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Polygenic Risk and Nutrient Intake Interactions on Obesity Outcomes: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Background: Diet is an important determinant of body weight and may modulate genetic susceptibility to obesity.

Objective: This systematic review and meta-analysis aimed to synthesize evidence related to interactions between polygenic risk and nutrient intakes on obesity outcomes.

Methods: MEDLINE, EMBASE, Web of Science, and Cochrane Library were systematically searched to identify observational studies that assessed interactions between polygenic risk and nutrient intakes on obesity-related outcomes. Random effects meta-analyses were performed for pooled polygenic risk score (PRS)–total fat intake and PRS–protein intake interaction coefficients on body mass index (BMI).

Results: Twenty-six publications were retrieved with studies conducted among European, Asian, and African samples. Dietary fats (saturated fat, omega-3, and trans fat) and energy intake were most frequently reported to interact with PRS on obesity outcomes, but the total number of studies available was low. No significant interactions were identified in meta-analyses of PRS interactions with total fat intake and protein intake on BMI. Several studies were rated as low quality, heterogeneity was high, and although study samples were racially diverse, PRSs tended to be based on samples of European ancestry.

Conclusion: Evidence of interactions between polygenic risk and nutrient intakes on obesity outcomes is limited and inconsistent. Further research addressing limitations related to study quality and polygenic risk characterization is needed.

Abbreviations: BMI, body mass index; DCH, Diet, Cancer and Health; FFQ, food frequency questionnaire; GOLDN, Genetics of Lipid-Lowering Drugs and Diet Network study; GWAS, genome-wide association studies; HPFS, Health Professionals Follow-up Study; KoGES, Korean Genome and Epidemiology Study; MESA, Multi-Ethnic Study of Atherosclerosis; MONICA, Monitoring Trends and Determinants of Cardiovascular Disease; MUFA, monounsaturated fatty acids; NHS, Nurses' Health Study; NOS, Newcastle–Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRS, polygenic risk score; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; SFA, saturated fatty acids; SNP, single nucleotide polymorphism; uPRS, unweighted polygenic risk score; WC, waist circumference; WGHS, Women's Genome Health Study; wPRS, weighted polygenic risk score.

Guiomar Masip and Hannah Yang Han have equal contributions.

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1 | Introduction

Obesity is a highly prevalent disease globally and is associated with multiple comorbidities and an increased risk of premature mortality [1–6]. Hence, to prevent these undesirable consequences, it is of utmost importance to understand the mechanisms behind obesity. Over the past decades, a highly obesogenic food environment has emerged with high consumption of energy-dense foods, sugars, and fats [7, 8]. This modern environment is implicated in the high prevalence of overweight and obesity in society; however, genetic susceptibility is also an important factor. Studying the interplay between diet and obesity genetics is important to clarify mechanisms underlying obesity and advance the field of precision nutrition [9].

Classically, the genetic influence on obesity is considered to arise in two forms: monogenic and polygenic. Monogenic obesity is caused by variation in a single gene and typically begins in childhood but is rare in the general population [10]. Polygenic obesity is the common form and results from the cumulative effect of multiple genetic variants, each contributing a relatively small influence on the overall genetic risk [11–13]. Genome-wide association studies (GWAS) have discovered numerous genetic loci associated with body mass index (BMI), though these loci at most explain 23% of BMI variance [12, 14]. Therefore, other factors are at play in the etiology of obesity including environmental factors such as diet. Gene–diet interactions may account for some of the “missing heritability” left unexplained by GWAS [15].

Several studies have investigated gene–diet interactions on obesity using candidate gene approaches. For example, previous work on *FTO* and *MC4R*, two genes with variants strongly associated with obesity, has reported that diet may moderate associations between these gene variants and obesity outcomes [16]. However, since polygenic obesity is the common form in the population, expanding gene–diet interaction research to evaluate diet/nutrient interactions with polygenic risk scores (PRSs) relevant to obesity is an important direction. A previous systematic review and meta-analysis identified overall diet quality as a moderator of the association between genetic risk of obesity and anthropometric outcomes [17]. In addition, a separate systematic review identified whole grains, fruits and vegetables, and diets low in total and saturated fats as moderators of obesity genetic risk [18]. However, mediation and moderation were not reported separately in that review, which impacts the accuracy of interpretations, and a specific focus on the moderating role of nutrient intakes is lacking. Given these gaps and limitations, a review of PRS–nutrient interactions in obesity development/management is needed.

Thus, the objective of this systematic review was to critically evaluate the existing literature on polygenic risk and nutrient intake interactions on obesity-related outcomes. Observational studies were the focus because of the prevalence of cohort studies with genetic, lifestyle, and health data available that enable investigations of gene–environment interactions [19]. As a result, literature examining responses to nutrition interventions according to polygenic risk of obesity was not considered but is a topic for future investigation.

2 | Methods

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The objective was to synthesize all available evidence on PRS–diet interactions in obesity outcomes (PROSPERO registration: CRD42022312289).

2.1 | Search Strategy

Four databases were used, namely, Ovid MEDLINE, EMBASE, ISI Web of Science, and Cochrane Library, to perform a comprehensive electronic systematic search. A librarian validated the MeSH terms and keywords used in the search strategy (Supporting Information S1–S4). The search was restricted to observational studies conducted in humans, published in English, and between January 1, 2012, and September 6, 2023. The start date of this time period was selected to focus on literature that utilized recent GWAS loci in gene–diet interaction studies.

EndNote citation software was used to import all retrievals and remove duplicates. The citation organizer Rayyan was used for title/abstract screening of the nonduplicate retrievals. Four authors (G.M., H.Y.H., T.M., and D.E.N.) conducted the title/abstract screening and full-text screening by dividing the retrievals in half. Thus, all retrievals were screened and reviewed in a blinded manner by two authors. Reference lists of articles that underwent full-text review were also manually reviewed to capture any additional articles. Disagreements were resolved by consensus or by a third author.

2.2 | Study Selection

Articles were considered eligible if they met these inclusion criteria: (a) peer-reviewed observational studies (i.e., retrospective or prospective cohort studies, cross-sectional studies, and case-control studies); (b) reported obesity-related outcome(s): BMI (kg/m^2), waist circumference, body composition, body weight change, or BMI group representing overweight or obesity (e.g., for children/adolescents: BMI z-score > 1 defined as overweight, > 2 as obese; for adults: BMI ≥ 25 and < 30 as overweight, BMI ≥ 30 as obese or alternate categories [21]); (c) energy- and nutrient intake–related exposure(s): energy intake, macronutrient intake, and micronutrient intake; (d) use of a PRS (considered as a combination of loci informed by GWAS); and (e) assessment of PRS–nutrient intake interaction on an obesity-related outcome. Exclusion criteria comprised the following: (1) studies that did not meet the above-mentioned inclusion criteria, (2) nonhuman studies, (3) interventional studies, (4) published abstracts, (5) letters/case report, (6) reviews, and (7) meta-analysis.

2.3 | Data Extraction

The following information was extracted: (a) article title, (b) authors, (c) publication year, (d) study design, (e) length of follow-up (only for prospective cohort studies), (f) cohort name (if available), (g) sample size, (h) age group, (i) participant biological sex, (j) country, (k) principal dietary exposure (energy

intake, macronutrient intake, or micronutrient intake), (l) principal outcome (obesity-related), (m) number of single nucleotide polymorphisms (SNPs) in the PRS, and (n) interaction term assessed.

2.4 | Risk of Bias and Quality Assessment

The methodological quality of articles was assessed using two assessment tools: the Newcastle–Ottawa Scale (NOS) to assess the quality of longitudinal studies [22] and the NOS adapted version for cross-sectional studies [23]. NOS aimed to assess the following: selection of study group, comparability of the groups, and ascertainment of either exposure or outcome with slight variation in scoring criteria depending on study type (see Appendix S1). Quality was rated as follows: low quality (0–3 points), moderate quality (4–6 points), and high quality (> 6 points). In cases of an article reporting both cross-sectional and longitudinal results for the same cohort (which were both extracted in this review), the NOS for longitudinal studies was used to score study quality. As such, the quality assessment of articles reporting both cross-sectional and longitudinal results for the same cohort is reported in the characteristics of longitudinal studies.

In addition, the genetic methodological scale from Campbell and Rudan was also used to assess study quality, given the focus on PRS–nutrient intake interactions [24]. This assessment approach evaluated the following: interaction as primary study goal, test for interaction, correction for multiple testing, adjustment for ancestry, Hardy–Weinberg equilibrium, test for group similarity at baseline, sample size, and sufficient details of study procedure. Quality ratings were defined as follows: low quality (–8 to 1 points), moderate quality (2–5 points), and high quality (6–8 points) (see Appendix S1).

A sensitivity assessment of the number of significant PRS–nutrient interactions reported was conducted by excluding studies ranked as low quality in either the NOS or genetic methodological scale. In addition, patterns of results were also evaluated according to the age group of the study sample (adults only vs. children and/or adolescents).

2.5 | Meta-Analysis

Articles with similar dietary measures and obesity-related outcomes were considered for meta-analysis. To ensure that the effect sizes between studies were comparable, an analytical plan was developed using a uniform dietary measure and adjusting for a specific set of variables to evaluate the interaction coefficients. Additional information on the analytical plan is described in Appendix S2. Authors of eligible articles were contacted with a request to either reconduct the analyses following the plan or share specific de-identified raw variables.

For the meta-analysis, the restricted maximum likelihood estimator random effects model was used to pool the beta coefficient of the interactive associations along with the corresponding 95% confidence intervals for each type of nutrient [25]. As a small number of studies were ultimately included in the meta-analysis, the Knapp–Hartung method was used to adjust

the confidence interval [26]. Between-study heterogeneity was assessed using Cochran's Q test and the I^2 test [27]. Prespecified subgroup analysis by sex was conducted to further explore the potential for sex-specific effects of PRS–nutrient interactions on BMI. Publication bias was visually assessed with funnel plots. All statistical analyses were conducted in R using the Meta package with two-tailed $p < 0.05$ considered significant.

3 | Results

3.1 | Summary of Retrieved Studies

Out of 5272 studies screened, a total of 114 full-text publications were assessed (Figure 1). One additional article was identified from a manual search of reference lists. Overall, 26 full-text articles were included in the systematic review of nutrient intakes as the dietary exposure of interest (Table 1) [28–53]. From the included studies, 16 studies were cross-sectional [30, 33–35, 39, 42–49, 51–53], 8 studies were longitudinal [28, 29, 31, 32, 36–38, 50], and 2 studies reported cross-sectional and longitudinal findings [40, 41]. No case–control or retrospective cohort studies were identified. From the included studies, 22 assessed PRS–fat intake [28, 30, 33–37, 39–53]; 19 PRS–carbohydrates, fiber, or protein intake [28, 29, 33, 34, 38, 40–53]; 9 PRS–energy intake [28, 33, 41, 42, 47, 49, 50, 52, 53]; and 5 PRS–micronutrient intake (Table 2) [31, 32, 35, 36, 53]. Brief summaries of the characteristics of retrieved studies and dietary assessment methods are provided in Appendix S3.

3.2 | Polygenic Risk Score Assessment

PRSs were constructed with different approaches and for a variety of obesity-related traits. Most PRSs included GWAS loci related to anthropometric measures, such as BMI [54, 55], WC [56], and WHR [57], but some included loci related to metabolic traits considered relevant to obesity (serum lipid [58] and micronutrient levels [59]). However, the number of SNPs used in PRSs varied between studies (even for the same trait), which was either due to differences in SNP relevance/availability for the investigative cohort or different PRS construction approaches. Among the retrieved studies, 10 accounted for the different effect sizes of the SNPs used in the PRS calculation by using weighted-PRSs (wPRSs) [30, 33–38, 40, 42, 53]. Fifteen studies used an unweighted-PRS (uPRS) [28, 29, 31, 32, 39, 41, 43–46, 48–52], and one study used both types of PRSs [47]. uPRSs were mostly utilized among studies involving non-European samples or children/adolescent studies, with some SNPs being selected from candidate gene studies, given limited GWAS available in such samples.

3.3 | Interaction of Fat Intake With PRS

Dietary fat intake was the most frequently studied nutrient for interactions with PRSs and obesity outcomes (Figure 2). Thirteen of 22 publications reported that some form of fat intake moderated associations between polygenic risk and adiposity phenotypes [28, 30, 33, 35–37, 39–41, 43, 46, 51, 53]. Two cross-sectional studies in European ancestry cohorts reported

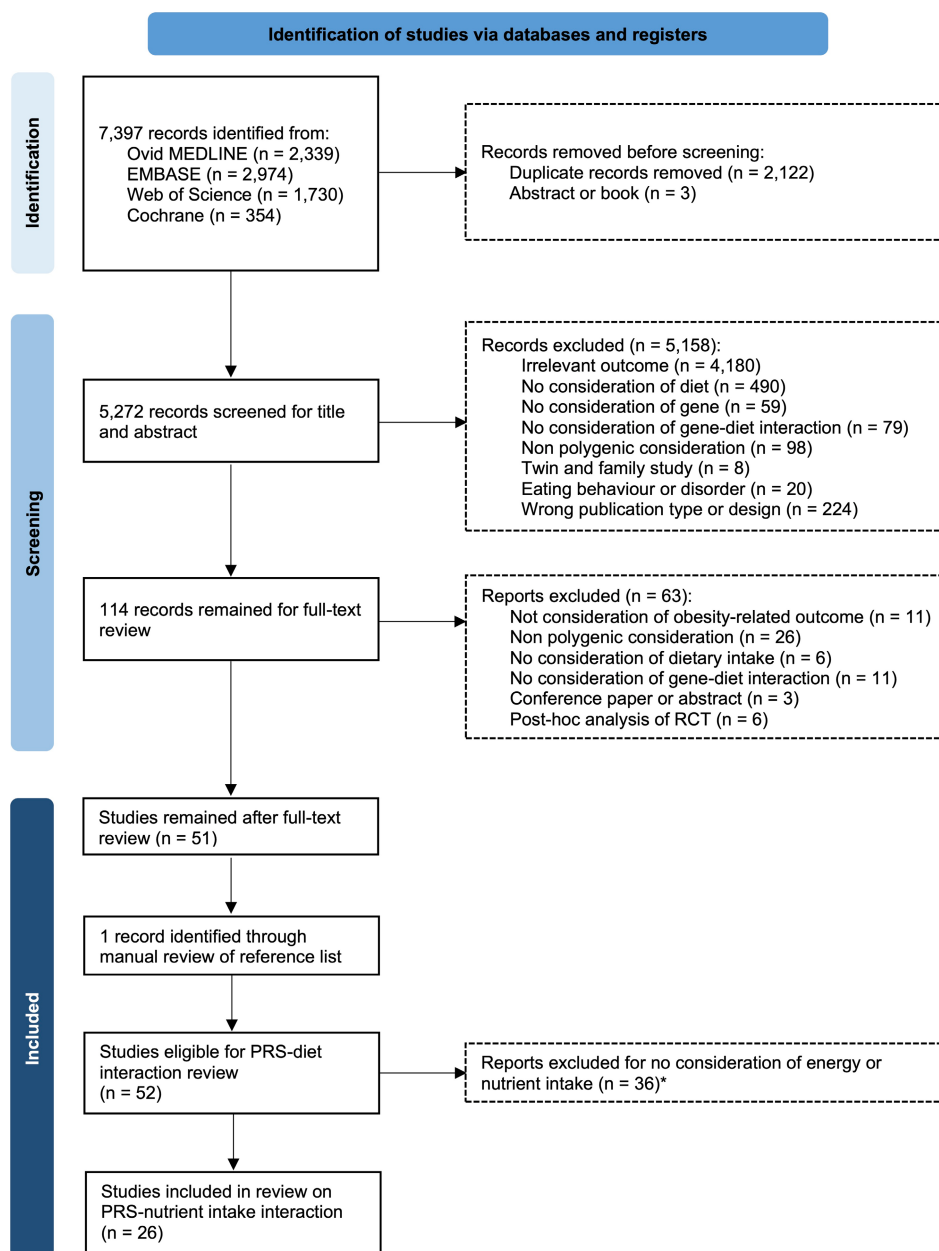


FIGURE 1 | Flowchart of study selection. Adapted from [20]. For more information, visit: <http://www.prisma-statement.org/>. * The search strategy captured a comprehensive set of dietary exposures. The present systematic review focuses on synthesizing evidence for polygenic risk interactions with nutrient intakes on obesity outcomes. Additional dietary exposures will be reported separately.

interactions for saturated fatty acids (SFA) [30, 33], whereas pooled analysis of US healthcare professional cohorts reported that high trans-fat intake accentuated the association between a wPRS-BMI and BMI (0.04 kg/m² per 10 risk allele increase with a 1 SD increase in trans-fat, 0.1 kg/m² per 10 risk allele increase with 1% energy increase in trans-fat) [35, 36], whereas omega-3 intake attenuated it (−0.02% kg/m² per 10 risk allele increment and 1SD increase in % energy) [36, 37]. As for younger samples, a UK longitudinal study reported that low MUFA and PUFA intake increased the association between a uPRS-Obesity and fat mass index in children [28].

When considering samples of non-European ancestries, in Japanese adults, high wPRS-BMI individuals had a significantly higher BMI with increased animal fat intake but a

significantly lower BMI with increased vegetable fat intake [40]. Higher SFA, PUFA, MUFA, or total fat intake interacted with a uPRS-Metabolic on waist circumference in Ghanaian adults [43], whereas in Asian Indians, a uPRS-lipids interacted with fatty acid intake on waist circumference, with only SFA interactions remaining after additional covariate adjustment [51]. The high uPRS group had −0.01 cm versus the low uPRS group in participants with low SFA intake, with no differences in those with high SFA [51].

A longitudinal KoGES study identified that reducing fat intake led to greater reduction in body fat mass among those with high genetic susceptibility [41], and a cross-sectional sample of Yup'ik people reported omega-3 PUFA intake strengthened associations between a uPRS-BMI and BMI (interaction effect size: 0.01 kg/

TABLE 1 | General characteristics of cohort studies.

Reference	Study name	Study type	Country (ancestry)	Number of participants	Sex	Age (years)	Follow-up (years)	Dietary assessment method	PRS ^a	Weighted or unweighted PRS
European cohorts										
Riedel et al. 2013 [28]	ALSPAC	Longitudinal	United Kingdom (European)	2346	F, M	9.8 ± 0.3	2	3-day FR	8-SNPs PRS-Obesity ^a	U
Ankarfeldt et al. 2014 [29]	MONICA, DCH, Inter99	Longitudinal	Denmark (European)	1257 (MONICA), 2167 (DCH), 3630 (Inter99)	F, M	41.4 (30.6, 61.1; MONICA), 53.0 (50.0, 58.0; DCH), 45.0 (34.7, 59.8; Inter99)	~5	7-day FR (MONICA), FFQ (DCH, Inter99)	50-SNPs PRS-Obesity, 33-SNPs PRS-BMI, 14-SNPs PRS-WHR, 6-SNPs PRS-WC	U
Casas-Augustench et al. 2014 [30]	GOLDN, MESA	Cross-sectional	United States (European)	782 (GOLDN), 2035 (MESA)	F, M	48.9 ± 0.6 (GOLDN), 62.9 ± 0.2 (MESA)	—	Semi-quantitative FFQ (GOLDN), FFQ (MESA)	63-SNPs PRS-Obesity (GOLDN), 59-SNPs PRS-Obesity (MESA)	W
Larsen et al. 2014(a) [31]	MONICA, DCH, Inter99	Longitudinal	Denmark (European)	1329 (MONICA), 2167 (DCH), 4073 (Inter99)	F, M	50.5 (30.6, 61.1; MONICA), 53.0 (50.0, 58.0; DCH), 45.1 (34.7, 59.8; Inter99)	5	7-day FR (MONICA), FFQ (DCH, Inter99)	54-SNPs PRS-Obesity, 33-SNPs PRS-BMI, 18-SNPs PRS-WHR, 6-SNPs PRS-WC	U
Larsen et al. 2014(b) [32]	MONICA, DCH, Inter99	Longitudinal	Denmark (European)	1329 (MONICA), 2167 (DCH), 4073 (Inter99)	F, M	50.5 (30.6, 61.1; MONICA), 53.0 (50.0, 58.0; DCH), 45.1 (34.7, 59.8; Inter99)	5	7-day FR (MONICA), FFQ (DCH, Inter99)	50-SNPs PRS-Obesity, 33-SNPs PRS-BMI, 14-SNPs PRS-WHR, 6-SNPs PRS-WC	U
Celis-Morales et al. 2017 [33]	UK Biobank	Cross-sectional	United Kingdom (European)	48,170	F, M	56.5 ± 7.8	—	24h-FR	93-SNPs PRS-BMI	W
Tyrrell et al. 2017 [34]	UK Biobank	Cross-sectional	United Kingdom (European)	119,733	F, M	37–73	—	24h FR	69-SNPs PRS-BMI	W
Ding et al. 2018 [35]	NHS, HPFS, WGHs	Cross-sectional	United States (European)	5730 (NHS), 5730 (HPFS), 21,740 (WGHs)	F (NHS), M (HPFS), F (WGHs)	30–55 (NHS), 40–75 (HPFS), ≥ 45 (WGHs)	—	FFQ	97-SNPs PRS-BMI, 54-CNS-SNPs PRS-BMI, 43-no-CNS-SNPs PRS-BMI	W
Wang et al. 2018 [36]	NHS, HPFS	Longitudinal	United States (European)	8828 (NHS), 5218 (HPFS)	F (NHS), M (HPFS)	30–55 (NHS), 40–75 (HPFS)	20	Semi-quantitative FFQ	77-SNPs PRS-BMI, 97-SNPs PRS-BMI	W

(Continues)

TABLE 1 | (Continued)

Reference	Study name	Study type	Country (ancestry)	Number of participants	Sex	Age (years)	Follow-up (years)	Dietary assessment method	PRS ^a	Weighted or unweighted PRS
Huang et al. 2019 [37]	NHS, HPFS, WHI	Longitudinal	United States (European)	11,330 (NHS), 6773 (HPFS), 6254 (WHI)	F (NHS), M (HPFS), F (WHI)	57 ± 9 (NHS), 57 ± 11 (HPFS), 68 ± 5 (WHI)	10	Semi-quantitative FFQ (NHS), HPFS), FFQ (WHI)	77-SNPs PRS-BMI	W
Hüls et al. 2021 [38]	IDEFICS/I. Family	Longitudinal	Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden (European)	3098	F, M	2–16	6	FFQ and 24h FR	2.1M-SNPs PRS-BMI	W
Non-European cohorts										
Lemas et al. 2013 [39]	CANHR	Cross-sectional	Alaska, United States (Yup'ik)	1073	F, M	14–94	—	Biomarkers from blood	10-SNPs PRS-BMI ^a	U
Nakamura et al. 2016 [40]	Yamagata Study	Cross-sectional, longitudinal	Japan (Asian)	708	F, M	40–87	7	Semi-quantitative FFQ	29-SNPs PRS-BMI	W
Cha et al. 2018 [41]	KoGES	Cross-sectional, longitudinal	South Korea (Asian)	4293	F, M	50.8 ± 8.5	4	FFQ	19-SNPs PRSxFat intake, 37-SNPs PRSxCarbohydrate intake, 44-SNPs PRSxCalorie intake ^a	U
Chang & Dorajoo et al. 2018 [42]	SCHS, SP2	Cross-sectional	Singapore-China (Asian)	5723 (SCHS), 2094 (SP2)	F, M	45–74 (SCHS), 24–95 (SP2)	—	Semi-quantitative FFQ	78-SNPs PRS-BMI	W
Alsulami et al. 2020(a) [43]	GONG	Cross-sectional	Ghana (African)	302	F, M	38.2 ± 9.6	—	3-day 24h FR	4-SNPs PRS-Metabolic, 8-SNPs PRS-Metabolic, 12-SNPs PRS-Metabolic ^a	U
Alsulami et al. 2020(b) [44]	MINANG	Cross-sectional	Indonesia (Southeast Asian)	110	F	25–60	—	Semi-quantitative FFQ	15-SNPs PRS-Metabolic ^a	U
Surendran et al. 2020 [45]	GOOD	Cross-sectional	Sri Lanka (Asian)	109	F, M	25–50	—	FFQ	10-SNPs PRS-Metabolic, 10-SNPs PRS-Vitamin B12 ^a	U
Alsulami et al. 2021 [46]	BOLD	Cross-sectional	Brazil (South America)	200	F, M	19–24	—	Nonconsecutive 3-day FR	10-SNPs PRS-Metabolic ^a	U

(Continues)

TABLE 1 | (Continued)

Reference	Study name	Study type	Country (ancestry)	Number of participants	Sex	Age (years)	Follow-up (years)	Dietary assessment method	PRS ^a	Weighted or unweighted PRS
Lee et al. 2021 [47]	KARE, CAVAS, HEXA	Cross-sectional	South Korea (Asian)	8444 (KARE), 9300 (CAVAS), 17,350 (HEXA)	F, M	52.2 ± 8.9 (KARE), 62.2 ± 9.7 (CAVAS), 53.8 ± 7.9 (HEXA)	—	FFQ	62-SNPs PRS–BMI, 193-SNPs PRS–BMI	W, U
Park et al. 2021 [48]	KoGES	Cross-sectional	South Korea (Asian)	53,828	F, M	> 40	—	Semi-quantitative FFQ	5-interacting SNPs PRS–BMI, 7-interacting SNPs PRS–BMI ^a	U
Park 2022 [49]	KoGES	Cross-sectional	South Korea (East Asian)	53,828	F, M	> 40	—	Semi-quantitative FFQ	5-interacting SNPs PRS–Abdominal Obesity, 6-interacting SNPs PRS–Abdominal Obesity ^a	U
Wu et al. 2022 [50]	TPLS	Longitudinal	Taiwan (East Asian)	1135	F, M	10.4 ± 2.0	~2.5	2-day 24h FR	4-SNPs PRS–Obesity ^a	U
Wuni et al. 2022 [51]	CURES	Cross-sectional	India (Asian Indian)	497	F, M	44 ± 10	—	Semi-quantitative FFQ	3-SNPs PRS–Lipids ^a	U
Daily and Park 2023 [52]	KoGES	Cross-sectional	South Korea (East Asian)	66,835	F, M	> 40	—	Semi-quantitative FFQ	3-interacting SNPs PRS BFM, 6-interacting SNPs PRS–BFM ^a	U
Nakamura et al. 2023 [53]	J-MICC	Cross-sectional	Japan (East Asian)	12,918	F, M	35–69	—	FFQ	76-SNPs PRS–BMI	W

Abbreviations: Avon Longitudinal Study of Parents and Children (ALSPAC); body fat mass (BFM); body mass index (BMI); Cancer and Health Cohort (DCH); CardioVascular Disease Association Study (CAVAS); Center for Alaska Health Research study (CANHR); central nervous system (CNS); Chennai Urban Rural Epidemiological Study (CURES); Diet; Female (F); food frequency questionnaire (FFQ); food records (FR); Genetics of Lipid Lowering Drugs and Diet Network study (GOLDN); Genetics of Obesity and Diabetes Study (GOOD); Health EXA minee (HEXA); Health Professionals Follow-up Study (HPFS); interacting (x); Japan Multi-Institutional Collaborative Cohort Study (J-MICC); Korea Association Resource (KARE); Korean Genome and Epidemiology Study (KoGES); Lifestyle and Diabetes in Brazil (BOLD); Male (M); Monitoring Trends and Determinants of Cardiovascular Disease Study (MONICA); Multi-Ethnic Study of Atherosclerosis (MESA); Nurses' Health Study (NHS); Obesity; polygenic risk score (PRS); Singapore Chinese Health Study (SCHS); Singapore Prospective Study Program; single nucleotide polymorphism (SNP); The Genetics of Obesity and Nutrition in Ghana Study (GONG); the Minangkabau Indonesia Study on Nutrition and Genetics Study (MINANG); the Taiwan Puberty Longitudinal Study (TPLS); unweighted (U); waist circumference (WC); waist-to-hip-ratio (WHR); weighted (W); Women's Genome Health Study (WGHS); Women's Health Initiative Study (WHI).

^aPRS was created by adapting GWAS loci for study considerations (ancestry, age group, or specific study objectives).

TABLE 2 | Characteristics of dietary exposures and obesity outcomes in cohort studies.

Reference	Dietary exposure	Obesity outcome
European cohorts		
Riedel et al. 2013 [28]	Total energy (kcal), protein % TE, carbohydrates % TE, SFA % TE, MUFA % TE, PUFA % TE	Fat mass index (kg/m ²)
Ankarfeldt et al. 2014 [29]	Protein % TE	WC (cm), body weight (kg)
Casas-Augustench et al. 2014 [30]	Total fat % TE, SFA % TE, MUFA % TE, PUFA % TE	BMI (kg/m ²), WC (cm), WHR
Larsen et al. 2014(a) [31]	Calcium (mg/day)	BMI (kg/m ²), WC (cm), body weight (kg)
Larsen et al. 2014(b) [32]	Ascorbic acid (mg/day)	BMI (kg/m ²), WC (cm), WHR
Celis-Morales et al. 2017 [33]	Total energy (kcal/day), protein % TE, carbohydrates % TE, total fat % TE, SFA % TE, fiber (g/day)	BMI (kg/m ²), WC (cm)
Tyrrell et al. 2017 [34]	Protein % TE, fat % TE	BMI (kg/m ²)
Ding et al. 2018 [35]	PUFA % TE, trans fatty acids % TE, omega-3 PUFA (mg/day), MUFA:SFA ratio, sodium (g/day)	BMI (kg/m ²)
Wang et al. 2018 [36]	PUFA % TE, trans fatty acids % TE, omega-3 PUFA (mg/day), MUFA:SFA ratio, sodium (g/day)	BMI (kg/m ²), body weight (kg)
Huang et al. 2019 [37]	Omega-3 PUFA (g/day)	BMI (kg/m ²)
Hüls et al. 2021 [38]	Fiber (mg/kcal)	BMI (kg/m ²), WC (cm)
Non-European cohorts		
Lemas et al. 2013 [39]	Omega-3 PUFA (quartiles of intake)	BMI (kg/m ²), WC (cm), hip circumference (cm), thigh circumference (cm), body fat %
Nakamura et al. 2016 [40]	Animal protein (g/day), vegetable protein (g/day), carbohydrates (g/day), animal fat (g/day), vegetable fat (g/day), fiber (g/day)	BMI (kg/m ²)
Cha et al. 2018 [41]	Total energy (kcal), carbohydrates (g), fat (g)	Body fat mass (kg)
Chang & Dorajoo et al. 2018 [42]	Total energy (kcal/day) protein % TE, carbohydrates % TE, total fat % TE, SFA % TE, MUFA % TE, PUFA % TE, Starch % TE, fiber (g/day), cholesterol (mg/day)	BMI (kg/m ²)
Alsulami et al. 2020(a) [43]	Protein (g/day), carbohydrates (g/day), total fat (g/day), SFA (g/day), MUFA (g/day), PUFA (g/day), fiber (g/day)	BMI (kg/m ²), WC (cm), WHR, visceral fat %, body fat %
Alsulami et al. 2020(b) [44]	CHO % TE, protein % TE, fat % TE, fiber (g/day)	BMI (kg/m ²), WC (cm)
Surendran et al. 2020 [45]	Protein % TE, carbohydrates % TE, total fat % TE	BMI (kg/m ²), WC (cm), body fat %
Alsulami et al. 2021 [46]	Protein % TE, carbohydrates % TE, total fat % TE, SFA % TE, MUFA % TE, PUFA % TE	BMI (kg/m ²), WC (cm), body fat %
Lee et al. 2021 [47]	Total energy (kcal), protein (g), carbohydrates (g), fat (g)	BMI (kg/m ²), Obesity (BMI < 25 nonobese, BMI > 25 obese)
Park et al. 2021 [48]	Protein % TE, carbohydrates % TE, total fat % TE, SFA % TE, MUFA % TE, PUFA % TE, fiber (g/day)	BMI (kg/m ²)

(Continues)

TABLE 2 | (Continued)

Reference	Dietary exposure	Obesity outcome
Park 2022 [49]	Energy (% EER), protein % TE, CHO % TE, fat % TE, SFA % TE, MUFA % TE, PUFA % TE, cholesterol (mg/day), fiber (g/day)	Obesity (BMI < 25 nonobese, BMI > 25 obese), abdominal obesity (WC ≥ 90 cm for men, ≥ 85 cm for women)
Wu et al. 2022 [50]	Energy (kcal/day), CHO % TE, protein % TE, fat % TE	Tri-ponderal mass (kg/m ³) index growth trajectory
Wuni et al. 2022 [51]	Fat (g/day), protein (g/day), CHO (g/day), dietary fiber (g/day), SFA (g/day), PUFA (g/day), MUFA (g/day)	BMI (kg/m ²), WC (cm), WHR, obesity (BMI < 25 nonobese, BMI > 25 obese)
Daily and Park 2023 [52]	Energy (% EER), protein % TE, CHO % TE, fat % TE	Body fat mass
Nakamura et al. 2023 [53]	Energy (kcal/day), protein (g/day), SFA (g/day), MUFA (g/day), n-3 PUFA (g/day), CHO (g/day), soluble fiber (g/day), insoluble fiber (g/day), retinol (mcg/day), vitamin D (mcg/day), vitamin E (mg/day), vitamin B1 (mg/day), vitamin B2 (mg/day), folate (mcg/day), vitamin C (mg/day), iron (mg/day), calcium (mg/day)	BMI (kg/m ²)

Abbreviations: body mass index (BMI); carbohydrate (CHO); centimeter (cm); estimated energy requirement (EER); grams (g); kilocalories (kcal); kilogram (kg); meter (m); milligrams (mg); monounsaturated fatty acids (MUFA); percentage of total energy intake (% TE); polyunsaturated fatty acids (PUFA); saturated fatty acids (SFA); waist circumference (WC); waist-to-hip-ratio (WHR).

m²), percent body fat (interaction effect size: 0.03%), and waist circumference (interaction effect size: 0.02 cm) [39]. A Japanese study reported that the association between SFA and BMI was accentuated among adults with high wPRS–BMI (0.74 kg/m² per 10 g of SFA increase) versus low wPRS–BMI group (0.27 kg/m² per 10 g of SFA increase) [53]. A study of Brazilian young adults showed significant interactions between a uPRS for metabolic traits and fat intake on body percentage, though directionality was unclear [46].

3.4 | Interaction of Carbohydrates, Fiber, and Protein With PRS

Figure 3 shows results for PRSs and carbohydrates, fiber, or protein intake. Seven of 19 studies reported significant interactions for these nutrients [38, 40, 41, 43–45, 52]. However, in a longitudinal study of Japanese adults, interactions between a wPRS–BMI and carbohydrate, animal protein, vegetable protein, and fiber intake were reported on BMI, but such interactions were only evident for baseline outcomes [40]. Compared with those in the low wPRS–BMI group, the high PRS group had a significantly higher baseline BMI with higher fiber (0.15 kg/m² per 1 g of fiber increase) and vegetable protein intake (0.03 kg/m² per 1 g of protein increase) but a significantly lower baseline BMI with higher animal protein intake (−0.05 kg/m² per 1 g of protein increase) [40]. Another longitudinal study of Korean adults reported that greater reduction in carbohydrate intake over time was associated with greater reduction in body fat mass among individuals with a higher PRS score [41]. In a recent prospective study from the European IDEFICS/I.Family cohort, a higher fiber intake attenuated the risk of having obesity despite high genetic susceptibility among children and adolescents (BMI: −0.02 kg/m² per 1 unit PRS increase and 1 mg/kcal of fiber increase) [38].

A cross-sectional analysis of Ghanaian adults showed similar interactions between fiber and uPRS–Metabolic on body fat percentage and waist circumference [43]. Among other cross-sectional analyses, a study among Sri Lankan adults reported significant interactions for a wPRS–vitamin B12 and protein intake in % energy on logged waist circumference (0.037 cm per unit of PRS and protein increment) and a wPRS–Metabolic and carbohydrate intake in % energy on logged waist circumference (0.007 cm per unit of PRS and carbohydrate increase) and waist-to-hip ratio (0.015 per unit of PRS and carbohydrate increase) [45]. Similarly, a cross-sectional analysis of the KoGES study showed a significant interaction with protein but not carbohydrate intake. The positive association between a uPRS and fat mass was attenuated with high protein intake [52]. Another cross-sectional study of Indonesian women reported that lower protein intake was associated with lower waist circumference among women with a higher PRS score [44].

3.5 | Interaction of Energy Intake With PRS

Figure 3 shows the results for interactions between energy intake with PRSs on obesity outcomes, which were reported in four of nine studies [33, 41, 49, 52]. An interaction of energy intake with a wPRS–BMI on BMI (0.47 kg/m² per unit wPRS increase among low intake group vs. 0.56 kg/m² among high intake group) and waist circumference (1.04 cm per unit wPRS increase among low intake group vs. 1.17 cm among high intake group) was reported from the UK Biobank [33]. A study from KoGES Korean longitudinal cohort also reported that energy intake moderated the association between an obesity uPRS and total caloric intake on body fat percentage [41]. In these two studies, the strength of the PRS association with their respective obesity outcomes increased with increasing

PRS trait	# of SNPs in PRS	Reference	Total Fat	Animal Fat	Vegetable Fat	SFA	MUFA	PUFA	Trans fatty acids	MUFA:SFA ratio	Cholesterol	Omega-3 PUFA
BMI												
SNP x SNP	7	Park et al. 2021 ⁴⁸	1			1	1	1			1	
<i>SNP x SNP</i>	5	<i>Park et al. 2021⁴⁸</i>	1			1	1	1			1	
	10	Lemas et al. 2013 ³⁹										1
	29	Nakamura et al. 2016 ^{40*} †		1	1							
	69	Tyrrell et al. 2017 ³⁴	1									
	77	Huang et al. 2019 ^{37*} †										1
	76	Nakamura et al. 2023 ⁵³				1	1	1				
	78	Chang & Dorajoo et al. 2018 ⁴²	1			1	1	1			1	
	93	Celis-Morales et al. 2017 ³³	1			1						
	97	Ding et al. 2018 ³⁵						1	1	1		1
<i>Non-CNS related SNPs</i>	43	<i>Ding et al. 2018³⁵</i>						1	1	1		1
<i>CNS related SNPs</i>	54	<i>Ding et al. 2018³⁵</i>						1	1	1		1
	97	Wang et al. 2018 ^{36†}						1	1	1		1
	77	<i>Wang et al. 2018^{36†}</i>						1	1	1		1
	193	Lee et al. 2021 ⁴⁷	1									
	62	<i>Lee et al. 2021⁴⁷</i>	1									
Obesity												
	4	Wu et al. 2022 ^{50*} †	1									
	8	Riedel et al. 2013 ^{28*} †				1	1	1				
SNP interacting with fat intake	19	Cha et al. 2018 ^{41*} †	1									
	63	Casas-Augustench et al. 2014 ³⁰	1			1	1	1				
	59	<i>Casas-Augustench et al. 2014³⁰</i>	1			1	1	1				
Abdominal obesity												
SNP x SNP	6	Park 2022 ⁴⁹	1			1	1	1			1	
<i>SNP x SNP</i>	5	<i>Park 2022⁴⁹</i>	1			1	1	1			1	
Body fat mass												
SNP x SNP	6	Daily and Park 2023 ⁵²	1									
<i>SNP x SNP</i>	3	<i>Daily and Park 2023⁵²</i>	1									
Metabolic												
Serum lipids	3	Wuni et al. 2022 ⁵¹	1			1	1	1				
Metabolic risk	10	Alsulami et al. 2021 ^{46*}	1			1	1	1				
Metabolic risk	10	Surendran et al. 2020 ⁴⁵	1									
Serum Vitamin B12	10	Surendran et al. 2020 ⁴⁵	1									
Metabolic risk	12	Alsulami et al. 2020(a) ^{43*}	1									
<i>Metabolic risk</i>	4	<i>Alsulami et al. 2020(a)^{43*}</i>	1			1	1	1				
<i>Metabolic risk</i>	8	<i>Alsulami et al. 2020(a)^{43*}</i>	1									
Metabolic risk	15	Alsulami et al. 2020 (b) ⁴⁴	1									

FIGURE 2 | Summary of PRS–fat intake interactions on obesity-related outcomes. * Articles ranked as low quality in the methodological assessment of the quality of genetic associations in complex diseases. † Indicates longitudinal study. “1” indicates that the respective reference assessed PRS–fat intake interaction(s). Green: at least one statistically significant interaction was observed; red: no statistically significant interaction was observed. Smaller PRSs derived from main PRSs are in italics, and statistically significant interactions are highlighted in lighter colors. Abbreviations: body mass index (BMI), central nervous system (CNS), monounsaturated fatty acids (MUFA), polygenic risk score (PRS), polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), single nucleotide polymorphism (SNP), SNP-SNP interaction (SNP×SNP), waist circumference (WC), waist-to-hip ratio (WHR).

PRS trait	# of SNPs in PRS	Reference	Carbohydrates	Protein	Animal Protein	Vegetal Protein	Fibre	Starch	Energy	Ascorbic Acid	Calcium	Sodium	Vitamin B,E,D	Retinol	Iron
BMI															
SNP x SNP	7	Park et al. 2021 ⁴⁸	1	1			1								
SNP x SNP	5	Park et al. 2021 ⁴⁸	1	1			1								
	29	Nakamura et al. 2016 ^{40*}	1		1	1	1								
	33	Ankarfeldt et al. 2014 ^{29†}		1											
	33	Larsen et al. 2014(a) ^{31*}									1				
	33	Larsen et al. 2014(b) ^{32†}								1					
	69	Tyrrell et al. 2017 ³⁴		1											
	76	Nakamura et al. 2023 ⁵³	1	1			1		1	1	1		1	1	1
	78	Chang & Dorajoo et al. 2018 ⁴²	1	1			1	1	1						
	93	Celis-Morales et al. 2017 ³³	1	1			1		1						
	97	Ding et al. 2018 ³⁵										1			
Non-CNS related SNPs	43	Ding et al. 2018 ³⁵										1			
CNS related SNPs	54	Ding et al. 2018 ³⁵										1			
	97	Wang et al. 2018 ^{36†}										1			
	77	Wang et al. 2018 ^{36†}										1			
	193	Lee et al. 2021 ⁴⁷	1	1					1						
	62	Lee et al. 2021 ⁴⁷	1	1					1						
	2.1 M	Hüls et al. 2021 ^{38†}					1								
Obesity															
	4	Wu et al. 2022 ^{50*}	1	1					1						
	8	Riedel et al. 2013 ^{28*}	1	1					1						
SNPs interacting with CHO	37	Cha et al. 2018 ^{41*}	1												
SNPs interacting with energy	44	Cha et al. 2018 ^{41*}						1							
	50	Ankarfeldt et al. 2014 ^{29†}		1											
	54	Larsen et al. 2014(a) ^{31*}									1				
	50	Larsen et al. 2014(b) ^{32†}								1					
WC															
	6	Ankarfeldt et al. 2014 ^{29†}		1											
	6	Larsen et al. 2014(b) ^{32†}								1					
	6	Larsen et al. 2014(a) ^{31*}									1				
Abdominal obesity															
SNP x SNP	6	Park 2022 ⁴⁹	1	1			1		1						
SNP x SNP	5	Park 2022 ⁴⁹	1	1			1		1						
WHR															
	14	Ankarfeldt et al. 2014 ^{29†}		1											
	14	Larsen et al. 2014(b) ^{32†}								1					
	18	Larsen et al. 2014(a) ^{31*}									1				
Body fat mass															
SNP x SNP	6	Daily and Park 2023 ⁵²	1	1					1						
SNP x SNP	3	Daily and Park 2023 ⁵²	1	1					1						
Metabolic															
Serum Lipids	3	Wuni et al. 2022 ⁵¹	1	1			1								
Metabolic risk	8	Alsulami et al. 2020(a) ^{43*}	1	1			1								
Metabolic risk	4	Alsulami et al. 2020(a) ^{43*}	1	1			1								
Metabolic risk	10	Alsulami et al. 2021 ^{46*}	1	1											
Metabolic risk	10	Surendran et al. 2020 ⁴⁵	1	1											
Serum Vitamin B12	10	Surendran et al. 2020 ⁴⁵	1	1											
Metabolic risk	12	Alsulami et al. 2020(a) ^{43*}	1	1			1								
Metabolic risk	15	Alsulami et al. 2020(b) ⁴⁴	1	1			1								

FIGURE 3 | Legend on next page.

FIGURE 3 | Summary of PRS–nutrient and energy interactions on obesity-related outcomes. * Articles ranked as low quality in the methodological assessment of the quality of genetic associations in complex diseases. † Indicates longitudinal study. “1” indicates that the respective reference assessed PRS–nutrient and energy intake interaction(s). Green: at least one statistically significant interaction was observed; red: no statistically significant interaction was observed. Smaller PRSs derived from main PRSs are in italics, and statistically significant interactions are highlighted in lighter colors. Abbreviations: body mass index (BMI), central nervous system (CNS), carbohydrate (CHO), million (M), polygenic risk score (PRS), single nucleotide polymorphism (SNP), SNP–SNP interaction (SNP × SNP), waist circumference (WC), waist-to-hip ratio (WHR).

energy intake. Furthermore, two cross-sectional analyses of KoGES reported significant interactions between energy and a uPRS–body fat on odds ratio of high body fat [52] and energy and a uPRS–abdominal obesity on the odds ratio of abdominal obesity [49]. However, Daily and Park reported that high energy intake attenuated the genetic risk of body fat [52], whereas Park found that high energy intake accentuated the genetic risk of abdominal obesity [49]. In contrast, such an interaction was not observed among Singapore–Chinese adults [42], Korean adults [47], Japanese adults [53], Taiwanese adolescents [50], or European children [28].

3.6 | Interaction of Micronutrients and PRS

To date, five studies have assessed interactions between micronutrient intakes: sodium [35, 36], calcium [31, 53], ascorbic acid [32, 53], and other micronutrients, including vitamins A, B, D, E, and iron [53] (Figure 3). Sodium intake did not modify the genetic susceptibility to obesity as measured by BMI either cross-sectionally [35] or longitudinally [36] in European ancestry cohorts [36]. Calcium and ascorbic acid were evaluated in three cohorts: the MONICA study, the DCH study, and the INTER99 study [31, 32]. No significant interactions were observed between calcium consumption and a uPRS–Obesity in relation to changes in body weight or waist circumference [31]. However, a meta-analysis of DCH and INTER99 showed a change of -0.04 cm in waist circumference per 1000-mg higher calcium intake with each additional uPRS–WC risk allele [31].

Ascorbic acid intake was reported to interact with a uPRS–waist-to-hip ratio on waist circumference in a meta-analysis of DCH and INTER99 cohorts [32]. Each additional risk allele was associated with an average increase of 0.04 cm/year in waist circumference per 100 mg/day higher ascorbic acid intake. This interaction was not replicated with other PRSs or weight change [32]. In contrast, cross-sectional analyses of a Japanese adult cohort reported no significant interactions between a wPRS–BMI and retinol, vitamins B, C, D, E, iron, or calcium intake [53].

3.7 | Study Quality

Based on the NOS quality assessment tool, all the cross-sectional studies were of high or medium quality (Table S1). Reasons for ranking as medium quality included incomplete adjustment for important confounders (sex, age, and ancestry) or not accounting for items related to study group selection [30, 35, 42–46, 51]. The methodological assessment scale for the quality of genetic associations (Table S2) showed five

high-quality articles [33, 34, 47, 48, 53], nine medium-quality articles [30, 35, 39, 42, 44, 45, 49, 51, 52], and two low-quality articles [43, 46]. Reasons for low-quality scoring among cross-sectional studies included lack of correction for multiple testing or ancestry, test of group similarity at baseline, or a small sample size.

Among the longitudinal studies, according to the NOS quality assessment tool, three studies rated high quality [29, 31, 32] and seven studies rated medium quality (Table S3) [28, 36–38, 40, 41, 50]. No studies scored as low quality using the NOS tool. Similar to the cross-sectional studies, reasons for a medium-quality score included lack of adjustment for important confounders, but also not having an adequate follow-up length considered as > 2 years. When assessing with the methodological scale for genetic studies (Table S2), four articles rated medium quality [29, 32, 36, 38] and six articles rated low quality [28, 31, 37, 40, 41, 50]. The reasons for a low score among longitudinal studies included not correcting for multiple testing or ancestry, no reporting of Hardy–Weinberg equilibrium assessment, lack of a test of group similarity at baseline, and having a small sample size.

3.8 | Sensitivity Assessment of Narrative Review

Appendix S4 presents a summary of the literature assessment when low-quality studies were excluded, as well as when considering studies conducted among adults separately from children/adolescents (Tables S4 and S5). In general, the number of studies reporting significant gene–nutrient interactions decreased when excluding low-quality studies but was unaffected by excluding studies conducted among children/adolescents (Figures S1 and S2).

3.9 | Meta-Analysis

Out of 13 articles eligible for data pooling, two research groups shared cross-sectional summary statistics for PRS interaction with percent protein and fat intake on BMI derived from three separate cohort studies (the UK Biobank [34] and two Singaporean Chinese studies [42]). The meta-analysis did not show statistically significant interactions between the PRS and percent fat intake on cross-sectional BMI (Figure S3) or PRS and percent protein on cross-sectional BMI (Figure S4). Funnel plots showed asymmetry, suggesting the presence of publication bias (Figures S5 and S6). Further details on statistical heterogeneity and sex-specific subgroup analyses are presented in Appendix S5 and Figures S7 and S8. However, given the limited number of studies for which data could be pooled, the results for meta-analyses must be interpreted with caution.

4 | Discussion

To our knowledge, this is the first systematic review and meta-analysis of polygenic risk and nutrient intake interactions on obesity-related outcomes. We identified 26 articles that investigated such interactions, 20 of which reported some observations of statistically significant PRS–nutrient intake interactions [28, 30–33, 35–41, 43–46, 49, 51–53]. When excluding low-quality studies, 13 reported some observations of statistically significant interactions [30, 32, 33, 35, 36, 38, 39, 43, 45, 49, 51–53]. However, reports of PRS–nutrient interactions on obesity outcomes were inconsistent for individual nutrients. A summary of findings is provided below.

When excluding low-quality studies according to the genetic methodological scale, certain types of dietary fats (SFA, omega-3, and trans fat) and energy intake showed the most frequency of reported interactions with polygenic obesity risk, but only in two to four studies. Moreover, the direction of the interaction varied for SFA and omega-3. The varied directions may be related to the ancestry of the study sample, as reported directions appeared to be more consistent among European samples than in non-European samples.

Some additional reports of interactions were observed for carbohydrates, protein, and other fats, but the majority of studies reported null results for these nutrients, and low-quality studies were more prevalent in this literature. There were very limited and inconsistent or no reports of micronutrient interactions with polygenic risk on obesity outcomes. The meta-analysis did not identify significant pooled interactions between PRS and fat intake or protein intake on BMI, but the results should be interpreted with caution because of the limited number of studies included and the potential for publication bias. Lastly, synthesizing information on effect sizes of interactions was challenging as these details were not reported in a consistent manner, and some investigations provided only visual depictions (i.e., graphs). Among articles where effect sizes could be interpreted, they were small in nature but somewhat larger for SFA and overall energy intake.

The general use of FFQs or dietary recalls to collect nutrient intakes among the retrieved articles should be acknowledged. Although these methods are cost-effective and simple to administer in cohort studies, they are prone to measurement errors [60], especially among women or individuals with overweight/obesity [61, 62]. Few articles used more objective methods, such as food records [63] or blood biomarkers for omega-3 intake [64, 65]. Challenges in dietary assessment likely contribute to inconsistencies in the retrieved literature, highlighting the need for improved dietary assessment methods in gene–diet interaction research.

Prior studies have reported that nutrient intakes may moderate the association between obesity outcomes and individual obesity candidate genes including *FTO*, *MC4R*, *PPARG*, *APOA5*, or *UCP3* [66, 67]. Among these studies, individual obesity genes were mostly reported to interact with dietary fatty acids or energy intake, whereas only a limited number of studies reported gene–carbohydrate interactions [66, 67]. These observations may be explained by different gene expression pathways. For

example, *MC4R* and *FTO* genes are involved in both appetite and metabolic pathways [68–71], and the *PPARG* gene is involved in the adaptive thermogenesis pathway [72]. Of relevance, loci in *MC4R*, *FTO*, and *LEP* have been associated with lipid consumption and energy intake regulation [16], which may partly explain why most of the significant interactions identified in this systematic review were related to the intake of fatty acids and energy. However, interactions between PRS and nutrient intakes on obesity outcomes would likely differ according to the genetic loci included in a PRS and the weighting approach [73], which could explain the inconsistent findings reported in this review.

Indeed, the PRS evaluated in this review were calculated with different approaches and linked to various phenotypes. Although most phenotypes were related to anthropometry (particularly BMI), some were linked to metabolic traits. Of note, some studies applied unique approaches to PRS development that considered SNP interactions with diet or other SNPs [41, 48, 49, 52]. Such an approach could be extended by a genome-wide environment interaction study (GWEIS) to identify genetic loci that interact with diet on obesity [74, 75]. Therefore, additional discovery efforts in gene–nutrient interaction research are warranted, and future studies should aim to use similar PRS for target phenotypes that are appropriate for the sample's ancestry. Notably, over half of the retrieved articles included in this present review were conducted in non-European samples. Although this is encouraging for diversity and inclusion in genetic research, the PRSs utilized in those studies tended to be adapted from GWAS conducted in European populations. This poses challenges for the accuracy of results and underscores the need for more genomics research in non-European samples [76].

Careful attention to methodological aspects is needed to improve the study quality of future gene–diet interaction research. Lack of adjustment for ancestry (a potential source of confounding [77, 78]), lack of reporting Hardy–Weinberg equilibrium [79], and lack of reporting group similarity at baseline were the main contributors to the low-quality scores assessed with the genetic methodological scale. In addition, small sample sizes and cross-sectional designs are also considered as contributors to lower quality findings [80]. Thus, adequately powered studies with rigorous designs are needed, being aware of methodological details pertinent to genomics research [79, 81–83]. Data sharing with proper security protocols should be more widely adopted to improve the ability to pool data across studies for future meta-analyses. Finally, life course effects should also be considered in future work, as genetic susceptibility to obesity may vary across stages of life [84, 85].

A major strength of this evidence synthesis is the exhaustive search strategy, which enabled a comprehensive assessment of data obtained from the retrieved observational studies. Nevertheless, limitations are present. The focus on observational studies does not allow for drawing conclusions on causality, but prospective designs may reduce the risk of reverse causation [86]. Although study quality was evaluated using two methodological scales, development of a new tool to evaluate methodological quality and risk of bias in gene–environment interaction research would be advantageous, given certain unique considerations [87, 88]. The high heterogeneity of dietary exposures and PRS selection, differences in methodological

approaches, and difficulty accessing study data posed challenges for pooling data for meta-analysis. Lastly, randomized controlled trials (RCTs) were not considered in this investigation. RCTs examining genetic responses to dietary interventions commonly conduct post hoc analyses of genotype groups focusing on single genetic variants, thus being separate from the focus of this work on polygenic risk [89, 90]. RCTs designed with PRS considerations at the onset of the study could help to address the inconsistent observations and varied directions of interactive associations reported in this review [91, 92].

This systematic review illustrates that current observations of PRS–nutrient interactions in obesity are limited and inconsistent. Consumption of certain fatty acids and overall energy intake had the most frequent reports of interaction; however, limitations in study quality, PRS construction, and statistical methods prohibit clear conclusions. Given the observed challenges in the replication of study findings, future studies need to utilize comparable exposures and address current methodological issues in order to provide more robust evidence. Additional research in this area is valuable, as an improved understanding of gene–diet interactions in obesity will help to elucidate mechanisms of the expression of obesity-related genes and may assist in the development of targeted strategies and precision nutrition interventions for vulnerable subgroups.

Author Contributions

D.E.N. designed the research. G.M., H.Y.H., T.M., and D.E.N. conducted the systematic review and data extraction. G.M., H.Y.H., T.M., and D.E.N. summarized the data. H.Y.H. performed the statistical analyses. G.M. and H.Y.H. drafted the manuscript. T.M. and D.E.N. critically revised the manuscript. D.E.N. has primary responsibility for the final content. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

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