

RESEARCH ARTICLE

Sedentary behavior, physical activity, sleep duration and obesity risk: Mendelian randomization study

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Abstract

Background

Observational studies have suggested associations between sedentary behaviors (SB), physical activity (PA), sleep duration (SD), and obesity, but the causal relationships remain unclear.

Methods

We used Mendelian randomization (MR) with genetic variation as instrumental variables (IVs) to assess the causality between SB/PA/SD and obesity. Genetic variants associated with SB/PA/SD were obtained from Genome-wide association study (GWAS), and obesity data came from FinnGen. The primary MR analysis used the instrumental variable weighted (IVW) method, with sensitivity tests including Cochran Q, MR-Egger intercepts, and MR-Radial. Expression Quantitative Trait Loci (eQTL) analysis was applied to identify significant genetic associations and biological pathways in obesity-related tissues.

Results

The MR analysis revealed causal relationships between four SB-related lifestyle patterns and obesity. Specifically, increased genetic liability to television watching (IVW MR Odds ratio [OR] = 1.55, [95% CI]:[1.27, 1.90], $p = 1.67 \times 10^{-5}$), computer use ([OR] = 1.52, [95% CI]:[1.08, 2.13], $p = 1.61 \times 10^{-2}$), leisure screen time (LST) ([OR] = 1.62, [95% CI] = [1.43, 1.84], $p = 6.49 \times 10^{-14}$), and driving (MR [OR] = 2.79, [95% CI]:[1.25, 6.21], $p = 1.23 \times 10^{-2}$) was found to increase the risk of obesity. Our findings indicate that no causal relationships were observed between SB at work, sedentary commuting, PA, SD, and obesity. The eQTL analysis revealed strong associations between specific genes (RPS26, TTC12, CCDC92, NICN1) and SNPs (rs10876864, rs2734849, rs4765541, rs7615206) in both subcutaneous and visceral adipose tissues, which are associated with these SBs. Enrichment analysis

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further revealed that these genes are involved in crucial biological pathways, including cortisol synthesis, thyroid hormone synthesis, and insulin secretion.

Conclusions

Our findings support a causal relationship between four specific SBs (LST, television watching, computer use, driving) and obesity. These results provide valuable insights into potential interventions to address obesity effectively, supported by genetic associations in the eQTL and enrichment analysis. Further research and public health initiatives focusing on reducing specific SBs may be warranted.

Introduction

World Health Organization (WHO) declared obesity a global epidemic [1]. That affects people of all ages and socioeconomic groups, independent of a country's income level [2,3]. Over the past few decades, the prevalence of obesity has steadily risen, becoming a significant public health challenge globally [4]. Currently, approximately 30% of adults worldwide are affected by obesity, and this number is projected to increase to 33% by 2030 [5,6]. Obesity is a complex condition with multiple contributing factors, including genetics, behavior, and the environment [7]. It is associated with a higher risk of cancer [8], cardiovascular diseases, and increased mortality rates [9], while also bringing negative psychosocial consequences, such as social stigma and depression. In addition to adverse health effects, obesity takes a considerable toll on the economy, encompassing expenses for preventive measures, diagnostic procedures, pharmaceuticals, and treatment services [10]. Alarming, the projected medical costs associated with obesity are estimated to surge annually by a staggering £1.9–2 billion in the UK and a staggering \$48–66 billion in the USA by 2030 [11].

Sedentary behavior (SB), characterized by low energy expenditure activities (≤ 1.5 metabolic equivalents) [12], is a risk factor for obesity [13], and a health burden that influences mortality [14]. Conversely, physical activity (PA) involves musculoskeletal movements requiring additional energy expenditure and has demonstrated numerous health benefits, including improved weight management and a reduced risk of obesity [15,16]. Similarly, sleep duration (SD), an essential component of overall well-being, has been associated with metabolic processes, appetite control, and body weight regulation [17,18]. Rosenberger describes how these are related to the 24-hour activity cycle [19].

Observational studies [15,16,20] indicate that SB, PA, and SD are associated with obesity. For example, high levels of total SB, such as excessive television watching, are associated with obesity across all age groups. In participants who spend three hours or more daily in SB [21], the risk of being overweight or obese increases by 38%. Similarly, some observational studies suggest a connection between higher levels of PA and reduced obesity risk [15,22,23]. Individuals with a sedentary lifestyle have a significantly higher risk of developing obesity [22]. In contrast, young adult females with high levels of PA have a 142% lower likelihood of developing obesity than those with low PA levels [15].

Moreover, some studies [1,24,25] have demonstrated an association between SD and obesity. However, it should be noted that some SB/PA/SD studies have reported conflicting and/or inconsistent findings with the results mentioned above [26–28]. Although observational studies provide valuable insights, they are limited by potential confounding factors and reverse

causation, leading to gaps in understanding the causal relationship between SB/PA/SD and obesity. Experimental data on the topic is limited, unfortunately [23].

Mendelian randomization (MR) is a robust approach for establishing causality between exposures and outcomes [29]. It utilizes genetic variants as instrumental variables to minimize confounding [30], ensuring that genetic variations impact obesity development without reverse causality [31]. MR provides higher-quality evidence compared to observational studies, enabling causal inference on the effects of SB/PA/SD on obesity risk [32]. Our study objective was to examine casual associations between lifestyle behaviors (SB, PA, and SD) and obesity outcomes by analyzing large-scale genetic data and using robust analytical methods.

Methods

Study design

Our study complied with the standards of the Strengthening the Reporting of Observational Studies in Epidemiology using the Mendelian Randomization [S1 Checklist](#) [33].

Data source

To examine the causal effect of SB/PA/SD on obesity, we first selected ten lifestyle factors strongly associated with obesity based on observational studies. These factors derived from Genome-Wide Association Studies (GWAS) included various forms of SB: television watching (N = 437,887), computer use (N = 360,895), and driving (N = 310,555) [34]. We also incorporated additional GWAS data for leisure screen time (LST) (N = 526,725), covering activities like watching television, playing video games, or sitting in front of a computer; SB at work (N = 372,609), characterized by predominantly sitting and minimal heavy lifting; and sedentary commuting (N = 159,606), which refers to driving a car. Detailed definitions of the three phenotypes can be found in the supplementary data in Zhe Wang study [35]. Furthermore, our study assessed PA factors, including moderate-to-vigorous physical activity (MVPA), accelerometer-based activity with average acceleration (AccAve) (N = 91,084), and physical activity with accelerations over 425 milli-gravities (Acc425) (N = 90,667) [36], as well as sleep duration (SD) (N = 91,105) [36,37]. The data can be found on the GWAS catalog (<https://www.ebi.ac.uk/gwas/>). [Table 1](#) highlights the Characteristics of data sources.

We then utilized exposure-related single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) in our MR study ([Fig 1](#)). To ensure the validity of our MR analysis, we selected SNPs to meet three crucial assumptions: 1) strong association between the exposure and SNPs; 2) no association between the SNPs and potential confounding factors; and 3) the SNPs should solely impact the outcome through exposure ([Fig 2](#)) [29]. We performed rigorous screening and clumping of the significant SNPs ($p < 5 \times 10^{-8}$), after we clumped these SNPs in linkage disequilibrium (LD, clumping window: 10000kb, Clumping r^2 cutoff: 0.001). For phenotypes with fewer than three SNPs, we performed a secondary screening with relaxed P value thresholds of less than 5×10^{-7} (driving) and 5×10^{-6} (Acc425) while keeping all other screening conditions unchanged [38]. Ultimately, we identified a set of final SNPs associated with various SBs such as television watching (161 SNPs), computer use (47 SNPs), driving (5 SNPs), LST (115 SNPs), SB at work (9 SNPs), sedentary commuting (16 SNPs), MVPA (19 SNPs), AccAve (8 SNPs), Acc425 (26 SNPs), and SD (14 SNPs). All identified SNPs showed F-statistics greater than 10. Further details about these SNPs are provided in the [S2 Table](#) in [S2 File](#).

To avoid any sample overlap bias, we utilized the obesity datasets from FinnGen (<https://www.finnngen.fi/en>), which were updated in December 2022. The FinnGen datasets provided a robust and independent sample population with 21,375 cases and 355,786 controls, all of whom had European ancestry ([Table 1](#)).

Table 1. Characteristics of data sources.

Phenotype		Consortium	PMID	Author	Decent	Sample size
<i>Exposure</i>						
SB	LST	UK Biobank	36,071,172	Wang et al	Eur	526,725
	SB at work				Eur	372,605
	Sedentary commuting				Eur	159,606
	Television watching	UK Biobank	32,317,632	van et al	Eur	437,887
	Computer use				Eur	310,555
	Driving				Eur	422,218
PA	AccAve	UK Biobank	29,899,525	Klimentidis et al	Eur	91,084
	MVPA				Eur	377,000
	Acc425				Eur	91,084
SD		UK Biobank	30,531,941	Doherty et al	Eur	91,105
<i>Outcome</i>						
Obesity		FinnGen	36,653,562	Kurki MI et al.	Eur	377,161

Abbreviations: SB, sedentary behavior; PA, physical activity; LST, Leisure screen time; SB at work, Sedentary Behavior at work; AccAve, accelerometer-based physical activity with average acceleration; Acc425, accelerometer-assessed fraction of accelerations>425 milligravities; MVPA, moderate to vigorous physical activity; Eur, European; SD, Sleep duration.

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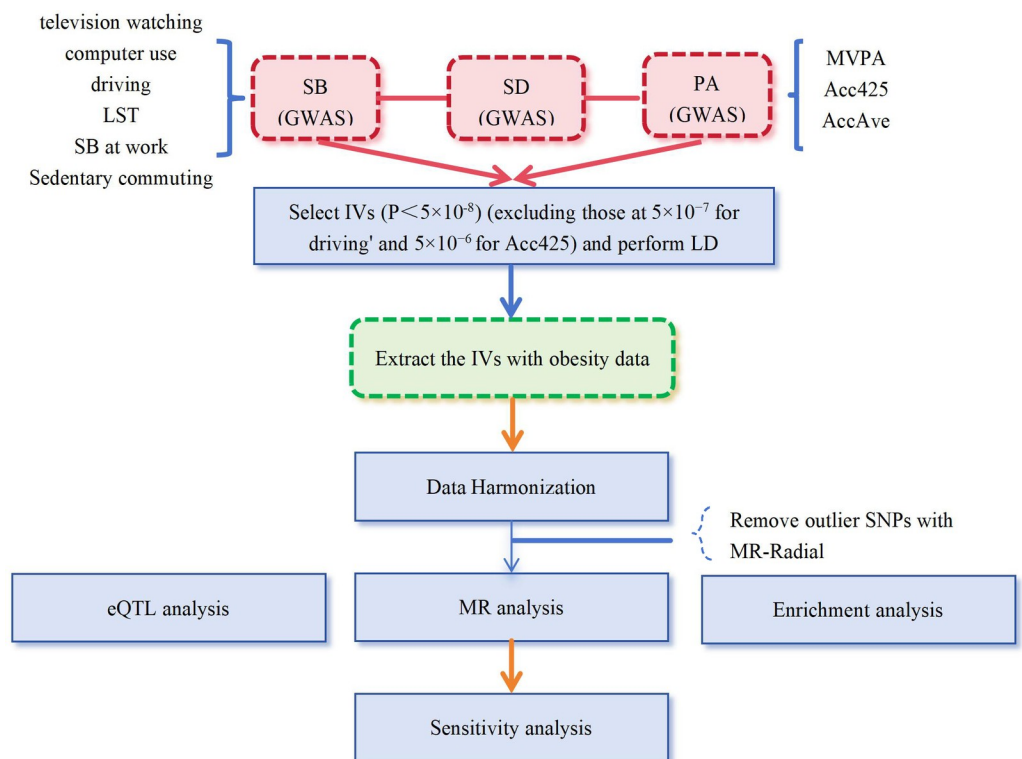


Fig 1. The process for instrumental variable selection and study design. SB, sedentary behavior, PA, physical activity; SD, sleep duration; LST, Leisure screen time; SB at work, Sedentary Behavior at work; MVPA, moderate to vigorous physical activity; Acc425, accelerometer-based physical activity with average acceleration; SD, Sleep duration; GWAS: Genome wide association study; IVs: Instrument variables; MR, Mendelian randomization; SNPs: single-nucleotide polymorphisms.

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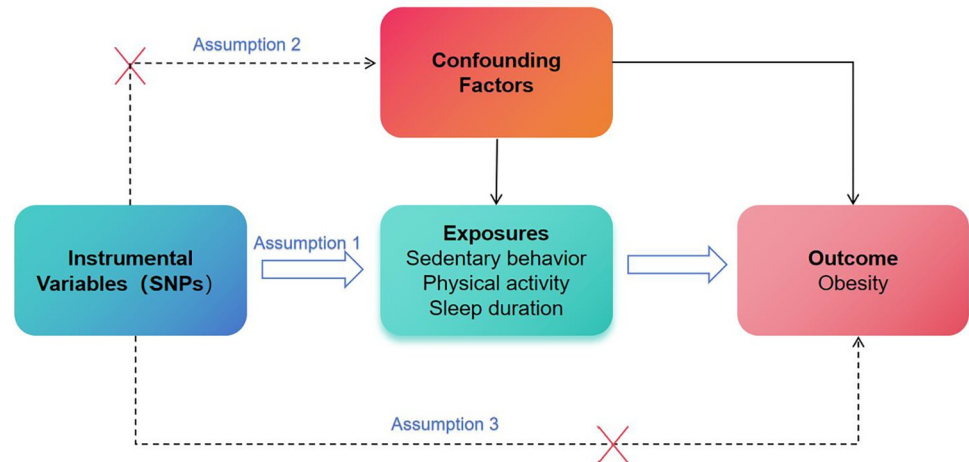


Fig 2. Instrumental variables fit the assumptions of MR. SNPs: single-nucleotide polymorphisms.

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MR and sensitivity analysis

To examine the causal effects of PA, SB, and SD on obesity, we employed several statistical methods in our MR study. The Instrumental Variable Weighted (IVW) method and weighted median with MR-Egger, Simple mode, and weighted mode were used for analysis. Depending on the presence of heterogeneity and pleiotropy in IVs, we selected the appropriate analysis approach. When there was no heterogeneity and pleiotropy in IVs, the fixed-effects model analysis using IVW was considered the most accurate. However, the random-effects model of IVW or methods like weighted median was preferred in heterogeneity. Additionally, when SNPs exhibited pleiotropy, MR-Egger analysis was used as an alternative to IVW and weighted median methods [39].

We performed the Cochran Q test to test for heterogeneity, and the funnel plot was used as a supplement. Detecting horizontal pleiotropy, which occurs when instrumental variables directly affect the outcome independent of the exposure factor, is crucial for maintaining the integrity of MR. To address this, we conducted an MR-Egger intercept analysis. Vertical pleiotropy, where an exposure influences an outcome through a common causal pathway, is acceptable for MR inference, unlike horizontal pleiotropy which poses challenges [40], we employed MR-Radial analysis to assess vertical pleiotropy and identify biased SNPs ($p < 0.05$). In case biased SNPs were detected, MR and sensitivity analyses were repeated after excluding these SNPs. Additionally, leave-one-out analysis was utilized to assess the robustness of the analysis results [41].

The eQTL analysis

The Genotype-Tissue Expression (GTEx) project provides the largest atlas of human gene expression and catalog of trait loci [42,43]. We downloaded the GTEx Analysis V8 eQTL release from the GTEx Portal (<https://gtexportal.org>). Instrumental SNPs of significant exposures in MR analysis were used to extract significant eQTLs and eQTL nominated genes in obesity-relevant tissues (subcutaneous adipose and visceral adipose). These variant-gene pairs in both tissues were further calculated using the GTEx v8 eQTL Calculator. The expression of eQTL in specific tissues was measured by Normalized effect size (NES).

Enrichment analysis

In this study, we used the online tool KOBAS-i v3.0 (<http://bioinfo.org/kobas/>) for functional enrichment analysis of genes identified by eQTL analysis with the KEGG pathway [44]. We analyzed genes expressed in the two types of adipose tissue, respectively. In the set of genes significantly tested after Bonferroni corrections, allelic fold change (aFC) in log₂ scale >1 was regarded as an up-regulated gene. otherwise, it was a down-regulated gene. The value was calculated using a hypergeometric distribution and the false discovery rate < 0.05 was considered significant statistically.

Statistical analysis

All statistical analyses were conducted in R version 4.2.3, utilizing the R package Two Sample MR (version 0.5.7). We applied a Bonferroni correction factor of 10 in our statistical analysis, corresponding to the 10 distinct exposures investigated. This approach, considering the multiple independent analyses performed, led us to set a significance threshold at $p < 0.005$ (0.05/10), ensuring a more robust and reliable interpretation of our results.

Ethics statement

All the data used in this study were sourced from publicly available online databases. As such, participants' written informed consent had been previously obtained.

Results

The MR analysis used the Inverse Variance Weighted (IVW) method and revealed, causal relationships between obesity and four genetically predicted specific types of SB: LST (Odds ratio [OR] = 1.62, [95% CI] = [1.43, 1.84], $p = 6.49 \times 10^{-14}$), television watching ([OR] = 1.55, [95% CI] = [1.27, 1.90], $p = 1.67 \times 10^{-5}$), computer use ([OR] = 1.52, [95% CI] = [1.08, 2.13], $p = 1.61 \times 10^{-2}$), and driving ([OR] = 2.79, [95% CI] = [1.25, 6.21], $p = 1.23 \times 10^{-02}$). However, no causal relationships were observed with SB at work or sedentary commuting. The detailed findings are depicted in [Table 2](#) and [Fig 3](#). The forest plot and leave-one-out analysis (LOO) plot results are listed in [S3 Fig](#) in [S1 File](#).

We found no evidence for the causality of genetically predicted relationships among the three indicators: PA, SD, and obesity (MVPA: IVW: OR = 0.88, [95% CI] = [0.52–1.48], $p = 0.70$; Acc425: OR = 0.73, [95% CI] = [0.52–1.01], $p = 0.05$; AccAve: IVW: OR = 0.96, [95% CI] = [0.83–1.10], $p = 0.53$; SD: IVW: OR = 0.94, [95% CI] = [0.76–1.17], $p = 0.60$). The weighted median and MR-Egger are listed in [Table 2](#).

Sensitivity analyses

The MR-Egger intercept and MR-Radial analyses indicated no evidence of pleiotropy in the relationship between PA/SB/SD and obesity. These results strengthen our confidence in drawing robust conclusions from our findings ([Table 3](#)). Furthermore, the MR-Egger intercepts for all other results were more significant than $p > 0.05$, indicating the absence of horizontal pleiotropy ([Table 3](#)). However, we did identify heterogeneity in the results when examining the relationship between AccAve and obesity, as indicated by the Cochran Q test ($Q = 22.28$, $p = 5.70 \times 10^{-05}$). The MR-Radial global test identified that the SNPs rs34517439, rs9293503, and rs62443625 were biased in the results. We conducted further analysis by eliminating these biased SNPs and re-performing MR analysis and sensitivity analysis for AccAve and obesity. This time, the Cochran Q test ($p = 0.05$) and the MR-Radial global test ($p = 0.54$) showed no evidence of heterogeneity in the results, confirming the robustness of the findings.

Table 2. MR estimates of the causal association between SB/PA/SD and the risk of obesity.

Exposure	Obesity			F-statistic
	Methods	OR (95% CI)	p	
LST	MR Egger	1.79 (0.99, 3.21)	0.06	113.19
LST	Weighted median	1.72 (1.44, 2.05)	1.58×10 ⁻⁹	
LST	IVW	1.62 (1.43, 1.84)	6.49×10 ⁻¹⁴	
LST	Simple mode	1.91 (1.33, 2.74)	9.47×10 ⁻⁰⁴	
LST	Weighted mode	1.83 (1.29, 2.60)	1.50×10 ⁻⁰³	
Television watching	MR Egger	2.04 (0.92, 4.55)	0.09	47.57
Television watching	Weighted median	1.65 (1.24, 2.20)	5.83×10 ⁻⁴	
Television watching	IVW	1.55 (1.27, 1.90)	1.67×10 ⁻⁵	
Television watching	Simple mode	2.38 (1.19, 4.74)	0.02	
Television watching	Weighted mode	2.24 (1.21, 4.14)	0.01	
Computer use	MR Egger	27.49 (1.34, 563.20)	0.05	28.11
Computer use	Weighted median	1.60 (1.00, 2.56)	0.05	
Computer use	IVW	1.52 (1.08, 2.13)	1.61×10 ⁻²	
Computer use	Simple mode	1.61 (0.67, 3.84)	0.30	
Computer use	Weighted mode	1.86 (0.77, 4.46)	0.18	
Driving	MR Egger	2.61 (0.01, 627.55)	0.74	43.88
Driving	Weighted median	1.61 (0.79, 3.27)	0.19	
Driving	IVW	2.79 (1.25, 6.21)	1.23×10 ⁻²	
Driving	Simple mode	1.39 (0.55, 3.50)	0.50	
Driving	Weighted mode	1.39 (0.55, 3.54)	0.50	
SB at work	MR Egger	2.74 (0.18, 41.59)	0.54	124.45
SB at work	Weighted median	1.17 (0.77, 1.76)	0.46	
SB at work	IVW	1.23 (0.86, 1.75)	0.26	
SB at work	Simple mode	1.01 (0.54, 1.88)	0.97	
SB at work	Weighted mode	1.01 (0.56, 1.84)	0.97	
Sedentary commuting	MR Egger	0.80 (0.46, 1.41)	0.50	53.31
Sedentary commuting	Weighted median	1.09 (0.78, 1.52)	0.63	
Sedentary commuting	IVW	1.19 (0.92, 1.55)	0.18	
Sedentary commuting	Simple mode	1.07 (0.67, 1.73)	0.78	
Sedentary commuting	Weighted mode	1.06 (0.66, 1.69)	0.83	
MVPA	MR Egger	0.08 (0.00, 1.68)	0.65	30.49
MVPA	Weighted median	0.87 (0.44, 1.73)	0.15	
MVPA	IVW	0.88 (0.52, 1.48)	0.70	
MVPA	Simple mode	1.50 (0.44, 5.10)	0.63	
MVPA	Weighted mode	0.64 (0.18, 2.19)	0.53	
Acc425	MR Egger	1.43 (0.56, 3.70)	0.48	17.78
Acc425	Weighted median	0.82 (0.53, 1.27)	0.38	
Acc425	IVW	0.73 (0.52, 1.01)	0.05	
Acc425	Simple mode	0.79 (0.39, 1.60)	0.53	
Acc425	Weighted mode	0.80 (0.41, 1.58)	0.54	

(Continued)

Table 2. (Continued)

Exposure	Obesity			F-statistic
	Methods	OR (95% CI)	p	
AccAve	MR Egger	0.96 (0.37, 2.49)	0.94	1979.98
AccAve	Weighted median	0.94 (0.88, 1.01)	0.12	
AccAve	IVW	0.96 (0.83, 1.10)	0.53	
AccAve	Simple mode	0.91 (0.81, 1.02)	0.20	
AccAve	Weighted mode	0.92 (0.83, 1.01)	0.19	
SD	MR Egger	0.83 (0.43, 1.57)	0.58	40.65
SD	Weighted median	0.96 (0.71, 1.29)	0.78	
SD	IVW	0.94 (0.76, 1.17)	0.60	
SD	Simple mode	0.90 (0.53, 1.55)	0.72	
SD	Weighted mode	0.82 (0.49, 1.38)	0.48	

Abbreviations: SB, sedentary behavior; PA, physical activity; SD, sleep duration; CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; IVW, Inverse variance weighted; LST, Leisure screen time; SB at work, Sedentary Behavior at work; MVPA, moderate to vigorous physical activity; Acc425, accelerometer-based physical activity with accelerations >425 milli-gravities; AccAve, accelerometer-based physical activity with average acceleration; SD, Sleep duration.

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eQTL analysis

In our comprehensive study of subcutaneous and visceral adipose tissues, we identified a substantial number of eQTLs associated with prolonged SB, TV watching, computer use, driving, and LST. Specifically, we found 214 eQTLs related to TV watching, 79 related to computer use, 14 related to driving, and 139 related to LST.

The Adipose-subcutaneous tissue found a strong association between the gene *RPS26* and the rs10876864 with TV watching ($p = 1.4 \times 10^{-233}$, NES = -1.2) ($p = 1.4 \times 10^{-233}$, NES = -1.2). This association was also evident in the visceral adipose tissue ($p = 3.4 \times 10^{-175}$, NES = -1.2). For eQTLs associated with computer usage, the gene *TTC12* and rs2734849 in the subcutaneous adipose tissue demonstrated a noteworthy connection ($p = 1.9 \times 10^{-48}$, NES = -0.63). In the context of driving, the visceral adipose tissue exhibited a significant association between the gene *CCDC92* and rs4765541 ($p = 3.6 \times 10^{-27}$, NES = 0.34), in the eQTLs related to LST, a prominent association was observed between the gene *NICN1* and rs7615206 in the subcutaneous adipose tissue ($p = 5.80 \times 10^{-4}$, NES = -0.09).

Enrichment analysis

In the gene upregulation KEGG enrichment analysis, we found that these genes are mainly involved in multiple biological pathways. These include the synthesis and secretion of cortisol, thyroid hormone synthesis, insulin secretion, and the longevity-regulating pathway, which showed the most significant enrichment. The analysis also highlighted other pathways such as the synthesis and secretion of aldosterone, the synthesis, secretion, and action of parathyroid hormone, and lysosomal pathways, as detailed in S4 Fig in [S1 File](#) and S2 Table in [S2 File](#).

Discussion

Our study provided genetic evidence supporting the causal relationship between obesity and four types of SB: television watching, LST, computer use and driving. No causal relationships

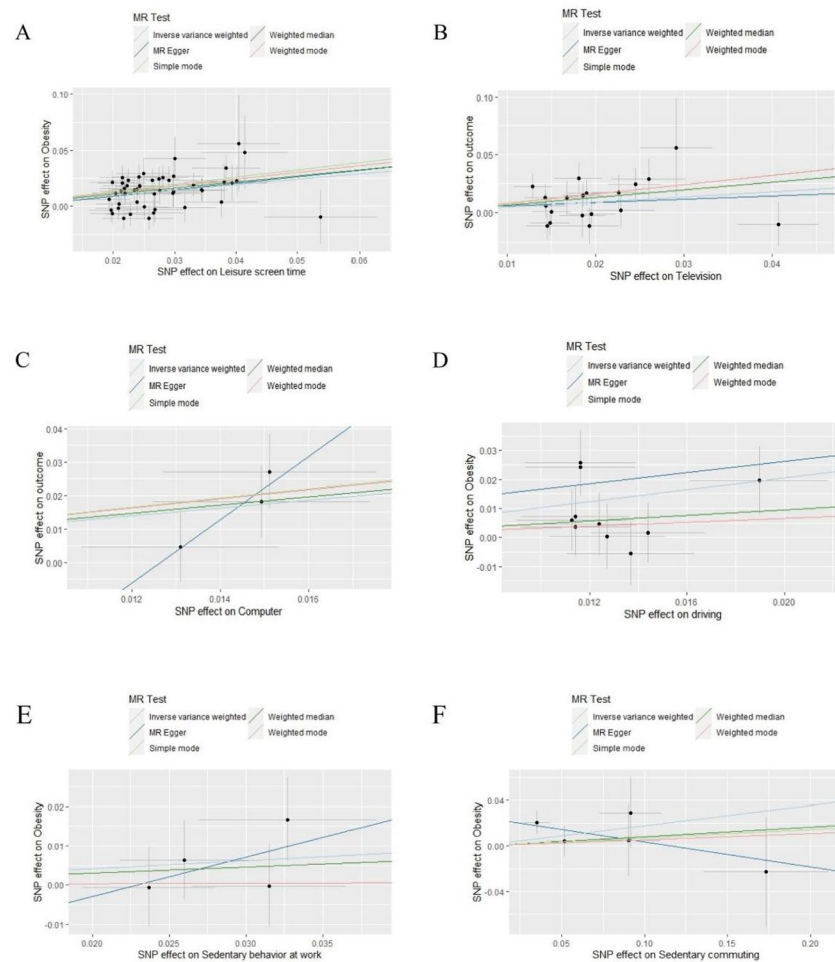


Fig 3. Sensitivity analyses of MR results about SB to Obesity. A: Scatter plots show genetically predicted of Leisure screen time (LST); B: Scatter plots show genetically predicted of Television watching; C: Scatter plots show genetically predicted of Computer use; D: Scatter plots show genetically predicted of Driving on Obesity; E: Scatter plots show genetically predicted of Sedentary behavior at work (SB at work); F: Scatter plots show genetically predicted of sedentary commuting. Note: The term ‘genetically predicted’ refers to the application of genetic methods for predicting individuals’ inclinations toward specific behaviors, leveraging genetic information.

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were observed between SB at work, sedentary commuting, PA, SD, and obesity. These findings provided genetic insights into the association of complex traits of SB with obesity. Sensitivity analyses indicated no heterogeneity, horizontal pleiotropy, or influential SNPs identified through the LOO analysis, which further strengthens the reliability and robustness of the results.

Previous observational studies have shown a correlation between SB and obesity [45,46], with dose-response studies indicating a nonlinear association [21]. Furthermore, an observational study involving European and American adults revealed that sitting time is associated with obesity, independent of PA [47,48]. All the studies mentioned above only provided evidence to arouse awareness of SB’s possible impact on obesity. Despite the risk of reverse causality in observational studies, our cost-effective MR approach identified significant causal effects of most types of SB on obesity development, excluding those related to work and commuting. These findings are consistent with prior research on television watching and computer use [21,49]. Additionally, a recent GWAS highlighted the significant impact of LST on

Table 3. Sensitivity analysis of the causal association between PA/SB/SD and the risk of obesity.

Exposure	Outcome	MR-Egger		Cochran Q test	
		Intercept	<i>p</i>	Q_value	<i>p</i>
LST	Obesity	0.004	0.65	57.67	0.12
Television watching	Obesity	0.003	0.79	59.66	0.22
Computer use	Obesity	-0.12	0.44	16.91	0.53
Driving	Obesity	0.01	0.76	9.08	0.43
Sedentary commuting	Obesity	0.01	0.52	1.93	0.86
SB at work	Obesity	0.01	0.52	1.93	0.86
MVPA	Obesity	0.04	0.17	3.95	0.68
Acc425	Obesity	-0.02	0.17	9.47	0.39
AccAve	Obesity	-0.001	1.00	3.94	0.05
SD	Obesity	0.01	0.68	7.61	0.37

Abbreviations: LST, Leisure screen time; SB at work, Sedentary Behavior at work; MVPA, moderate to vigorous physical activity; Acc425, accelerometer-based physical activity with accelerations >425 milli-gravities; AccAve, accelerometer-based physical activity with average acceleration; SD, Sleep duration.

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obesity, suggesting it is much greater than the reverse [35]. Nevertheless, our study offers solid evidence of a causal relationship between specific types of SB and obesity, contributing significantly to research in this field. It is also crucial to acknowledge that certain types of SB, such as SB at work, did not demonstrate a causal association with obesity, which is an important consideration for future research and public health strategies.

The association between SB and obesity is influenced by direct physiological mechanisms and complex genetic factors. SB reduces muscle activity [50,51], leading to decreased lipoprotein lipase activity essential for lipid metabolism, contributing to fat accumulation and potential obesity [50–52]. It is also associated with higher postprandial glucose and lipid levels, raising the risk of obesity [53,54]. Our study reveals that various SBs, such as TV watching, computer use, driving, and LST, have a significant genetic component, as evidenced by our eQTL analysis in both subcutaneous and visceral adipose tissues. The identification of numerous behavior-specific eQTLs highlights a complex interaction between genetics and lifestyle. For example, the association between the RPS26 gene and the rs10876864 in relation to TV watching, observed in both types of adipose tissues, suggests a genetic inclination towards the effects of extended visual media consumption on fat tissue function. Associations with other genes like TTC12, CCDC92, and NICN1 in contexts of computer use, driving, and LST further support this. Additionally, our study explores the impact of SB on distinct biological processes in various fat tissues, particularly in hormone secretion pathways vital for endocrine regulation. A key finding is the pronounced gene enrichment related to cortisol synthesis and secretion in visceral adipose tissue, indicating that SB might modulate cortisol levels, thus affecting the balance between visceral fat and metabolic health. This aligns with the Rodriguez et al study [55] indicating that cortisol release and fat accumulation are aberrantly regulated in obesity. Furthermore, SB's potential impact on thyroid hormone synthesis, energy metabolism, and body temperature regulation is notable. The observed gene enrichment related to insulin secretion in visceral fat tissues implies that SB might indirectly heighten the risk of metabolic diseases like diabetes, a significance also emphasized in the study by Chen et al [56]. This comprehensive analysis enhances our understanding of the complex genetic underpinnings, biological mechanisms, and their association with obesity.

In the field of obesity research, various scholars have presented differing viewpoints. Some observational studies [15,53] have found that increasing PA can reduce the risk of obesity and

that there is a longitudinal correlation between SD and obesity [53]. However, other studies, such as those by Song et al. [57] and Bell et al. [22], have pointed out that the relationship between PA, SD, and obesity is not clear and remains controversial. Our MR results indicated that PA and longer SD are associated with a decreased trend in obesity risk. These results align with some observational studies [15,22] suggesting a potential protective effect of PA and SD against obesity. However, these associations are not sufficient to prove a causal relationship. Observational studies [57] indicate that obesity is influenced by interactions between SB, PA, and genetic factors like the MC4R gene variant, without PA alone showing a direct causal effect [22]. Additionally, both prolonged and short SD, along with lower sleep satisfaction, are linked to increased obesity risk across all ages [1,25], potentially due to their impact on appetite control, which can lead to higher food intake and reduced energy expenditure [6]. However, the precise biological mechanisms between sleep and obesity remain unclear. Therefore, although previous literature provides evidence suggesting that PA and SD might be beneficial in resisting obesity, our study results indicate that there is no direct causal association between these factors and obesity risk. To more comprehensively understand the impact of PA and SD on obesity risk, it is necessary to delve deeper into the biological mechanisms between them. This may include studying changes in sleep patterns, appetite regulation, energy metabolism, and how these changes affect the development of obesity. By gaining a deeper understanding of these biological processes, we can better comprehend how PA and SD influence the risk of obesity and provide a scientific basis for future prevention and treatment strategies.

Historically, while interventions focused on PA and sleep or diet [23], the role of SB in obesity was neglected, and traditional calorie-focused approaches have not consistently achieved long-term weight control success [54]. Through our exploration into the causal relationships between SB, PA, SD and obesity, we identified distinct causal associations between four SBs and obesity. Notably, we found significant positive associations between these four SBs and the risk of obesity. These findings challenge previous obesity strategies and suggest that prolonged sitting should be a focal point for interventions targeting people with obesity. However, further randomized controlled trials (RCTs) are recommended to confirm its effectiveness.

Our study has several strengths. First, we comprehensively analyzed six types of SB in GWAS data and explored the biological mechanisms of how SB contributes to its development, which allowed us to gain deeper insights into the diverse impacts of different SBs on obesity. Second, we minimized potential bias from different racial backgrounds by focusing on individuals with European ancestry. Third, we used separate GWAS and Finnish databases to select exposure and outcome data to avoid overlapping samples. Fourth, we conducted multiple sensitivity analyses to assess the validity of MR assumptions and applied MR-radial to minimize heterogeneity to the greatest extent possible. However, our study also has limitations. First, its findings primarily apply to European populations, with limited generalizability due to sparse disease information in GWAS data, hindering stratified analyses. Second, while offering robust evidence, our results necessitate careful interpretation due to possible unmeasured confounders and residual influences from unobserved pleiotropy. Third, the analysis power might be compromised by the small number of SNPs for certain traits, and the scarcity of SNPs for driving could yield imprecise estimates. Finally, multicollinearity among phenotypes such as LST, watching television, and computer use may obscure the ability to isolate their independent impacts.

Conclusion

Our study underscores the importance of adopting an active lifestyle and reducing SB to combat the risk of obesity effectively. Compared to encouraging regular PA and SD, reducing

specific SBs (especially LST, television watching, computer use, and driving) could be a more targeted and practical approach to combat obesity. Additionally, our analysis suggests genetic associations and biological pathways related to obesity, enhancing our understanding of its mechanisms. Future research should delve deeper into these aspects to devise more targeted and effective obesity prevention and management strategies.

Supporting information

S1 Checklist. STROBE-MR guideline.

(DOCX)

S1 File. S3 Fig. Forest plot and LOO plot for SBs on obesity. S4 Fig. Result of eQTL enrichment analysis.

(DOCX)

S2 File. S1 Table. Instrument variables of LST. S2 Table. Instrument variables of television watching. **S3 Table.** Instrument variables of computer use. **S4 Table.** Instrument variables of driving. **S5 Table.** Instrument variables of SB at work. **S6 Table.** Instrument variables of sedentary commuting. **S7 Table.** Instrument variables of MVPA. **S8 Table.** Instrument variables of AccAve. **S9 Table.** Instrument variables of Acc425. **S10 Table.** Instrument variables of SD. **S11 Table.** Result of eQTL. **S12 Table.** Result of eQTL enrichment analysis.

(XLSX)

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