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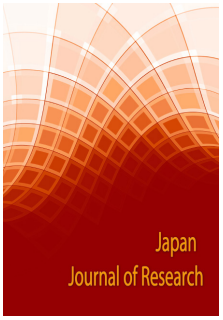

Replacing Sedentary Time with Physical Activity to Reduce Type 2 Diabetes Risk: Insights from Genetic Causal Evidence

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Keywords

Type 2 diabetes; Mendelian randomization; Sedentary behavior; Physical activity; Television watching; Causal inference

Abstract

Background: *Sedentary behavior and physical activity are known lifestyle factors associated with type 2 diabetes (T2D), yet their causal roles remain uncertain.*

Methods: *We performed a bidirectional two-sample Mendelian randomization (MR) analysis to investigate the causal effects of three leisure sedentary behaviors (television watching, computer use, driving) and two physical activity phenotypes (moderate-to-vigorous [MVPA] and vigorous physical activity [VPA]) on T2D. GWAS summary statistics were derived from large-scale European cohorts. The inverse variance weighted (IVW) method was used as the primary analytical approach, complemented by weighted median and MR-Egger methods. Sensitivity analyses assessed heterogeneity and horizontal pleiotropy.*

Results: *Forward MR analysis showed a significant positive causal effect of television watching on T2D (IVW OR = 1.760, P < 0.001). VPA demonstrated an inverse association trend (IVW OR = 0.535, P = 0.080), although this did not reach the conventional threshold for statistical significance (P < 0.05). No significant associations were found for computer use, driving, or MVPA. Reverse MR analyses indicated no significant causal effect of T2D on any behavioral traits. Sensitivity analyses did not detect notable pleiotropy.*

Conclusion: *Our findings provide genetic evidence supporting a causal role of specific sedentary behaviors and physical activity in T2D development. Interventions targeting television viewing may offer potential benefits for primary prevention.*

Introduction

Type 2 diabetes (T2D) is a metabolic disorder characterized by insulin resistance and β-cell dysfunction, and it is one of the most prevalent chronic diseases worldwide [1]. In 2017, the global prevalence of T2D was estimated at 6.28%, ranking as the ninth leading cause of death and the seventh leading contributor to global disease burden. The prevalence is highest in developed regions and Pacific Island nations, largely associated with higher economic status, urbanization, obesity, and sedentary lifestyles. Projections suggest that by 2040, the global prevalence will reach 7,862 per 100,000 population [2,3]. T2D significantly increases the risk of cardiovascular disease, renal failure, retinopathy, and other complications, imposing substantial economic costs and public health burdens [4,5]. Although obesity and poor dietary habits are well-established major risk factors, a growing body of evidence indicates that sedentary behavior and physical activity also play independent and critical roles in the development of diabetes [6,7]. Therefore, identifying and clarifying the causal relationships between these behavioral factors and T2D is of great importance for prevention and intervention strategies.

Leisure sedentary behavior (LSB) refers to low-energy expenditure activities performed during non-working hours, such as television viewing, non-occupational computer use, and driving. These behaviors are typically characterized by a metabolic equivalent (MET) of ≤1.5 [8,9]. Numerous observational studies have demonstrated a strong association between LSB and the incidence of type 2 diabetes (T2D), often showing a clear dose–response relationship [10]. In contrast, Moderate to vigorous physical activity (MVPA) and vigorous physical activity (VPA) have been consistently shown to reduce T2D risk significantly [11]. However, different subtypes of LSB may exert differential effects on metabolic health. For example, television viewing is often accompanied by excessive caloric intake, blue light exposure, and sleep disturbances, whereas driving behavior may be more influenced by commuting patterns [12]. Importantly, most existing evidence is derived from observational studies, which are prone to residual confounding and reverse causality, leaving the causal nature of these associations uncertain. Therefore, it is essential to apply more rigorous causal inference methods to evaluate the independent effects of distinct behavioral patterns on T2D risk.

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Although previous studies have suggested potential associations between LSB, physical activity (PA), and T2D, the causal nature of these relationships remains unclear. In this study, we applied a bidirectional two-sample Mendelian randomization (MR) approach, leveraging large-scale genome-wide association study (GWAS) summary statistics and using genetic variants as instrumental variables to assess the causal effects of LSB and PA on T2D risk. Compared with traditional observational studies, the MR method minimizes confounding and reverse causality, thereby strengthening the validity of causal inference[13]. This study not only evaluates the overall causal effects of LSB and PA on T2D but also incorporates reverse MR analyses to examine whether T2D, in turn, influences behavioral patterns. The findings aim to provide a more robust evidence base for public health policy and support the targeted application of behavioral interventions in the primary prevention of diabetes.

Materials and methods

Study Design

This study adopted a bidirectional two-sample MR design to evaluate the potential causal relationship between LSB, PA, and T2D. MR is an analytical method that leverages genetic variants strongly associated with an exposure as instrumental variables (IVs), allowing for causal inference under specific assumptions. We first extracted single nucleotide polymorphisms (SNPs) significantly associated with LSB and PA from large-scale GWAS. Summary statistics for T2D were then obtained from an independent GWAS dataset, ensuring no sample overlap between exposure and outcome sources. Forward MR analyses were performed to assess the causal effects of LSB and PA on T2D, while reverse MR analyses examined whether T2D influences these behavioral traits. To verify the robustness of the results, we conducted a series of sensitivity analyses using multiple complementary methods. All exposure and outcome data were derived from individuals of European ancestry to reduce potential bias caused by population stratification.

Data sources

GWAS summary data for LSB were obtained from the UK Biobank via the MRC IEU OpenGWAS platform (https://gwas.mrcieu.ac.uk/), including three phenotypes: time spent watching television (UKB ID: ukb-b-5192), time spent using computer (ukb-b-4522), and time spent driving (ukb-b-3793). PA data were sourced from the European Bioinformatics Institute, including self-reported moderate to vigorous physical activity levels (MVPA, ebi-a-GCST006097) and vigorous physical activity (VPA, ebi-a-GCST006098), both assessed using the short form of the International Physical Activity Questionnaire. GWAS summary statistics for the outcome variable, T2D, were derived from a FinnGen Database, with all participants of European ancestry. Detailed information on each GWAS dataset is provided in Table 1.

Table 1. *MR analyses data sources*

Trait	Year	Sample size	GWAS ID	Ethnicity
Television watching	2018	437887	ukb-b-5192	European
Computer use	2017	261987	ukb-b-6	European
Driving	2018	310555	ukb-b-3793	European
MVPA	2018	377234	ebi-a-GCST006097	European
VPA	2018	261055	ebi-a-GCST006098	European
T2D	2021	215654	finn-b-E4_DM2	European

T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Instrument Selection and Quality Control

To ensure the strength and independence of instrumental variables in the MR analysis, the following criteria were applied for SNP selection. Variants associated with each exposure at genome-wide significance ($P < 5\times10^{-8}$) were initially selected; when fewer than 10 SNPs met this threshold, a relaxed cutoff of $P < 5\times10^{-7}$ was used to retain adequate analytical power. Linkage disequilibrium (LD) filtering was performed using an r^2 threshold of < 0.001 and a window size of 10,000 kb to ensure independence among SNPs. F-statistics were then calculated, and SNPs with $F \leq 10$ were excluded to minimize weak instrument bias. For all exposures, more than 10 independent SNPs were retained, satisfying the standard requirements for MR analysis.

Statistical Analysis

The primary MR analysis was conducted using the IVW method, which combines the ratio estimates of individual SNPs by weighting them according to the inverse of their variance, providing a consistent estimate under the assumption that all instruments are valid. To improve robustness against potential violations of instrumental variable assumptions, we employed complementary methods including weighted median estimation, which can yield consistent estimates even if up to 50% of instruments are invalid, and MR-Egger methods. Pleiotropy refers to a genetic variant influencing the outcome through pathways other than the exposure of interest. Specifically, horizontal pleiotropy can bias causal estimates. The MR-Egger intercept test was thus used to detect such directional pleiotropy, with a significant non-zero intercept indicating potential bias. To assess the consistency of causal estimates across instruments, This study is among the was employed to quantify heterogeneity among SNP-specific effects. A significant Q statistic suggests that some SNPs may violate MR assumptions, potentially due to pleiotropy or invalid instruments. Additionally, funnel plots were generated to visually examine the symmetry of SNP effect estimates, helping to identify potential directional biases. All statistical analyses were performed using R software (version 4.3.3), primarily utilizing the TwoSampleMR package.

Results

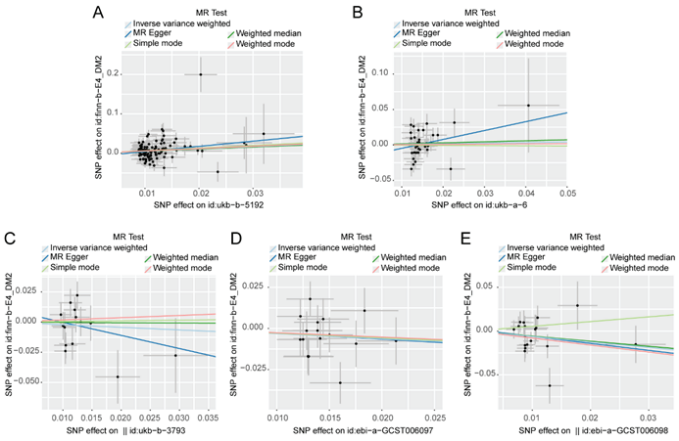
Forward MR Analysis: Causal Effects of LSB and PA on T2D

MR results indicate a significant causal effect between television watching and T2D. Using the IVW method, the OR was 1.760 (95% CI: 1.313–2.359, P < 0.001), supported by the weighted median method (OR = 1.690, P = 0.001). Although MR Egger, simple mode, and weighted mode methods did not yield statistically significant results, the effect directions were largely consistent. In contrast, computer use was not significantly associated with T2D across any method (IVW OR = 1.087, P = 0.684). Similarly, driving showed no significant causal relationship with T2D (IVW OR = 0.806, P = 0.545). For physical activity traits, MVPA exhibited a non-significant negative association (IVW OR = 0.729, P = 0.122), while VPA showed borderline significance (IVW OR = 0.535, P = 0.080),

Table 2. MR Results (Forward Analysis)

Exposure	Outcome	MR Method	Number of SNPs	OR	95% CI (Lower)	95% CI (Upper)	P-value
Television watching	T2D	MR Egger	105	3.735	0.885	15.764	0.076
		Weighted median	105	1.690	1.240	2.304	0.001
		IVW	105	1.760	1.313	2.359	<0.001
		Simple mode	105	1.936	0.891	4.205	0.098
		Weighted mode	105	1.822	0.959	3.462	0.070
Computer use	T2D	MR Egger	33	3.491	0.257	47.346	0.355
		Weighted median	33	1.157	0.773	1.730	0.478
		IVW	33	1.087	0.728	1.623	0.684
		Simple mode	33	0.971	0.383	2.465	0.951
		Weighted mode	33	1.037	0.462	2.329	0.930
Driving	T2D	MR Egger	14	0.336	0.012	9.547	0.535
		Weighted median	14	0.977	0.431	2.214	0.955
		IVW	14	0.806	0.401	1.620	0.545
		Simple mode	14	1.055	0.221	5.033	0.947
		Weighted mode	14	1.202	0.287	5.036	0.805
MVPA	T2D	MR Egger	17	0.697	0.043	11.342	0.803
		Weighted median	17	0.730	0.432	1.232	0.238
		IVW	17	0.729	0.489	1.088	0.122
		Simple mode	17	0.750	0.282	1.995	0.573
		Weighted mode	17	0.768	0.305	1.935	0.583
VPA	T2D	MR Egger	18	0.451	0.045	4.531	0.508
		Weighted median	18	0.560	0.232	1.353	0.198
		IVW	18	0.535	0.266	1.077	0.080
		Simple mode	18	1.719	0.331	8.927	0.528
		Weighted mode	18	0.450	0.131	1.540	0.220

T2D, Type 2 diabetes; IVW, Inverse variance weighted; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.



SNP, single-nucleotide polymorphisms; T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Figure 1. *Scatter plots for television watching on T2D (A), computer use on T2D (B), driving on T2D (C), MVPA on T2D (D), VPA on T2D (E).*

suggesting that this may play a potential protective role. Detailed estimates are presented in Table 2 and visualized in Figure 1.

Reverse MR Analysis: Causal Effects of T2D on LSB and PA

We evaluated the reverse causal effects of T2D on LSB and PA traits. Overall, no significant associations were found. For television watching, the IVW method yielded an OR of 1.003 (95% CI: 0.995–1.012, P = 0.449), consistent with MR Egger and weighted median estimates. Although Simple mode indicated a modest inverse effect (OR = 0.977, P = 0.034), this method is generally less robust and should be interpreted with caution. Computer use and driving showed no significant causal effect across all methods (P > 0.3). For PA, T2D was negatively associated with MVPA using the weighted median method (OR = 0.985, P = 0.009); however, the IVW and MR Egger results were not statistically significant. No significant effects were observed for VPA. In summary, genetically predicted T2D does not appear to causally influence LSB or PA traits, as shown in Table 3 and Figure 2.

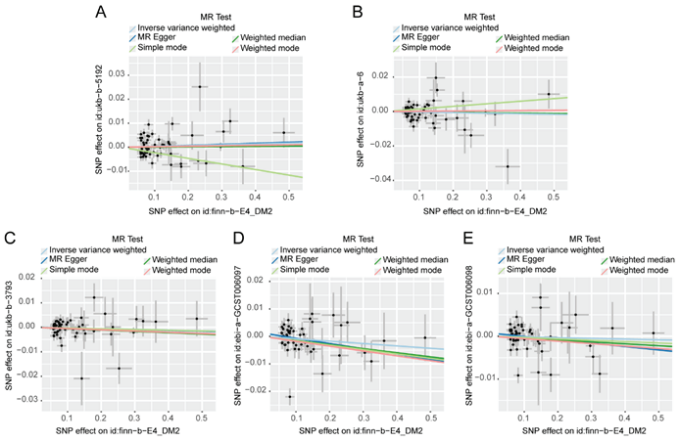
Sensitivity Analyses

To assess the reliability of both forward and reverse MR models, we conducted tests for heterogeneity and horizontal pleiotropy. In the forward MR analysis, Cochran's Q test

Table 3. MR Results (Reverse Analysis)

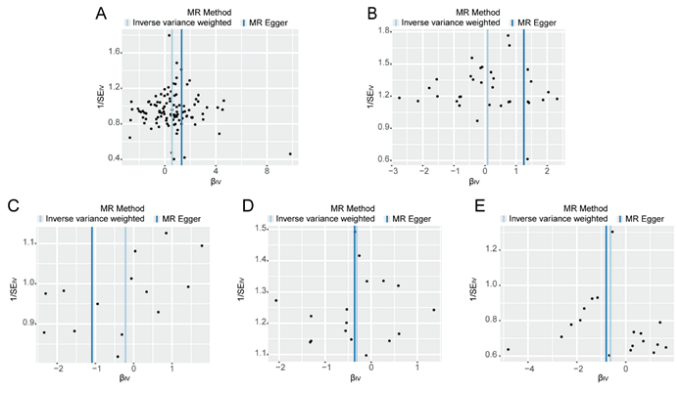
Exposure	Outcome	MR Method	Number of SNPs	OR	95% CI (Lower)	95% CI (Upper)	P-value
Television watching	T2D	MR Egger	58	1.004	0.986	1.023	0.651
		Weighted median	58	1.001	0.991	1.011	0.867
		IVW	58	1.003	0.995	1.012	0.449
		Simple mode	58	0.977	0.957	0.998	0.034
		Weighted mode	58	1.002	0.992	1.012	0.688
Computer use	T2D	MR Egger	56	0.997	0.977	1.018	0.799
		Weighted median	56	0.998	0.985	1.011	0.725
		IVW	56	0.997	0.987	1.007	0.512
		Simple mode	56	1.015	0.987	1.044	0.305
		Weighted mode	56	1.001	0.987	1.016	0.857
Driving	T2D	MR Egger	58	0.997	0.984	1.010	0.611
		Weighted median	58	0.994	0.985	1.004	0.269
		IVW	58	0.997	0.991	1.003	0.364
		Simple mode	58	0.997	0.979	1.016	0.753
		Weighted mode	58	0.995	0.984	1.006	0.373
MVPA	T2D	MR Egger	58	0.981	0.962	1.001	0.067
		Weighted median	58	0.985	0.974	0.996	0.009
		IVW	58	0.991	0.982	1.001	0.082
		Simple mode	58	0.984	0.960	1.009	0.207
		Weighted mode	58	0.983	0.970	0.995	0.008
VPA	T2D	MR Egger	58	0.992	0.981	1.004	0.182
		Weighted median	58	0.996	0.989	1.002	0.191
		IVW	58	0.998	0.993	1.004	0.552
		Simple mode	58	0.997	0.983	1.010	0.646
		Weighted mode	58	0.994	0.986	1.003	0.183

T2D, Type 2 diabetes; IVW, Inverse variance weighted; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.



SNP, single-nucleotide polymorphisms; T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Figure 2. *Scatter plots for T2D on television watching (A), T2D on computer use (B), T2D on driving (C), T2D on MVPA (D), T2D on VPA (E). .*



T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Figure 3. *Funnel plot of the causal relationship between television watching on T2D (A), computer use on T2D (B), driving on T2D (C), MVPA on T2D (D), VPA on T2D (E).*

Table 4. Heterogeneity and Horizontal Pleiotropy (Forward Analysis)

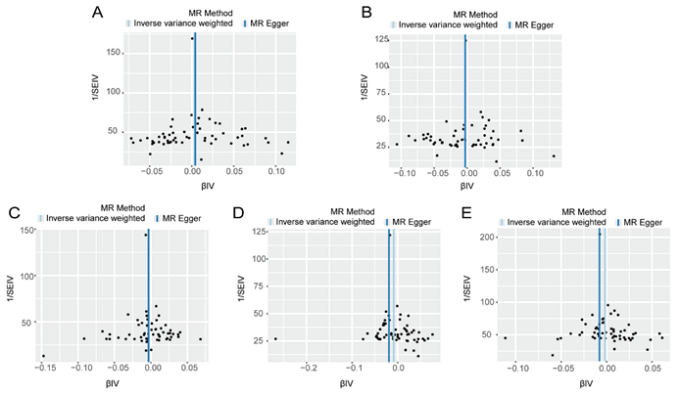
Variable		Heterogeneity				Horizontal Pleiotropy	
		MR Egger		IVW		MR-Egger	
Exposure	Outcome	Q-value	P-value	Q-value	P-value	Intercept	P-value
Television watching	T2D	227.783	<0.001	230.203	<0.001	0.009	0.298
Computer use	T2D	70.536	<0.001	72.330	<0.001	0.017	0.381
Driving	T2D	21.381	0.050	21.870	0.060	0.011	0.610
MVPA	T2D	17.568	0.286	17.570	0.350	0.001	0.975
VPA	T2D	23.592	0.099	23.627	0.130	0.002	0.880

T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Table 5. Heterogeneity and Horizontal Pleiotropy (Reverse Analysis)

Variable		Heterogeneity				Horizontal Pleiotropy	
		MR Egger		IVW		MR-Egger	
Exposure	Outcome	Q-value	P-value	Q-value	P-value	Intercept	P-value
T2D	Television watching	178.292	<0.001	178.327	<0.001	0.000	0.917
T2D	Computer use	109.840	<0.001	109.848	<0.001	0.000	0.952
T2D	Driving	61.577	0.283	61.585	0.315	0.000	0.931
T2D	MVPA	108.130	<0.001	110.760	<0.001	0.001	0.248
T2D	VPA	97.845	<0.001	100.422	<0.001	0.001	0.230

T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.



T2D, Type 2 diabetes; MVPA, Moderate to vigorous physical activity; VPA, Vigorous physical activity.

Figure 4. *Funnel plot of the causal relationship between T2D on television watching (A), T2D on computer use (B), T2D on driving (C), T2D on MVPA (D), T2D on VPA (E)..*

indicated significant heterogeneity in the associations between television watching and T2D (MR Egger Q = 227.783; IVW Q = 230.203), as well as between computer use and T2D (Q = 70.536 and 72.330, respectively; all P < 0.001), suggesting inconsistency among the genetic instruments. In contrast, no significant heterogeneity was observed for driving, MVPA, or VPA, indicating greater consistency in SNP effects across these models. The MR-Egger intercepts were non-significant for all traits (all P > 0.05); for instance, the intercept for television watching was 0.009 (P = 0.298), suggesting the absence of directional pleiotropy and supporting the validity of the forward MR models (Table 4). The funnel plot displayed a symmetric distribution of SNPs, underscoring the relative stability of the results (Figure 3).

In the reverse MR analysis, significant heterogeneity was observed for T2D in relation to television watching, computer use, MVPA, and VPA (all P < 0.001), while no heterogeneity was detected in the T2D on driving model (Q = 61.577, P = 0.283). All MR-Egger intercepts in reverse models were non-significant; for example, the intercept for T2D on television watching was 0.000 (P = 0.917), indicating no evidence of horizontal pleiotropy. Although some models, particularly those involving television watching and computer use, exhibited heterogeneity, no evidence of directional pleiotropy was found in either forward or reverse pathways (Table 5). The funnel plot displayed a symmetric distribution of SNPs, underscoring the relative stability of the results (Figure 4). Overall, these results support the methodological validity and relative robustness of the MR models used in this study.

Discussion

T2D is a globally prevalent metabolic disorder strongly associated with adverse lifestyle factors, particularly sedentary behavior and insufficient physical activity [14,15]. Although numerous observational studies have suggested that sedentary behavior may increase T2D risk while physical activity offers protective benefits, the causal interpretation of such findings remains limited due to potential confounding and reverse causality [16]. In this study, we employed a bidirectional two-sample MR approach to systematically evaluate the causal effects of three specific leisure sedentary behaviors (television watching, computer use, and driving) and two types of physical

activity (MVPA and VPA) on T2D from a genetic perspective. Our aim was to provide more robust evidence to inform primary prevention strategies for diabetes.

Our study revealed that television watching was causally associated with increased risk of T2D across multiple MR methods, suggesting that sedentary leisure behavior may play a direct role in diabetes pathogenesis. In contrast, no significant causal effects were observed for computer use or driving. Regarding physical activity, while MVPA showed no significant effect, VPA exhibited a consistent inverse association trend, indicating a potential preventive benefit. Reverse MR analysis found no evidence that T2D causally influences sedentary behavior or activity levels, supporting a unidirectional pathway from behavior to disease. Notably, this study evaluate distinct LSB subtypes, highlighting behavioral heterogeneity in T2D risk profiles.

The observed causal relationship between television watching and increased T2D risk may be explained by a combination of metabolic and behavioral mechanisms. On one hand, prolonged sedentary behavior reduces skeletal muscle energy expenditure and suppresses insulin signaling pathways, thereby promoting insulin resistance and impairing glucose metabolism [16-18]. On the other hand, television viewing is often accompanied by unhealthy lifestyle factors such as excessive caloric intake, delayed meal timing, and poor sleep quality, all of which synergistically exacerbate glucose dysregulation [19]. In contrast, VPA has been shown to significantly enhance glucose uptake and insulin sensitivity by activating signaling pathways such as AMPK and GLUT4, and by improving mitochondrial function and reducing inflammation [20-22]. These mechanisms may underlie the inverse association trend observed for VPA in our study and provide biological plausibility for the genetic evidence supporting a causal link.

Our findings are broadly consistent with previous observational studies in terms of directionality, but offer stronger evidence for causality. Numerous prospective cohort studies have demonstrated a positive association between sedentary behavior, particularly television viewing, and the risk of developing T2D [23,24]. For example, Grøntved et al. reported that each additional two hours of television viewing per day was associated with a 20% increase in T2D risk (RR = 1.20, 95% CI:1.14-1.27), with a clear linear dose-response relationship [25]. Increasing physical activity has been shown to substantially mitigate this risk. Several prospective studies have reported that replacing sedentary time with physical activity can significantly reduce mortality and metabolic disease risk. Zhu et al. found that in individuals with prediabetes or T2D, replacing 30 minutes of sedentary time with light or moderate-to-vigorous physical activity (LPA/MVPA) reduced all-cause mortality by 9-40% [26]. Similarly, Swindell et al. showed that such substitutions improved cardiometabolic biomarkers [27]. These findings underscore that both light and more intense physical activity are beneficial for reducing the risk of T2D, highlighting the importance of reducing sedentary behaviors, particularly television viewing, as a key component of lifestyle interventions. Unlike conventional observational studies that are susceptible to confounding and reverse causality, our study employed a Mendelian randomization framework, providing more robust evidence for causality from a genetic perspective.

This study has several methodological strengths. First, a bidirectional two-sample MR design was employed to systematically evaluate the causal relationship between LSB, PA, and T2D in both directions, effectively minimizing confounding and reverse causality. Second, LSB was disaggregated into specific behavioral subtypes for MR analysis, allowing us to uncover heterogeneous effects of different sedentary patterns on T2D risk. Third, the results were validated using multiple analytical methods, and sensitivity analyses further supported the robustness of the findings.

However, this study also has several limitations. First, the exposure variables were primarily based on self-reported behavioral data, which may be subject to recall bias and measurement error, potentially weakening the validity of the genetic instruments. Second, although no significant directional pleiotropy was detected in sensitivity analyses, the possibility of residual unmeasured pleiotropy cannot be entirely ruled out. Third, all GWAS summary statistics used in this study were derived from individuals of European ancestry, which may limit the generalizability of our findings to other ethnic populations. Future research involving objective measurements of behavioral traits and more ethnically diverse cohorts is warranted to validate these causal associations.

In conclusion, this study provides the first genetic evidence supporting the potential causal roles of specific leisure sedentary behaviors and vigorous physical activity in the development of type 2 diabetes. Our findings suggest that television watching is a clear risk factor for T2D, while vigorous physical activity may offer protective benefits. Other LSB subtypes and MVPA showed no significant causal effects. These results extend our understanding of the behavioral etiology of T2D and offer causal support for behavioral interventions aimed at primary prevention. Future research should examine these associations across different populations, age groups, and sexes, ideally incorporating objective activity measurements to improve precision and translational relevance.

Availability of data and materials

All data from the website: https://gwas.mrcieu.ac.uk.

Conflict of Interest

All authors declared that they have no conflicts of interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Acknowledgements

Not applicable.

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