2 years of age was found to partly mediate the association between the BMI-GRS and BMI z-scores with a mediation ratio decreasing from 47% to 24% between the ages 2 and 5.

The role of eating-related traits in mediating genetic susceptibility to obesity has also been investigated in adults. In the first study based on two independent population-based Finish cohorts, the Dietary, lifestyle and genetic determinants of obesity and metabolic syndrome Study (4,632 individuals aged 25–74 years) and the FinnTwin12 Study (1,231 twins aged 21–26 years), the association between a GRS of obesity assessed from 90 BMI-associated SNPs and measures of BMI and waist circumference was found to be partly mediated through higher levels of uncontrolled eating and emotional eating [39]. A second study replicated these findings using data from two cohorts of adults in France (EDEN cohort) and in the UK (Fenland cohort) [40]. Results showed that both emotional eating and uncontrolled eating mediated the association between a GRS of obesity (96 SNPs for Fenland and 27 SNPs for EDEN) and BMI. In a third study based on 768 adults from the Quebec Family Study (QFS) [41], we showed that individuals at greater genetic risk of obesity (based on 97 BMI-associated SNPs) reported more habitual and situational disinhibited eating and a greater tendency to feel hungry in response to both internal and external cues. These EB traits partly mediated the association between genetic susceptibility to obesity and BMI and waist circumference measures [41]. A fourth study investigated the mediating role of EB in genetic susceptibility to weight gain in 2,464 British adults aged 45–65 years who had repeated measurements of BMI on four occasions at 5-year intervals over 20 years [42]. Results revealed a significant mediating role of DIS and hunger accounting for 33.7% and 9.9%, respectively, of the relationship between genetic susceptibility to obesity and average BMI measurements from 45 to 65 years. There was no significant increase in the mediating effect in a model incorporating both mediators (% mediation 33.9%), suggesting that in this sample the mediating effect was driven mostly by DIS rather than hunger [42].

Two recent studies undertaken in adults used a more powerful approach to assess genetic susceptibility to obesity by computing a polygenic risk score (PRS) of obesity incorporating whole-genome-based SNPs irrespective of their genome-wide significance. In the first study undertaken in the FinnTwin16 cohort of Finnish twins, four EB patterns identified using principal component analysis and a score of diet quality based on a short food frequency questionnaire, were tested for their role in mediating the association between genetic susceptibility to obesity and BMI ($n = 949$) and waist circumference ($n = 874$) [43]. Among the four EB patterns tested, only the snacking and the infrequent and unhealthy EB patterns mediated the association between the obesity PRS and both measures of obesity. The emotional and external EB pattern only mediated the association of the PRS with BMI [43]. When tested without referring to infrequent eating, the diet quality score alone did not mediate the association between the PRS and obesity [43]. In a second recent study undertaken in 750 participants from QFS, we investigated the mediating effects of diet quality and intake of

13 specific food groups on the association between genetic susceptibility to obesity and BMI and waist circumference [44]. Dietary intakes were assessed using a 3-day food record from which a diet quality score (the Nutrient Rich Food Index 6.3) and food groups were derived. We found that the association between the obesity PRS and BMI was partly mediated by poor diet quality, high intakes of fat and high-fat foods and sugar-sweetened beverages, and low intakes of vegetables, fruits, and dairy products. Similar trends were observed for waist circumference [44].

Finally, only two studies investigated the mediating role of traits related to PAL in mediating genetic susceptibility to obesity. The first study based on 7,318 individuals from the Offspring and third-generation cohorts of the Framingham Heart Study (FHS) examined possible mediation effects of PAL and time spent sitting (TSS, as an indicator of physical inactivity) on the association between the *FTO* rs9939609 SNP and BMI [45]. Mediation analyses revealed that the association between the *FTO* genotype and BMI was partly mediated by TSS (%mediation ~3%–4%), but not by PAL. In another study, the role of PAL, TSS, and EI as putative mediators of the relationship between *FTO* rs9939609 SNP and BMI was examined in 201 young adults from the Nigerian population [29]. Mediation analyses revealed a combined mediating effect of PAL, TSS, and EI in the association between *FTO* genotype and BMI ($\beta_{indirect}$ = 0.39; 95% CI: 0.30–0.50). Analyses also revealed a significant mediating effect of each mediator tested separately [29]. These studies were limited by their use of only one *FTO* SNP to assess genetic susceptibility to obesity.

One assumption of mediation analysis common to the studies reviewed above is that the alleged mediator is causally involved in the pathway linking the exposure to the outcome, which also implies that the mediator must precede the effect. Causality and temporality are thus important limitations of mediation analyses that have been published so far. These limitations can be addressed by performing Mendelian randomization to identify eating or lifestyle mediators causally related to obesity before undertaking mediation analysis. The assessment of genetic susceptibility to obesity based on a relatively small number of SNPs associated with obesity represents another limitation of most studies undertaken so far. The use of PRSs incorporating whole-genome-based SNPs irrespective of their genome-wide significance represents a more powerful approach to estimate of an individual's genetic susceptibility to a trait and should be considered in future studies.

Summary and Conclusion

Moderation and mediation represent two complementary approaches to investigate gene-environment interaction in obesity or the cause-effect relationship between genetic susceptibility to obesity and various obesity outcomes. One way to investigate this cause-effect relationship is to explain *When*, for *Whom*, and in *What* circumstances the cause influences the outcome and this refers to the concept of moderation. Another way to investigate this cause-effect relationship is to explain *How* the effect occurs and this refers to the concept of mediation. Both approaches can help refine weight loss and maintenance programs. In the case of moderation, it may help identify a subgroup of the population for whom the intervention is likely to benefit the most. In the case of mediation, it may help to design intervention programs that will target a mediator causally related to the outcome, which could potentially increase impact of the intervention on the outcome. So far, gene-environment interactions in obesity have mainly been investigated through moderation. Future studies relying on mediation and allowing for both moderation and mediation will contribute to improve our understanding of the role of eating and lifestyle habits in explaining how genetic susceptibility to obesity impacts body weight or other obesity-related traits.

Conflict of Interest Statement

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Author Contributions

Louis Pérusse was responsible for conceptualizing, writing, and revising the article. Raphaëlle Jacob, Vicky Drapeau, Clare Llewellyn, Benoît J. Arsenault, Alexandre Bureau, Marie-Ève Labonté, Angelo Tremblay, and Marie-Claude Vohl read, edited and approved the final manuscript.

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