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Evidence for shared genetics between physical activity, sedentary behaviour and adiposity-related traits

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Summary

Observational, cross-sectional and longitudinal studies showed that physical activity and sedentary behaviour are associated with adiposity-related traits, apparently in a bidirectional manner. Physical activity is also suggested to suppress the genetic risk of adiposity. Since phenotypic associations with genetic variants are not subject to reverse causation or confounding, they may be used as tools to shed light on cause and effect in this complex interdependency. We review the evidence for shared genetics of physical activity and adiposity-related traits and for gene-by-physical activity interactions on adiposity-related traits in human studies. We outline limitations, challenges and opportunities in studying and understanding of these relationships. In summary, physical activity and sedentary behaviour are genetically correlated with body mass index and fat percentage but may not be correlated with lean body mass. Mendelian randomisation analyses show that physical activity and sedentary behaviour have bidirectional relationships with adiposity. Several studies suggest that physical activity suppresses genetic risk of adiposity. No studies have yet tested whether adiposity enhances genetic predisposition to sedentariness. The complexity of the comprehensive causal model makes the assessment of the single or combined components challenging. Substantial progress in this field may need long-term intervention studies.

KEYWORDS
adiposity, genetic determinants, physical activity, sedentary behaviour

1 | INTRODUCTION

Cross-sectional studies have revealed that low physical activity and sedentary behaviour are associated with higher adiposity.[1–4] Yet, in contrast to the prevailing expectations, observational longitudinal studies suggest that higher adiposity at baseline is associated with lower physical activity and longer time spent sedentary at follow-up, indicating that greater adiposity may lead to lower levels of physical activity.[5–10] Some, but fewer, longitudinal studies have suggested the opposite—expected—direction in the relationship, namely, a negative correlation between physical activity and weight gain after several years of follow-up.[11,12] Inference of causal relationships between physical activity/sedentary behaviour and adiposity is limited by the nature of observational longitudinal studies with repeated assessments at single time points at fairly long intervals, before, during and after which the changes in the variables cannot be monitored. Furthermore, in such studies, body weight and physical activity changes preceding the baseline assessments may be followed by changes in the opposite direction after baseline, which

Abbreviations: BMI, Body mass index; GRS, Genetic risk score; GWAS, Genome-wide association study; MVPA, Moderate-to-vigorous physical activity.

may create spurious associations between baseline values and subsequent weight changes.

Genetic variants provide a tool for shedding light on cause and effect because phenotypic associations with the inherited genetic susceptibilities are not subject to reverse causation or confounding.[13,14] This provides opportunities for disentangling the possible causal, bidirectional relationships between physical activity and adiposity traits. However, an additional layer of complexity to understanding this relationship is the converging evidence that adiposity-predisposing genetic variants interact with physical activity, suggesting that physical activity of individuals genetically predisposed to obesity may reduce the expression of the predisposition. This implies that the relationship between physical activity and adiposity traits may differ between individuals, depending on genetic factors. The evidence of pleiotropic genetic effects between physical activity/sedentary behaviour and obesity[15] and the importance of gene–environment interactions in human obesity have been previously reviewed by others.[16,17]

In the present review, we critically appraise the current evidence of genetic determinants of physical activity traits (including sedentary behaviour) and their relation to adiposity-related traits in human studies, while addressing animal studies only ad hoc. We provide a brief overview of (1) the genetic determinants of physical activity, sedentary behaviour and adiposity-related traits; (2) the evidence of shared genetics between physical activity and adiposity-related traits, including the use of Mendelian randomisation to disentangle the causal bidirectionality; (3) gene-by-physical activity interactions on adiposity-related traits; and finally discuss (4) limitations, assumptions and complexities of the reviewed evidence, as well as future research needs and implementation perspectives. Figure 1 outlines the conceptual framework of the review.

2 | GENETIC DETERMINANTS OF PHYSICAL ACTIVITY, SEDENTARY BEHAVIOUR AND ADIPOSITY-RELATED TRAITS

The definition, epidemiological assessment methods and heritability estimates of physical activity, sedentary behaviour and body mass index (BMI) are outlined in the supporting information Table S1. In summary, estimates of genetic contributions vary by study design for all three types of phenotypes: physical activity (twin and family-based studies: 27%–84%[18]; SNP-based estimates in population-based studies: 5%–8% for self-reported physical activity[19,20] and 11%–22% for accelerometer-assessed physical activity[19,20]), sedentary behaviour (twin and family-based studies: 9%–48%[18]) and adiposity-related traits (twin and family-based studies: 40%–80% in adults and children[21–24]; SNP-based estimates in population-based studies: 30%–40% in adults and 30% in children[25,26]). However, the heritability estimates are sufficiently high to warrant gene discovery studies.

As reviewed by others,[27,28] genome-wide association studies (GWAS) have been effective in the identification of more than 1,000 genetic loci associated with adiposity-related outcomes, such as adult BMI,[29] body fat percentage,[30] and obesity as a binary trait,[31] and child BMI-standard deviation score[32] and obesity.[33] The vast majority of these loci were identified for adult BMI (N = 941 loci, explaining 6% of adult BMI variance[29]). Gene set enrichment analysis suggests that processes in the brain, including hypothalamic control of energy intake and expenditure but also other processes, regulate BMI.[29,34] Pathway analysis identified gene sets associated with BMI that were enriched for potentially relevant mouse behavioural phenotypes, such as physical activity and impaired motor coordination.[34] Overall, the effect sizes of common variants implicated in obesity are modest. The homozygous carriers of the strongest known common risk variant for obesity in the first intron of the *fat mass and obesity associated* (*FTO*) locus weigh ~3 kg more and have a 1.67-fold greater risk of obesity than noncarriers.[35] Recent studies have shown that accounting for behaviours associated with adiposity, such as physical activity or smoking, in the statistical model may increase power for gene discovery,[36,37] by taking gene–behaviour interaction effect into account (discussed later) and explaining some of the nongenetic variance in the adiposity traits.

The progress in the identification of genetic variants associated with physical activity has been slower than for adiposity-related traits.[15,38] Two GWAS identified altogether 15 genetic loci associated with physical activity-related traits and sedentary behaviour using self-reported and accelerometer-assessed information in the UK Biobank.[19,20] Genes near the identified loci for accelerometer-assessed physical activity showed expression enrichment in the central nervous system,[19,20] as well as in adrenal, pancreatic and skeletal muscle tissue.[20] Conserved genomic regions across mammals are enriched for physical activity and sedentary behaviour traits, suggesting an evolutionary role for physical in/activity.[20] The GWAS included single SNP associations with self-reported moderate-to-vigorous physical activity (MVPA) (rs429358 variant in *APOE*) and self-reported engagement in strenuous sports or other exercise (rs62253088 variant in *CADM2*). Both SNPs remained genome-wide significant after additional adjustment for BMI.[19] While the association between *APOE* and MVPA may be due to selection bias,[19] notably previous studies reported associations of variation in *APOE* with greater increase in aerobic capacity after 6 months of supervised exercise training,[39] and associations of variation in *CADM2* with several personality, cognitive and behavioural traits, such as risk-taking behaviour,[34,40,41] suggesting a role in the reward system of the brain.

3 | SHARED GENETICS BETWEEN PHYSICAL ACTIVITY AND ADIPOSITY-RELATED TRAITS

3.1 | Genetic correlations between physical activity and adiposity-related traits

Genetic correlation provides an estimate of genetic effects that are shared between two traits and may arise due to horizontal pleiotropy, where the same gene set affects different phenotypes independently,

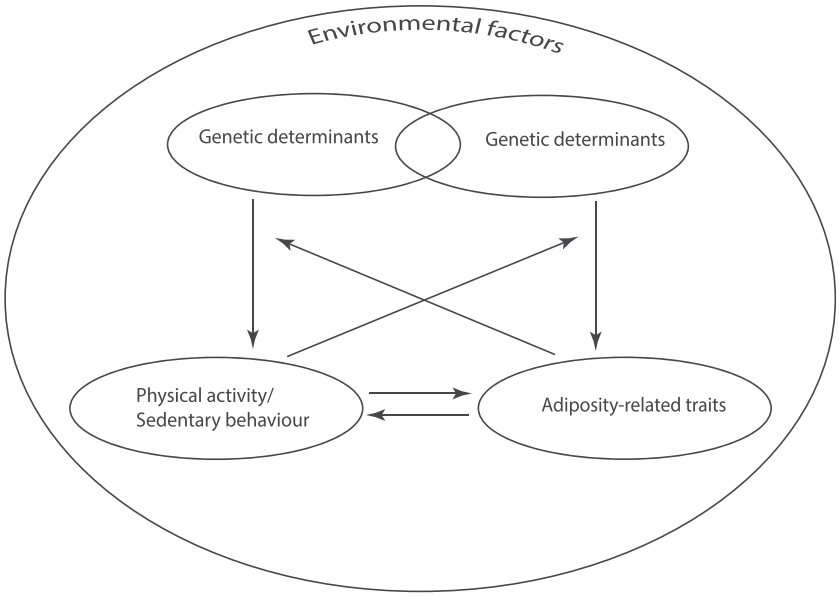

FIGURE 1 Illustrative summary of the reviewed evidence pointing towards overlapping genetic determinants between physical activity/sedentary behaviour and adiposity-related traits, a bidirectional causal relation between physical activity/sedentary behaviour and adiposity-related, as well as gene-physical activity interactions modifying adiposity-related traits. Evidence on gene-adiposity modification of the physical activity/sedentary behaviour remains to be established

or vertical pleiotropy, where the gene set affects one mediating phenotype, which then affects another phenotype, as illustrated in Figure 2. Several studies using twin and family research designs,[42–48] and recently also studies in unrelated individuals utilising LD Hub[19,20] (supporting information Table S2), assessed genetic correlations between physical activity and adiposity-related traits. Three of these studies used accelerometer-assessed physical activity,[19,20,49] whereas seven studies used self-reported measures.[42–48]

Simonen et al[42] surveyed longitudinal exercise participation in twins from the age 12 until adulthood. They found that 56% of covariation between physical activity and body fat percentage could be explained by genetic factors as negative pleiotropy, where gene variants associated with higher levels of exercise are related to lower body fat percentage (supporting information Table S2). A family study reported significant inverse genetic correlations between leisure-time physical activity and sports activities and body fat percentage (ρ_G = −0.46 [SE 0.20] and ρ_G = −0.66 [SE 0.32], respectively).[44] Similarly, a twin study found a negative genetic correlation between sport index and body fat percentage (ρ_G = −0.50 [SE 0.12]).[45] Both studies found weaker genetic correlations with general measures of adiposity, such as BMI and waist circumference, than with body fat percentage (supporting information Table S2). Another twin study showed significant moderate inverse genetic correlations of physical activity with BMI and waist circumference in women (ρ_G = −0.22 [SE 0.04], ρ_G = −0.14 [SE 0.04]), but not in men (ρ_G = −0.08 [SE 0.06], ρ_G = −0.07 [SE 0.03])[46] (supporting information Table S2). Two later

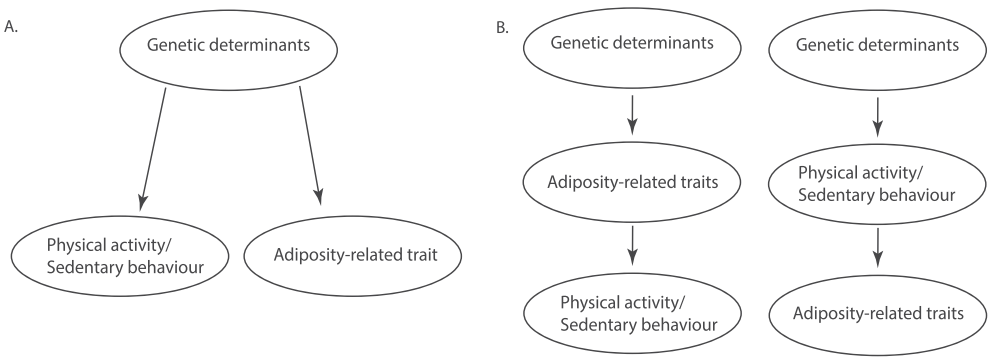

FIGURE 2 Types of pleiotropy. Genetic correlations between physical activity/sedentary behaviour and adiposity-related traits may arise due to horizontal pleiotropy or vertical pleiotropy. (A) Horizontal pleiotropy (also called biological pleiotropy) arises due to genetic determinants that influence two or more traits, that is, physical activity/or sedentary behaviour and adiposity-related traits, at the same time. For example, the propensity to increase body fat and the preference for an inactive lifestyle, or a pathway common to both traits, such as mechanisms related to the central nervous system. (B) Vertical pleiotropy (also called mediated pleiotropy) occurs when one phenotype is causally influencing a second phenotype, that is, genetic determinants known to be associated with adiposity-related traits are also associated with physical activity/or sedentary behaviour. However, adiposity itself may be a risk factor for decreased levels of physical activity/or increased sedentary behaviour. Importantly, in cases of vertical pleiotropy, the genetic determinants will be associated with both adiposity and physical activity/or sedentary behaviour, if tested separately. Vertical pleiotropy could run in the opposite sequence as well, as illustrated

studies, a family and a twin study, using self-reported measures of physical activity in adults, did not significantly replicate these findings[47,48] (supporting information Table S2). Butte et al[49] explored genetic correlations in children by studying 1,030 children with a mean age of 11 years who were from families with three or more children. Physical activity was objectively measured over a 3-day period using accelerometers. The siblings showed significant genetic correlations of light physical activity with BMI (ρ_G = −0.38 [SE 0.12]), fat mass (ρ_G = −0.32 [SE 0.13]) and waist circumference (ρ_G = −0.32 [SE 0.26]) but not with fat free mass (ρ_G = −0.14 [SE 0.13]) (supporting information Table S2).

Recently, the use of LD score regression of GWAS summary statistics available on the LD Hub web resource[50] in combination with the UK Biobank data[19,20] allowed estimation of molecular genetic correlations of physical activity-related traits with hundreds of other traits and diseases. Highly significant negative genetic correlations between physical activity and adiposity-related traits were observed, and the strongest was with body fat percentage (supporting information Table S2).[19,20] The correlations for objectively measured physical activity were greater than for self-reported measures.[19]

Overall, the findings on genetic correlations generated by GWAS summary-level results complement and are consistent with the previous findings from twin and family study designs, suggesting shared genetic influences, that may arise due to horizontal or vertical pleiotropy, on physical activity and adiposity-related traits. Physical activity exhibits greater negative genetic correlations with body fat percentage and fat mass than with BMI,[19,20,42,44,46] but not with lean body mass.[49]

3.2 | Genetic correlations between sedentary behaviour and adiposity-related traits

At least three studies have examined genetic correlations of sedentary behaviour with adiposity traits. The results indicate that sedentary behaviour and adiposity share alleles in the opposite direction as compared to physical activity, consistent with the mutual inverse relationship of these phenotypes (supporting information Table S2). Nelson et al[43] identified a significant genetic correlation between sedentary behaviour (assessed as time spent watching television) and BMI *z*-score (ρ_G = 0.10 [SE not given]) in a large (*N* = 4,368) sample of young siblings with mean age of 17 years. A study by Butte et al[49] on children found significant genetic correlations of accelerometer-assessed sedentary time with BMI (ρ_G = 0.32 [SE 0.12]), fat mass (ρ_G = 0.35 [SE 0.12]) and waist circumference (ρ_G = 0.26 [SE 0.12]) but not with fat free mass ([ρ_G = 0.15] SE 0.12). A study in the UK Biobank using LD score regression[20] showed a similar pattern of genetic correlations of accelerometer-assessed time spent sitting/standing with adiposity-related traits (supporting information Table S2). Sedentary behaviour and lean body mass were not genetically correlated.[49] Similar to physical activity, the studies that measured sedentary behaviour objectively found the highest genetic correlations.[20,49]

3.3 | Candidate genes showing associations with both physical activity and adiposity-related traits

Among the GWAS-identified genetic variants for physical activity, the *APOE*-rs429358 variant associated with higher self-reported MVPA was also associated with lower BMI in the UK Biobank.[19] However, the observed association between *APOE* and MVPA may be due to selection bias. The *CADM2*-rs62253088 variant also showed an association with BMI,[34] but for unexplained reasons the physical activity-increasing allele was associated with higher BMI in the UK Biobank.[19] Prior to the identification of genetic variants for physical activity in GWAS, several studies tested for associations of GWAS-identified genetic variants for adiposity-related traits with physical activity. In a study of 492 men and women, *MC4R*-rs17782323 and *TMEM18*-rs6548238 were associated with physical activity volume. Other studies suggest that genetic variation in *MC4R* and *LEPR* is associated with physical activity phenotypes.[51–53] Taken together, these studies suggest that genetic risk for obesity co-occurs with genetic propensity for lower physical activity.

3.4 | Mendelian randomisation studies of physical activity/sedentary behaviour and adiposity-related traits

Mendelian randomisation helps to assess whether there is a causal relation between physical activity and adiposity in either direction, provided that a series of assumptions are met (see supporting information Figure S1).[14,54,55]

Richmond et al[56] performed Mendelian randomisation analysis in 4,296 eleven-year old children to assess the possible causal effect of BMI on objectively assessed physical activity. They used a genetic risk score (GRS) calculated from 32 genetic variants associated with BMI in adults[57] and the *FTO*-rs1558902 variant[57] as instrumental variables. The GRS instrument indicated that higher BMI is associated with less total physical activity and time spent in MVPA and longer time spent sedentary. With the *FTO*-rs1558902 as instrument, the associations showed the same direction of effect and were statistically significant for time spent sedentary and nonsignificant for total physical activity and MVPA. Similar results were obtained when fat mass index was used as the measure of adiposity.

We applied Mendelian randomisation to assess the causal association of BMI with objectively measured physical activity in three cohorts of 679 Finnish and Danish children aged 3–8 years.[58] We used a GRS comprised of 15 genetic variants specifically associated with childhood BMI as the instrument.[59] Our study indicated that higher genetically predicted BMI is associated with increased sedentary time,[58] However, we did not find evidence of an effect of genetically predicted BMI on total physical activity or MVPA, which could be due to the younger age and smaller sample sizes that were available compared to the study by Richmond et al. We performed a meta-analysis of the results from the above-mentioned studies as part of this current review. The meta-analysis suggests that genetically

instrumented BMI is associated with increased sedentary time (β = 0.23, 95% CI 0.06; 0.40, p_{meta} = 0.008) and reduced MVPA (β = −0.17, 95% CI −0.34; 0.00, p_{meta} = 0.049), but there was no significant association with total physical activity (β = −0.16, 95% CI −0.33; 0.02, p_{meta} = 0.079) (Figure 3).

Corresponding studies of the reciprocal results of physical activity or sedentary behaviour on lower or higher BMI in children have not been possible until recently but have now become feasible through the discovery of GWAS-identified loci associated with physical activity. Doherty et al[20] found an inverse causal relationship between overall physical activity and body fat percentage (beta SD [%] per SD higher overall physical activity: −0.14 [SE 0.012], $p = 2.6 \times 10^{-29}$) and BMI (beta SD [kg/m^2] per SD higher overall activity: −0.14 [SE 0.015], $p = 8.7 \times 10^{-20}$). Thus, there appears to be a bidirectional relationship between physical inactivity and adiposity.

4 | GENE BY PHYSICAL ACTIVITY INTERACTIONS INFLUENCING ADIPOSITY-RELATED TRAITS

Gene–environment interactions could explain part of the variation in BMI, and elucidation of such interactions may contribute to deciphering the biology underlying the development of obesity. Several twin and family studies in adults and children, and a study based on genome-wide chip data in the Framingham Heart Study, estimated that higher levels of physical activity reduce the heritability of BMI and related traits.[46,48,60–63]

The obesity risk locus most frequently studied for interaction with physical activity is the *FTO* locus. Soon after the discovery of *FTO* in GWAS for BMI, published in 2007,[35,64] Andreasen et al[65] reported that the association between *FTO* and BMI may be attenuated by

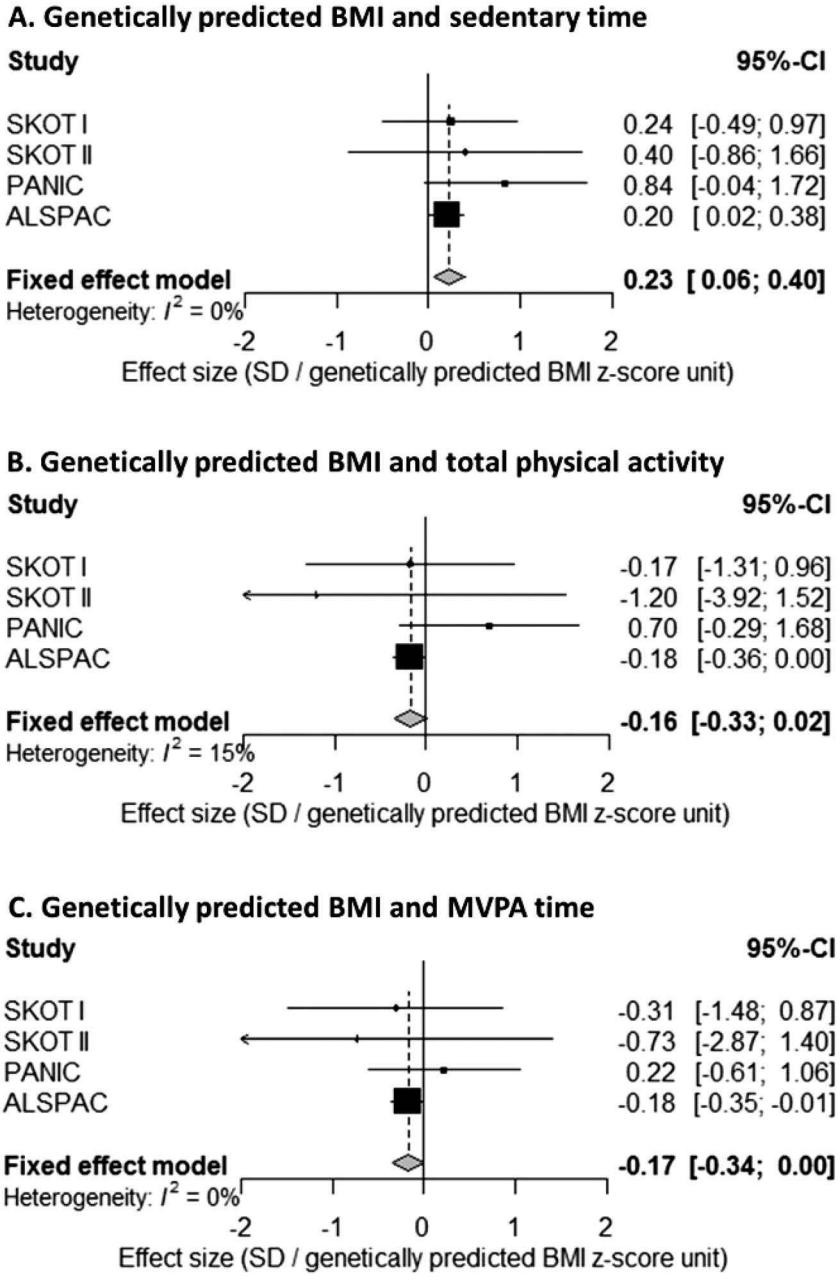

FIGURE 3 Fixed effects meta-analysis of the outcomes of Mendelian randomisation analysis between genetically instrumented BMI and sedentary time (A, p_{meta} = 0.008), total physical activity (B, p_{meta} = 0.079), and time spent in MVPA (C. p_{meta} = 0.049) in SKOT I (n = 208), SKOT II (n = 79), PANIC (n = 400) and ALSPAC (n = 4,296) cohorts. No heterogeneity was observed between the four studies included in this meta-analysis (I^2 < 15%). Abbreviations: MVPA, moderate-to-vigorous physical activity; SKOT, a prospective cohort study of diet and well-being in Young Danish children; PANIC, the physical activity and nutrition in children cohort study; ALSPAC, Avon longitudinal study of parents and children

physical activity.[66,67] These initial results were later confirmed in a meta-analysis of 45 studies totalling 218,166 adults, finding that the association of the *FTO*-rs9939609 risk allele with the odds of obesity was attenuated by nearly 30% in adults who were physically active.[68] While large studies using accelerometer-assessed physical activity are yet missing to confirm these results, the meta-analysis included three studies (N_{range} = 768–810) that measured physical activity objectively, either by a heart rate sensor or an accelerometer. Of these three studies, two studies (MRC Ely and HAPI) showed a direction of interaction effect consistent with an attenuation of the association of *FTO*-rs9939609 on BMI in physically active individuals, whereas one study (RISC) suggested the opposite direction of effect.[68] Furthermore, a relatively small study of 1,280 European adults reported that moderate-equivalent physical activity, objectively assessed by accelerometers, attenuated the effect of *FTO*-rs9939609 on BMI.[69]

Applying a GRS based on multiple BMI associated genetic variants may have a greater statistical power to detect interaction with physical activity than an analysis of a single SNP. A 40% lower effect size of a 12-SNP GRS on BMI was found in 13,874 individuals who were physically active compared to 6,004 individuals who were physically inactive.[70] A meta-analysis of 111,421 individuals, applying the same 12-SNP BMI GRS, replicated the finding.[71] When the 12 SNPs included in the GRS were tested separately, only the *FTO* locus showed a statistically significant interaction.[71] Similarly, a longitudinal multiethnic study of 17,423 participants investigating the *FTO* locus and 13 other obesity risk loci found that physical activity significantly attenuated the effect of *FTO*-rs1421085 on adiposity[72] but not that of the other 13 SNPs. In this study, no interaction was found when *FTO* was combined with the other 13 SNPs into a GRS.[72]

In 2017, a meta-analysis of BMI GWAS by physical activity interactions, including 200,452 individuals from 60 studies, identified a significant interaction of the *FTO*-rs9941349 variant on BMI.[36] This study thus replicated the finding of the previous meta-analysis that was focused on the *FTO* locus only,[68] confirming that the association between *FTO* and physical activity on BMI is around 30% attenuated in individuals who are physically active.[36] No other loci interacting with physical activity on BMI, waist circumference adjusted for BMI or waist-to-hip ratio adjusted for BMI were identified.[36]

4.1 | Gene by physical activity interactions in the UK Biobank

UK Biobank[73] and other large cohorts offer a unique opportunity to examine gene–environment interactions in large and relatively homogenous samples, in which several lifestyle and environmental variables are assessed by standardised methods, providing the opportunity to investigate several such factors simultaneously. Recently, a study in 119,132 participants of the UK Biobank replicated the interaction between *FTO* and physical activity on BMI.[74] The study examined additional simultaneously collected lifestyle measures and concluded that the interaction between *FTO* and physical activity does not seem to be confounded by other lifestyle factors, such as dietary intake, alcohol consumption, sleep duration, age, socioeconomic status, current smoking or TV watching.[74] In a study of up to 120,000 participants of the UK Biobank, a significant interaction between a 69-SNP BMI GRS and physical activity on BMI was found.[75] In this study, physical activity was one of the 12 tested obesogenic environmental and lifestyle factors, and it was concluded that several components and not just one isolated factor of the obesogenic environment accentuate the genetic risk of obesity.[75] A later study in the UK Biobank applied a hypothesis-free approach to test interactions between a 94-SNP BMI GRS and 131 self-reported lifestyle variables, also including physical activity.[76] Overall, 15 lifestyle factors showed significant interactions with the 94-SNP GRS on BMI. Five of these were measures of physical activity, namely, usual walking pace, frequency of stair climbing, frequency of moderate physical activity, frequency of vigorous physical activity and frequency of walks. The interactions between the GRS and physical activity were more pronounced for frequencies of physical activity behaviour rather than durations assessed in minutes/day.[76]

4.2 | Gene by sedentary behaviour interactions

Sedentary behaviour and its ability to modify the effect of adiposity-associated genetic variants on obesity have been less studied. Whereas some reports did not identify an interaction between *FTO* risk variants and self-reported time spent sitting[77] or TV watching,[74] others demonstrated significant interactions between prolonged TV watching and a 32-SNP BMI GRS on BMI.[78] The interaction of the 32-SNP BMI GRS with TV watching was independent of the interaction with physical activity.[78] In nearly 120,000 participants of the UK Biobank, TV viewing amplified the association of a 69-SNP BMI GRS with BMI.[75] Additionally, TV watching was one of the 15 significant lifestyle interactions on BMI in the UK Biobank study that utilised a 94-SNP BMI GRS and tested 131 self-reported lifestyle variables.[76] These studies used self-reported measures of sedentary behaviour. However, a recent study in 9,645 US Hispanics/Latinos reported significant interactions between accelerometer-assessed sedentary behaviour and a 97-SNP BMI GRS on measures of adiposity, but not on fat free mass.[79]

4.3 | Interpretation of the gene by physical activity interaction studies

In summary, these studies suggest that engagement in physical activity by individuals genetically predisposed to obesity may reduce the expression of the predisposition in these individuals. However, the results of a study that explored the contribution of genotype–covariate interaction effects at common genetic loci across different environments, including exercise, concluded that exercise contributes only little to the variation in BMI at the population level.[80] The interaction between the common *FTO* risk variant and physical activity on BMI does not seem to be confounded by other lifestyle factors,[74] but

there could be other unobserved factors that contribute to the observed interaction effect.

Reddon et al summarised the evidence supporting a hypothesis that epigenetic changes (including DNA methylation, histone modification and noncoding RNA),[17] may underlie the interactions between environmental exposures and genetic variation.[17] Specifically, exercise seems to alter DNA methylation of genes in skeletal muscle and adipose tissue, including numerous candidate genes for obesity.[81] It may also be that BMI variants related to central nervous system functions play a role in the observed interactions between BMI GRS and physical activity on BMI. Thus, one potential mechanism that could mediate the interaction between the *FTO* locus and physical activity is changes in DNA methylation. Changes in DNA methylation may also mediate the association between *FTO* and BMI. This is plausible because the *FTO* obesity risk variants are located in the first intron that appears to serve as an enhancer[82] and because *FTO* variants are associated with DNA methylation levels.[83] While *FTO* remains the only single locus identified to interact with physical activity, gene–environment interactions on adiposity-related traits are likely to be more general for adiposity-associated loci since interactions between BMI GRS and physical activity were still significant after excluding *FTO* from a 94-SNP BMI GRS.[76]

Importantly, more work is needed to establish whether gene–environment interactions are causal and their functional basis. Researchers working in this field may ideally undertake additional analysis to determine validity of gene–environment interaction results as demonstrated by Tyrrell et al.[75,84] Such analysis could include negative control exposures that are unlikely to causally interact with obesity genes to address latent confounding, as well as meta-heuristic sampling and dummy environment exposures variables to test whether gene–environment interactions may be driven by features of the distribution of the adiposity-related trait under investigation per se.[75,84]

5 | DISCUSSION

5.1 | Limitations in measures

Physical activity and sedentary time are often assessed by questionnaires that are generally low cost and easy to administer (supporting information Table S1). Subjective recall-based methods have generally low reliability and validity. The development of objective measurement methods (e.g., accelerometers, heart rate monitors or activity monitors combining both), which quantify the duration, intensity and frequency of physical activity, may overcome some of the limitations of questionnaires and should be included in GWAS of physical activity-related traits.

Similarly, the majority of large genetic epidemiology studies use BMI as a proxy for overall adiposity in both children and adults. However, BMI does not distinguish between fat and fat free mass, which has proven to be important in genetic studies of adiposity-related traits. Ideally, gene discovery efforts should focus on more refined adiposity measures, such as accurate direct measures of the amount and also bodily distribution of adipose tissue (e.g., dual energy X-ray absorptiometry and other imaging techniques) to identify novel loci associated with adiposity.[27]

Even though major progress has been made, we are still far from explaining the high heritability estimates for many complex traits, including adiposity-related traits and physical activity/sedentary behaviour. The thus far largest GWAS of BMI included 700,000 individuals and identified 941 independent SNPs that were associated with BMI at < genome-wide significance.[29] Taken together, the genome-wide significant SNPs explained around 6% of variance of BMI, illustrating that more refined molecular measurements and methods are needed to get closer to explaining the missing heritability of BMI as estimated from family, twin and SNP heritability studies.

5.2 | Limitations of study design

In general, genetic studies are often limited by modest sample sizes, resulting in low power and false negative findings. Furthermore, compared to studies with large sample sizes, multiple smaller studies may result in an excess of false positive findings. Additional genetic variants associated with physical activity, and adiposity-associated genetic variants that interact with physical activity, may be identified once the sample sizes increase. The large heterogeneity in the genetic correlation estimates between physical activity and adiposity traits among the results from the summarised twin and family studies that may be a result from small sample sizes. Meta-analyses conducted so far, taking advantage of the increase in power by including more individuals, focused, however, mostly on one lifestyle measure at a time and required a data harmonisation that often simplified the measures to more crude ones. Thus, physical activity is often dichotomized to reduce between-study heterogeneity. The UK Biobank includes several hundred thousand individuals and can overcome some of these limitations. Nevertheless, there are limitations to the UK Biobank data including selection bias[85] and collider bias.[86] Therefore, the GWAS results for physical activity-related traits published thus far should not be regarded as a definitive set of association results.

5.3 | Mendelian randomisation assumptions

While Mendelian randomisation has great potential to shed light on the causal relationship between physical activity and adiposity, there are possible limitations that need to be carefully accounted for, including population stratification, canalisation, power deficiency, pleiotropy and linkage disequilibrium.[14] Importantly, the core assumption that the instrumental variable (genotype) is independent of factors that potentially confound the observational associations need to be addressed by examining associations between confounding factors and genotypes. The existence of horizontal pleiotropy, where a genetic variant or score has an effect on an outcome (e.g., physical activity) independent of its effect on the exposure (adiposity), would

violate the underlying Mendelian randomisation assumption of what constitutes a valid instrumental variable. Providing evidence against pleiotropy is in general difficult since genetic variants may influence several and possibly unknown intermediate phenotypes. Other limitations of the approach of Mendelian randomisation in investigating the causal association between physical activity and adiposity-related traits may be the weakness of the instrument (e.g., GRS), explaining a relatively small proportion of variance in the exposure[87] and thereby requiring correspondingly larger sample sizes to get reliable results.

5.4 | Complexities of the causal models

The putative relationship between physical activity/sedentary behaviour and adiposity-related traits, illustrated in Figure 1, implies the co-existence of causal bidirectionality between the traits. It also shows possible correlations or concordances of these influences in excess of that expected from the causal bidirectionality between the traits and, in addition, effect modification by one of the phenotypes on the genetic influences on the other phenotype. Taken together, these relationships produce a very complex model. The bidirectionality of the causal inverse relationship between physical activity and adiposity is particularly disadvantageous by creating a basis for a vicious cycle that makes development of adiposity self-promoting by even very slight energetic imbalances.[88] Furthermore, the model misses another, yet unaddressed, dimension of complexity, namely, the possible other environmental influences such as diet, smoking and sleep, which may have causal associations with both physical activity and adiposity traits and modify the bidirectional relationship between the traits. Nevertheless, applying multivariate Mendelian Randomisation approaches may help to resolve confounding.[89]

Clearly, a valid demonstration of the existence and quantification of any single causal relation, or its modification by other factors, requires the other factors to be controlled, either by keeping them fixed or adjusted for, which may not be achievable in human observational studies. Assuming that these other causal relationships do not exist or do not play a role when investigating one of them implies a serious risk of biased or even spurious results. These problems apply to the assessment of both the genetic influences on either of the phenotypes and the use of these influences in Mendelian randomisation study designs to elucidate the direct bidirectional mutual influences between the phenotypes.

An important consequence of the demonstrated bidirectionality is that the interpretation of the cross-sectional investigations of the possible modifying influence of physical activity on the genetic influences on adiposity-related traits may be problematic. If it is true that increased adiposity leads to reduced physical activity, then a true modification of the genetic influence on BMI by physical activity would imply a positive feedback loop. This may be indistinguishable from a direct effect of physical activity on BMI, independent of the genetic influence on BMI. In general, valid assessment of such modifying effects rests on the assumption of independence of the modifier and the factor, the effect of which is modified. This is clearly questionable in the present context. If there are no modifying effects, then the present scenario may lead to an invalid conclusion that low physical activity enhances the genetic influence on adiposity.

5.5 | Future research needs

The identification of physical activity-associated GWAS loci in the UK Biobank[19,20] has shown the possibilities provided by "mega-biobanks", large-scale publicly available human genetic databases. Mega-biobanks that include extensive phenotypic and health-related information, coupled with electronic health record linkage and genome-wide genetic data on hundreds of thousands of individuals, may transform the understanding of complex trait genetics.[90] Mega-biobanks that employ a prospective design and follow participants for multiple years (i.e. through recall or health records) may enable the discovery of novel gene–environment interactions for obesity in the near future. Future studies should also address possible interaction effects between genetic variants and polygenic risk scores associated with physical activity/sedentary behaviours and adiposity traits on physical activity-related phenotypes. This could shed light on the question whether the beneficial effects of "high physical activity" genotypes are attenuated in individuals with obesity.

Prospective observational studies, clinical trials and lifestyle intervention studies may pave the way to better characterise any causal mechanisms underlying gene–environment interactions. Detection of a possible true modifying effect of physical activity on the genetic influence on adiposity would require a longitudinal study design. Ideally, such a study should compare individuals with a similar degree of adiposity, but different genetic predispositions and different levels of physical activity, while otherwise being comparable, to see if development of adiposity over time with maintained physical activity level eventually differs between these groups. However, the selection of participants with a similar degree of adiposity but different known genetic predisposition could lead to the groups being differentially enriched for unknown obesity risk variants, which could mask a potential interaction effect. Therefore, a large randomised trial will be needed to complement the results from nonrandomised study designs.

The obvious complexity of the causal models (Figure 1) requires appropriate statistical models to achieve valid estimates of the individual paths in the models. The development of new statistical methods to capture gene–environment interactions in particular promises further progress in the field.[91] Manning et al proposed a method to jointly meta-analyse beta coefficients for a SNP's main effect and its interaction with an environmental variable.[92] Applying this joint meta-analysis method in appropriately sized consortia with relevant environmental variables is expected to lead to both identification of novel associations with complex traits and more refined characterisation of already existing signals.[92] Selection of "environmental extremes" where subcohorts are selected from the tails of the environmental exposure distribution may leverage the discovery of interaction effects.[93] Moreover, applying a framework for analysing genome-wide

gene–covariate interaction effects within a population sample showed promising results in providing additional evidence for gene–age and gene–environment interaction effects that may explain some of the phenotypic variance of BMI.[80]

5.6 | Implementation perspectives

The main goal in identifying genetic markers is to illuminate the biological mechanisms that underlie physical activity behaviour, which could ultimately open avenues for improved preventive and therapeutic strategies.[94,95] With further progress in identifying genes and genetic mechanisms contributing to differences in physical activity, future findings may contribute to the understanding and prevention of obesity and the many conditions and diseases shown to be associated with physical inactivity.[96] Such findings may aid reducing the substantial economic burden on healthcare systems worldwide caused by physical inactivity, estimated to be 67.5 billion US dollar in 2013.[97]

The findings in children that genetic predisposition to higher BMI may lead to increased sedentary time and decreased MVPA and vice versa, compatible with a bidirectional causality,[20] have important implications. In particular, it may be worthwhile to pay more attention to the sedentary time-increasing and MVPA-decreasing effect of adiposity in children and the role of physical activity for the reduction of adiposity.

While the whole population benefits from a physically active lifestyle, individuals who are genetically predisposed to obesity may gain an even greater benefit. If true, this is an important message to the public, considering that "blaming ones genes" on the development of overweight and obesity may not hold as one of the many excuses for not adapting to a physically active lifestyle. However, we are still lacking adequate intervention studies to confirm the hypothesis that lifestyle interventions specifically targeted at individuals at genetic risk of obesity may increase the success rate of weight loss programs. In the future, where personalised genomic profiling may become a routine, individuals at the highest risk of obesity could be encouraged to adapt an active lifestyle. However, the question remains whether physical activity may possibly be even more beneficial in individuals with obesity for other reasons than a genetic predisposition. Nevertheless, such information should be provided with proper counselling; a large meta-analysis showed that simply communicating the results of DNA-based risk estimates does not motivate risk-reducing behaviour.[98]

6 | CONCLUSIONS

In this review and as summarised in Figure 1, we described past and ongoing efforts to disentangle genetic mechanisms underlying physical activity and sedentary behaviour in relation to their complex relationship with adiposity-related traits. In conclusion, there is evidence from genetic correlation studies suggesting that physical activity/sedentary behaviour may, in part, share genetic influences with adiposity-related traits. Mendelian randomisation analyses suggest that there is a bidirectional causal relationship between physical activity/sedentary behaviour and adiposity-related traits, creating potential for a vicious cycle. Furthermore, there is growing evidence that a genetically determined risk of adiposity is amenable to physical activity although this still needs support from intervention studies. It still remains to be established if this interaction effect exists the other way too, namely, if genetically determined levels of physical activity are modified by adiposity. Taken together, there is evidence for all the reviewed relationships between physical activity/sedentary behaviour and adiposity-related traits, highlighting a very complex model but thereby also requires cautious interpretation of all the single components. Future prospective studies, including intervention studies, with large sample sizes and objective measures of physical activity-related traits are warranted to fully disentangle these relationships between physical activity/sedentary behaviour and adiposity-related traits.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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