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Gene-Environment Interaction Between the FTO Gene and Physical Activity on Body Mass Index: A Systematic Review of Evidence Published from 2021 to 2026

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Abstract. The fat mass and obesity-associated (FTO) gene is the strongest common genetic determinant of body mass index (BMI), and physical activity (PA) has been proposed to attenuate its effect. Evidence published since 2021 has not been systematically synthesized. This systematic review summarizes recent human evidence (January 2021 to December 2026) on the interaction between FTO variants and PA on BMI and related adiposity outcomes. PubMed was searched on 2 September 2026 using a sensitive three-block strategy combining FTO, PA, and BMI terms. Eligible studies were human observational or interventional studies that formally tested an FTO × PA interaction on BMI or adiposity. Screening, data extraction, and quality assessment with a simplified Newcastle-Ottawa scale were performed, and findings were synthesized qualitatively following PRISMA 2020. Of 92 records identified, 18 studies met the eligibility criteria (sample sizes 16-20,906; eight cross-sectional, three cohort, two case-control, and five interventional studies). Eleven studies (61%) reported a significant attenuating interaction, whereby higher PA or structured exercise reduced the effect of FTO risk alleles on adiposity (for example, a 47% attenuation in Danish adults and an approximately two-fold lower obesity risk in physically active Korean risk-allele carriers), whereas seven studies, mostly small or selected samples, reported null interactions. In conclusion, recent evidence generally supports that higher PA attenuates FTO-associated adiposity, but heterogeneity in PA measurement, genotyped variants, and populations, together with a preponderance of cross-sectional designs, tempers certainty (low-to-moderate on a GRADE-style assessment).

Keywords: FTO gene, physical activity, body mass index, gene-environment interaction, systematic review

1. Introduction

Obesity is one of the leading preventable causes of morbidity worldwide. According to the World Health Organization, worldwide obesity has more than doubled since 1990, and in 2022 an estimated 2.5 billion adults were overweight, of whom more than 890 million were living with obesity [1]. Body mass index (BMI), defined as weight in kilograms divided by the square of height

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in meters, remains the most widely used population-level indicator of adiposity, and elevated BMI is causally linked to type 2 diabetes, cardiovascular disease, and several cancers. Because both genetic susceptibility and lifestyle behaviors determine BMI, understanding how they interact is central to precision prevention.

The fat mass and obesity-associated (FTO) gene was the first robustly replicated obesity-susceptibility locus identified by genome-wide association studies. In 2007, Frayling showed that the common intronic variant rs9939609 (T>A) was associated with BMI across multiple cohorts; each additional A allele increased BMI by approximately 0.4 kg/m², and homozygous carriers (about 16% of Europeans) had a 1.67-fold higher risk of obesity [2]. Subsequent functional work demonstrated that the obesity-associated FTO intron acts as an enhancer region influencing IRX3 and IRX5 expression and adipocyte thermogenesis, providing a mechanistic basis for its effect on energy balance [3].

Whether lifestyle can offset this genetic predisposition is a classic gene-environment interaction (G×E) question. In a landmark meta-analysis of 218,166 adults and 19,268 children, Kilpeläinen demonstrated that physical activity (PA) attenuated the effect of the FTO rs9939609 risk allele on BMI and obesity risk by approximately 30% in adults [4]. On the multiplicative scale typically used for etiologic interaction, the negative interaction coefficient indicates antagonism: the relative effect of the risk allele is smaller among physically active individuals. Expressed on the absolute scale, a substantial fraction of the genetic effect can be offset by behavior, which is the quantity of greatest public-health relevance.

Since that meta-analysis, and particularly during the last five years, numerous new studies have examined FTO × PA interactions in more diverse ancestries (East Asian, South Asian, Middle Eastern, and high-altitude populations), across the life course (children, adolescents, pregnant women, and post-bariatric patients), and using varied designs from cross-sectional surveys to randomized exercise trials. However, this recent evidence has not been systematically synthesized, and it is unclear whether the attenuating interaction reported before 2021 holds across populations, FTO variants, and PA measures. The objective of this systematic review is therefore to identify, appraise, and qualitatively synthesize human studies published between January 2021 and December 2026 that formally tested the interaction between FTO genetic variation and physical activity on BMI or related adiposity outcomes.

2. Methods

2.1. Study design and reporting standard

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement [5]. Because of substantial clinical and methodological heterogeneity, a qualitative (narrative) synthesis without statistical pooling was pre-specified. The review was not registered; a protocol defining the eligibility criteria, search strategy, and analysis plan was prepared before screening.

2.2. Eligibility criteria

Eligibility criteria were defined using the PICO framework. Population: humans of any age, sex, ancestry, or health status. Exposure/intervention: FTO genetic variation (any single-nucleotide polymorphism [SNP], haplotype, or FTO-based genetic risk score) together with a measure of physical activity, exercise, or sedentary behavior. Comparator: genotype and/or PA strata. Outcome: BMI or a related adiposity measure (obesity, waist circumference, body fat, weight or BMI change,

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or gestational weight gain). Study designs: cross-sectional, case-control, cohort, and interventional studies (randomized or single-arm). Crucially, studies were required to formally test the FTO × PA interaction (a multiplicative or additive interaction term, or an equivalent genotype-stratified analysis of the PA-outcome association); studies reporting only main effects were excluded. Only English-language reports published between 1 January 2021 and 31 December 2026 were eligible. Reviews, meta-analyses, animal or in-vitro studies, and conference abstracts were excluded.

2.3. Search strategy

PubMed was searched on 3 September 2026. The final strategy combined three concept blocks in title/abstract fields: ("FTO" OR "fat mass and obesity associated" OR "FTO gene") AND ("physical activity" OR "exercise" OR "sedentary" OR "physical inactivity") AND ("body mass index" OR "BMI" OR "obesity" OR "obese" OR "adiposity" OR "overweight"), filtered to the publication-date window above. Interaction-related keywords were deliberately omitted from the search because pilot searches showed that such filters missed eligible studies whose abstracts did not use interaction terminology; the interaction requirement was instead applied as an eligibility criterion during screening. The full search record is provided in the Supplementary Material.

2.4. Study selection and data extraction

All retrieved records were screened by title and abstract, and potentially eligible reports were assessed in full text. Reasons for full-text exclusion were recorded for every report. A standardized form was used to extract: first author and year, country and ancestry, sample size, age group, study design, FTO variant(s), PA measure and grouping, outcome definition, the interaction effect estimate with 95% confidence interval and P value where reported, covariates, and the main conclusion. The screening log and the completed extraction table are provided in the Supplementary Material.

2.5. Quality assessment

Methodological quality was assessed with a simplified scale adapted from the Newcastle-Ottawa Scale, covering six items: representativeness of the study sample, genotyping quality, PA measurement, confounder adjustment, outcome assessment, and rigor of interaction testing (one point each; maximum 6) [6]. The certainty of the body of evidence was then interpreted narratively using GRADE principles (risk of bias, inconsistency, indirectness, and imprecision) [7].

2.6. Data synthesis

Findings were synthesized qualitatively, grouped by study design and population (adult observational studies, studies in children and adolescents, intervention studies, and case-control studies). A meta-analysis was not performed because PA exposures, FTO variants, outcome definitions, and effect measures (odds ratios, β coefficients, and stratified means) were too heterogeneous to pool validly.

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3. Results

3.1. Study selection

The search identified 92 records, all of which were screened by title and abstract; 65 records were excluded at this stage. Twenty-seven full-text articles were assessed for eligibility, and nine were excluded: six did not test an FTO × PA interaction on an adiposity outcome, two examined ineligible outcomes (glycated hemoglobin and dietary behaviors), and one directly relevant study was excluded because the full text was available only in Spanish. Eighteen studies were finally included in the qualitative synthesis (Figure 1).

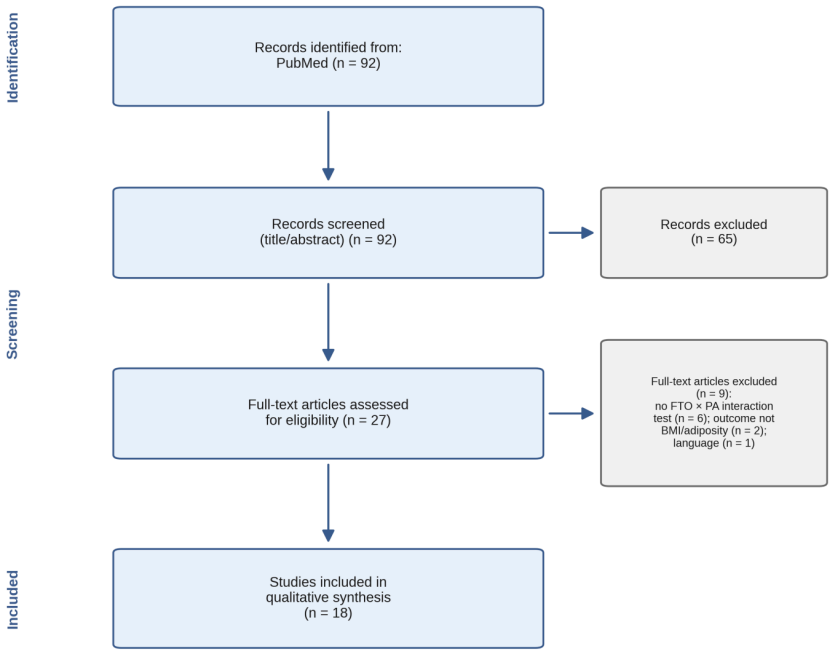

Figure 1. PRISMA 2020 flow diagram of study selection

3.2. Characteristics of included studies

The 18 included studies (Table 1) were published between 2021 and 2026 and together enrolled more than 59,000 participants (median 489 per study; range 16-20,906). Five studies were conducted in East Asian populations, four in Europe, three in the Middle East, two in South Asia, three in the Americas, and one in a high-altitude Tibetan population. Eight studies were cross-sectional, three were prospective cohorts, two were case-control studies, and five were interventional (three randomized trials, one controlled exercise intervention, and one single-arm pilot). The first-intron variant rs9939609 was examined in 11 studies; other variants included rs1421085, rs8050136, rs9930506, rs1121980, rs17817449, rs10163409, and FTO haplotypes. PA was self-reported by questionnaire in most observational studies, whereas intervention studies used supervised, objectively delivered exercise programs.

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Table 1. Characteristics of the 18 studies included in the qualitative synthesis

Study	Country (population)	N	Design	FTO variant(s)	PA measure	Key interaction finding
Cho, 2021 [8]	South Korea (KARE)	8,840	Cross-sectional	rs9939609	Self-report; intense PA ≥3 h/day	Attenuating: obesity OR 1.42 (1.13-1.79) in carriers; intense PA OR 0.62 (0.25-0.84)
Isgin-Atici, 2021 [9]	Turkey	400	Cross-sectional	rs9939609, rs10163409 (GRS)	Questionnaire PA	Significant: rs9939609 × PA on adiponectin, Pint = 0.027
Gong, 2021 [10]	China (Han)	2,216	Cross-sectional	rs9939609, rs8050136	Sedentary behavior; PA	Attenuating: sedentary + risk allele obesity OR 1.63 (1.09-2.45); PA reduced SNP effects
Nguyen, 2021 [11]	USA (breast-cancer survivors)	151	RCT (6-month weight loss)	rs9939609	Structured diet + exercise program	Null genotype × intervention interaction
Hiraike, 2021 [12]	Taiwan (Taiwan Biobank)	20,906	Prospective cohort (3.7 y)	rs1421085	Regular exercise habit	Attenuating: interaction on Δweight/ΔBMI, P = 0.030/0.034; carriers benefited most
Rana, 2021 [13]	Pakistan	578	Case-control	rs1421085	Self-reported PA (MDR)	Null for FTO × PA
Brand, 2022 [14]	Brazil	1,338	Cross-sectional (6-17 y)	rs9939609	Questionnaire PA; screen time; sleep	Null for PA; screen time × FTO significant
Wang, 2022 [15]	China (Han)	178	12-week aerobic-exercise intervention	rs8050136	Supervised moderate aerobic exercise	Conditional: genotype × sex on weight/BMI loss, P = 0.041/0.042; male carriers lost more

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Table 1. (continued)

Bila, 2023 [16]	Brazil	26	RCT (10-week aerobic vs resistance)	rs9939609	Supervised training	Attenuating: carriers in aerobic arm reduced body fat (P = 0.041), improved glycemia (P = 0.002)
Chermon, 2022 [17]	Israel	1,720	Cross-sectional	18 FTO SNPs (incl. rs9939609)	Self-reported PA (active/inactive)	Attenuating: inactive carriers obesity OR 2.54-3.77 vs active; Pint < 0.001
Andersen, 2023 [18]	Denmark	19,585	Cohort + functional studies	rs9939609	Self-reported PA (high/low)	Attenuating: high PA reduced FTO effect on BMI by 47% (P = 0.0013)
Rana, 2023 [19]	Pakistan	612	Case-control	rs9939609	Self-reported low PA	Significant: rs9939609 × low PA increased adiposity (P < 0.05)
Wang, 2024 [20]	China (Tibetan)	1,741	Cross-sectional	rs1121980, rs17817449	Leisure-time exercise; occupational PA	Null on multiplicative and additive scales
Roumi, 2024 [21]	Iran	96	RCT (8-week diet + PA)	rs9930506	Supervised diet + PA program	Attenuating: carriers BMI -1.21 vs +1.87 kg/m² in controls (P < 0.05)
Górczyńska-Kosiorz, 2024 [22]	Poland	279	Cross-sectional (young men)	FTO haplotypes/diplotypes	Measured PA level	Null across PA strata (BMI P = 0.53)
Kim, 2026 [23]	South Korea	16	Single-arm 8-week circuit training	rs9939609	Supervised circuit training + diet	Null: BMI -4.4% regardless of genotype
Chambers, 2026 [24]	UK	56	Cross-sectional pilot	rs9939609 (+MC4R)	IPAQ groups (SLPA/MPA/VPA)	Attenuating: genotype-BMI association abolished in vigorous-PA group

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Table 1. (continued)

Mantaj, 2026 [25]	Poland	115	Prospective cohort (pregnancy)	rs9939609	Self-reported PA	Null interaction; PA main effect on gestational weight gain ($P < 0.001$)

3.3. Quality assessment results

Quality scores ranged from 3 to 5 out of 6 (mean 4.6; Table 2). All studies scored on genotyping quality and outcome assessment. The most frequent weakness was PA measurement: ten of the 18 studies relied on self-reported PA without validated instruments or objective monitoring. Smaller or selected samples (for example, breast-cancer survivors, young male volunteers, and post-bariatric patients) lost points on representativeness, and two small pilots lost points on interaction-testing rigor.

Table 2. Simplified Newcastle-Ottawa quality assessment of the included studies (1 point per item; maximum 6)

Study	Represent-ativeness	Genotyping quality	PA measurement	Confounder adjustment	Outcome assessment	Interaction rigor	Total
Cho, 2021 [8]	1	1	0	1	1	1	5
Isgin-Atici, 2021 [9]	0	1	0	1	1	1	4
Gong, 2021 [10]	1	1	0	1	1	1	5
Nguyen, 2021 [11]	0	1	1	1	1	1	5
Hiraike, 2021 [12]	1	1	0	1	1	1	5
Rana, 2021 [13]	0	1	0	1	1	0	3
Brand, 2022 [14]	1	1	0	1	1	1	5
Wang, 2022 [15]	0	1	1	1	1	1	5
Bila, 2023 [16]	0	1	1	1	1	1	5
Chermon, 2022 [17]	1	1	0	1	1	1	5
Andersen, 2023 [18]	1	1	0	1	1	1	5
Rana, 2023 [19]	0	1	0	1	1	1	4
Wang, 2024 [20]	1	1	0	1	1	1	5
Roumi, 2024 [21]	0	1	1	1	1	1	5
Górczyńska-Kosiorz, 2024 [22]	0	1	1	1	1	1	5

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Table 2. (continued)

Kim, 2026 [23]	0	1	1	1	1	0	4
Chambers, 2026 [24]	0	1	1	0	1	0	3
Mantaj, 2026 [25]	0	1	0	1	1	1	4

3.4. FTO × physical activity interaction in adult observational studies

Ten adult observational studies examined the interaction, and seven supported an attenuating effect of PA. In the Korean KARE cohort (n = 8,840), rs9939609 risk-allele carriers had higher obesity risk (OR 1.42, 95% CI 1.13-1.79), but intense PA of at least three hours per day was associated with an approximately two-fold lower obesity risk among carriers (OR 0.62, 95% CI 0.25-0.84) [8]. In 1,720 Israeli adults, the FTO × PA interaction was highly significant ($P < 0.001$): physically inactive rs9939609 risk-allele carriers had an obesity odds ratio of 2.54 (95% CI 1.91-3.39) for heterozygotes and 3.77 (95% CI 2.47-5.75) for homozygotes compared with active non-carriers [17]. In up to 19,585 Danish adults, high PA attenuated the BMI-increasing effect of the rs9939609 A allele by 47% (β = -0.32 kg/m², SE 0.10, $P = 0.0013$), an effect independent of insulin sensitivity [18]. Longitudinal evidence came from the Taiwan Biobank (n = 20,906), where rs1421085 risk-allele carriers gained more weight and BMI than non-carriers if they did not exercise, but gained less if they exercised regularly ($P = 0.030$ for weight and $P = 0.034$ for BMI change), indicating that genetically susceptible individuals benefited most from exercise [12].

Sedentary behavior, the conceptual opposite of PA, showed the mirror-image pattern. Among 2,216 middle-aged Chinese adults, the combination of sedentary behavior and an FTO risk allele (rs9939609 or rs8050136) increased the odds of obesity (OR 1.63, 95% CI 1.09-2.45) and central obesity (OR 1.49, 95% CI 1.09-2.02) relative to non-sedentary non-carriers, whereas higher PA reduced the SNP effects [10]. A Turkish study (n = 400) reported a significant rs9939609 × PA interaction on adiponectin ($P_{interaction} = 0.027$) and showed that lifestyle factors modified central-obesity risk [9].

Three adult observational studies reported null interactions. In 1,741 Tibetan adults living at high altitude, neither multiplicative nor additive interaction measures (RERI, AP, SI) between FTO rs1121980/rs17817449 and leisure-time or occupational PA reached significance [20]. In 279 young Polish men, FTO diplotype associations with BMI and metabolic-syndrome components were null across PA strata (BMI $P = 0.53$) [22]. In a prospective study of 115 Polish pregnant women with obesity and early gestational diabetes, higher PA predicted appropriate gestational weight gain regardless of rs9939609 genotype ($P < 0.001$ for the PA main effect; null interaction) [25]. Finally, a small UK pilot (n = 56) found that the genotype-BMI association was abolished in the vigorously active group, suggesting that vigorous-intensity PA may be required to offset genetic susceptibility [24].

3.5. Evidence in children and adolescents

Three studies enrolled younger populations, with mixed results. In 1,338 Brazilian children and adolescents, the rs9939609 × PA interaction on waist circumference was null, whereas screen time and sleep duration significantly moderated the FTO association, suggesting that sedentary screen behavior may be the more relevant environmental modifier in youth [14]. Two small exercise trials

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in adolescents with overweight or obesity favored risk-allele carriers: in a 10-week randomized trial (n = 26 completers), carriers in the aerobic-training arm improved glycemia (P = 0.002), total cholesterol (P = 0.023), and body fat (P = 0.041), and in an eight-week diet-plus-PA trial in 96 Iranian male adolescents, rs9930506 AA/AG carriers achieved a greater BMI reduction than controls (-1.21 vs +1.87 kg/m², P < 0.05), with no effect in GG homozygotes [16, 21].

3.6. Evidence from intervention studies in adults

Three adult intervention studies gave largely null or conditional results. In a six-month weight-loss trial in 151 breast-cancer survivors, rs9939609 did not modify the intervention response after Bonferroni correction [11]. In a 12-week supervised aerobic-exercise intervention in 178 Chinese adults with overweight or obesity, a genotype × sex interaction was observed for weight and BMI loss (P = 0.041 and 0.042), with male A-allele carriers losing significantly more (P = 0.008 and 0.010) [15]. In a single-arm eight-week circuit-training pilot in 16 Korean adults with post-bariatric weight regain, BMI fell by 4.4% overall and the response was not attenuated by rs9939609 genotype [23].

3.7. Case-control evidence

Two Pakistani case-control studies reached opposite conclusions. In 578 adults, multifactor-dimensionality-reduction and regression analyses found no significant FTO rs1421085 × PA interaction (only TMEM18 showed an interaction), whereas in 612 adults the rs9939609 × low-PA interaction significantly increased adiposity anthropometrics (P < 0.05), with no interaction for metabolic traits [13, 19].

4. Discussion

4.1. Comparison with evidence published before 2021

The pre-2021 consensus, anchored by the meta-analysis of Kilpeläinen et al., was that PA attenuates the FTO effect on obesity risk by roughly 30% [4]. The recent evidence synthesized here is broadly consistent with that estimate: the largest new observational studies report attenuations of similar or greater magnitude (47% in Danish adults [10]; an approximately two-fold risk reduction in active Korean carriers), and 11 of 18 studies (61%) detected a significant attenuating interaction [8, 18]. The recent literature also extends the interaction to ancestries and life stages that were underrepresented before 2021, including East and South Asian, Middle Eastern, and high-altitude Tibetan populations, as well as children, pregnant women, and post-bariatric patients.

4.2. Potential biological mechanisms

Several mechanisms may explain why PA blunts the FTO effect. FTO risk variants are thought to influence appetite and energy intake through hypothalamic pathways and to reduce adipocyte thermogenesis via the IRX3/IRX5 regulatory circuit; PA increases energy expenditure and improves substrate oxidation, thereby counteracting both limbs [3]. Notably, Andersen et al. complemented their epidemiological interaction with functional data showing FTO expression in human skeletal muscle, suggesting a peripheral, muscle-based component to the interaction [18]. The Turkish finding of an FTO × PA interaction on adiponectin further implicates adipokine signaling as a potential mediator [9].

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4.3. Multiplicative versus additive interaction

Almost all included studies tested interaction on the multiplicative scale (a product term in logistic or linear regression), which is appropriate for etiologic inference; the consistently negative interaction coefficients indicate antagonism between PA and FTO risk alleles. Only the Tibetan study additionally reported additive-scale measures (RERI, AP, and the synergy index), all of which were null [20]. Because public-health impact depends on absolute rather than relative effects, future studies should routinely report both scales: expressing results as the proportion of the genetic effect offset by PA (for example, 30-47%) is more informative for prevention messaging than a P value for a product term alone.

4.4. Heterogeneity and null findings

Seven studies reported null interactions, and their pattern is instructive. Null results clustered in small or selected samples (16 post-bariatric patients, 151 cancer survivors, 279 young men), in a high-altitude population with a distinct genetic and environmental background, and where PA was not the relevant exposure (in Brazilian youth, screen time and sleep, but not PA, moderated the FTO effect) [11, 14, 20, 22, 23]. Heterogeneity in PA measurement (single-item questions versus validated IPAQ versus supervised exercise), in the genotyped variant (rs9939609, rs1421085, rs8050136, rs9930506, and haplotypes in strong linkage disequilibrium), and in outcome definition further complicates comparison and precluded meta-analysis. Multiple testing across many SNPs and behaviors, rarely corrected, also inflates the risk of false-positive interactions in smaller studies.

4.5. Strengths and limitations

Strengths of this review include a pre-specified protocol, a sensitive search strategy validated against known eligible studies, a formal interaction-testing requirement, and coverage of diverse populations and designs. Several limitations must be acknowledged. First, only PubMed was searched, and only English-language reports were included; one directly relevant Chilean study of accelerometer-measured sedentary behavior, which reported that sedentary time increased BMI more strongly in rs9939609 AA homozygotes than in TT carriers, was excluded on language grounds, so the synthesis may slightly understate supportive evidence [26]. Second, the five-year window, while capturing the most current evidence, excludes earlier individual studies. Third, screening and extraction were performed by a single reviewer, and publication bias could not be formally assessed without a meta-analysis. Fourth, the simplified quality scale, although adapted from the Newcastle-Ottawa Scale, has not been validated. Finally, FTO is a single locus: genome-wide polygenic score × lifestyle interaction studies suggest that gene-PA interplay extends far beyond FTO, and FTO-focused results should be interpreted within that broader polygenic context [27].

4.6. Implications for research and public health

For research, priorities include objective PA measurement (accelerometry), standardized reporting of both multiplicative and additive interaction, adequately powered non-European cohorts, and pre-registered analysis plans to control multiple testing. For public health, the message is encouraging and actionable: genetic susceptibility to obesity is not destiny. Physically active risk-allele carriers consistently show attenuated adiposity risk, and several intervention studies suggest that carriers

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may even benefit more from exercise than non-carriers [12, 21]. PA promotion therefore remains universally warranted, regardless of genotype.

5. Conclusions

Among human studies published from 2021 to 2026, the majority (11 of 18) support a significant gene-environment interaction in which higher physical activity attenuates the effect of FTO risk variants on BMI and adiposity, with an attenuation magnitude consistent with pre-2021 meta-analytic estimates. Null findings were concentrated in small, selected, or specialized populations. Heterogeneity in PA measurement, genotyped variants, and study design, together with the predominance of cross-sectional evidence, limits certainty to a low-to-moderate level. Future studies with objective PA measurement, standardized interaction reporting on both multiplicative and additive scales, and larger diverse cohorts are needed to confirm that being physically active can offset genetic susceptibility to obesity.

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