Genetic predisposition to television watching increases the risk of type 2 diabetes: a bidirectional and multivariable Mendelian randomization study

Songzan Chen
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Fangkun Yang
Zhejiang University School of Medicine Second Affiliated Hospital
Tian Xu
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Yao Wang
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Kaijie Zhang
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Guosheng Fu
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Wenbin Zhang (3313011@zju.edu.cn)
Department of Cardiovascular Diseases, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University. https://orcid.org/0000-0003-4746-9570

Original investigation

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Abstract

Background: Excessive sedentary behaviors have been reported to be associated with increased risk of type 2 diabetes, but whether this association is causal remains unclear. In current study, we aimed to investigate the causal association between domain-specific sedentary behaviors and the risk of type 2 diabetes using a two-sample Mendelian randomization (MR) study.

Methods: We identified 165 single nucleotide polymorphisms as instrumental variables for television watching, 43 for computer use and 5 for driving behavior from a recently published genome-wide association study (n = 408,815). Genetic association estimates for type 2 diabetes were obtained from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium (74,124 cases and 824,006 controls). The inverse variance-weighted method was used to estimate the effect of genetically predicted sedentary behaviors on the risk of type 2 diabetes. Reverse MR analysis was performed to investigate the reverse causation. The weighted median method, MR-Egger method, and MR Pleiotropy Residual Sum and Outlier method were employed in the sensitivity analyses. In addition, multivariable MR analysis and mediation analysis were conducted to explore the potential mechanistic elements.

Results: Genetic predisposition to excessive television watching was associated with increased risk of type 2 diabetes. The OR (95% CI) per 1.5h (1 standard deviation) increment in television watching time was 1.82 (1.61, 2.07) for type 2 diabetes. This association was substantially attenuated after adjustment for anthropometric traits (adjusting BMI: OR = 1.35, 95% CI = 1.17 – 1.57, $P = 4.1 \times 10^{-5}$; adjusting WHR: OR = 1.26, 95% CI = 1.09 – 1.45, $P = 1.4 \times 10^{-3}$) and educational attainment (OR = 1.49, 95% CI = 1.16 – 1.91, $P = 1.7 \times 10^{-3}$). There was limited evidence of associations of computer use and driving behavior with the risk of type 2 diabetes.

Conclusions: Our study clarifies the causal effect of excessive television watching on the increased risk of type 2 diabetes from a genetic perspective, which may be partly mediated via anthropometric and educational traits. Television watching may serve as a behavioral target to prevent incident diabetes.

Background

Over the past few decades, the epidemic of type 2 diabetes has been escalating world-wide.[1] It is currently estimated that over 350 million people world-wide suffer from this disease, and it will rise to 600 million by 2035.[2] The epidemic of type 2 diabetes and its complications pose a major global human health threat, making disease prevention an important priority.[3] A sedentary lifestyle has been reported to be one of the main drivers of type 2 diabetes, which is modifiable by intervention.[1] Accumulated evidence in prior observational studies have indicated prolonged sedentary time is associated with obesity,[4–6] metabolic syndrome,[7–9] as well as type 2 diabetes.[10–13] In addition, favorable metabolic outcomes might be obtained by reducing sedentary time, such as improved glucose tolerance.[14] However, despite this large body of evidence for the association between leisure time spent

on sedentary behaviors and the risk of type 2 diabetes, whether this association is causal remains unclear.

Mendelian randomization (MR) is a method to address the lifetime causal effect of the exposure on the outcome in observational studies that utilizes genetic variants associated with the exposure as instrumental variables (IVs) for the exposure.[15] MR can overcome some of the limitations of conventional observational studies such as bias of confounding and reverse causation.[16] Therefore, we are using MR approach to investigate whether there is evidence for a causal association between domain-specific sedentary behaviors and the risk of type 2 diabetes.

Methods

Study design

A two-sample MR study was designed to investigate the causal association between domain-specific sedentary behaviors and the risk of type 2 diabetes. The unbiased causality could be estimated if the following three assumptions were fulfilled (Fig. 1): (1) the genetic instrumental variables (IVs) were strongly associated with the exposure concerned; (2) the IVs were independent of any possible confounders; (3) the IVs influenced the outcome only via the exposure.[15] In addition to forward association, reverse MR analysis was also performed to explore the reverse causation. Subsequently, sensitivity analyses were conducted to assess the robustness of the primary results. Finally, to address any mechanistic elements of the association between sedentary behaviors and the risk of type 2 diabetes, additional multivariable MR analysis and mediation analysis were performed.

Data Sources

An overview of the data sources was shown in Table 1. The genetic data for sedentary behaviors were obtained from a recently published genome-wide association study (GWAS) with a total of 408,815 individuals of European ancestry form UK Biobank.[17] In that study, three phenotypes of sedentary behaviors were included: leisure television watching, leisure computer use and driving. The mean daily reported time for each sedentary behavior was 2.8 h (SD 1.5), 1.0 h (SD 1.2) and 0.9 h (SD 1.0), respectively.[17] The genetic data for type 2 diabetes were obtained from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium including 74,124 cases and 824,006 controls of European ancestry.[18] Summary statistics for physical activity were obtained from a prior GWAS of 91,105 European-descent participants from UK Biobank.[19] Summary statistics for body mass index (BMI) and waist-to-hip ratio (WHR) were obtained from a recently published GWAS meta-analysis for body fat distribution in 694,649 participants of European ancestry.[20] Summary statistics for educational attainment were obtained from Social Science Genetic Association Consortium (SSGAC), which included 1,131,881 individuals of European ancestry.[21] Summary statistics for systolic blood pressure (SBP) were obtained from a previously published GWAS meta-analysis of 757,601 individuals of European ancestry.[22] Summary statistics for smoking and drinking were obtained from a meta-analysis

of 1.2 million European-descent individuals.[23] All the original studies that provided data for our analyses had received ethics approval, and all participants had provided written informed consent.

Table 1
Overview of the datasets used for analyses.

Exposure/Outcome	Number of cases	Number of controls	Population	GWAS
Television watching	NA	408,815	European	van de Vegte YJ et al.[17]
Computer use				
Driving behavior				
Type 2 diabetes	74,124	824,006	European	Mahajan A et al.[18]
Physical activity	NA	91,105	European	Doherty A et al.[19]
Body mass index	NA	694,649	European	Pulit SL et al.[20]
Waist-to-hip ratio				
Educational attainment	NA	1,131,881	European	Lee JJ et al.[21]
Systolic blood pressure	NA	757,601	European	Evangelou E et al.[22]
Smoking	NA	1.2 million	European	Liu M et al.[23]
Drinking				

GWAS, genome-wide association study; NA, not available.

IV Selection

IV selection for sedentary behavior and type 2 diabetes was based on the corresponding GWAS summary dataset. To ensure the strong associations between IVs and exposure, single nucleotide polymorphisms (SNPs) that met the genome-wide statistical significance threshold ($P < 5 \times 10^{-8}$) were proposed as IVs for exposure. The pairwise-linkage disequilibrium (LD) was checked using LD-Link based on European.[24] The SNP was dropped when it was not available in the outcome dataset. In total, 165 SNPs were identified as IVs for leisure television watching, 45 for leisure computer use, 4 for driving behavior, and 238 for type 2 diabetes, respectively. The F statistics for each SNP was larger than 10, and the detailed information for IVs was presented in Table S1-S4.

Statistical analysis

Primary MR analysis

The inverse variance-weighted (IVW) method was used to estimate the effect of genetically predicted sedentary behaviors on the risk of type 2 diabetes. To do this, Wald ratio of each SNP was calculated and the relevant standard error (SE) was estimated using the Delta method. Subsequently, the overall estimate was generated by meta-analyzing each Wald ratio using the IVW method.[25] In addition to forward analysis, reverse MR analysis was also performed to estimate the effect of genetically predicted type 2 diabetes on these sedentary behaviors.

Sensitivity Analysis And Pleiotropy Assessment

The weighted median method,[26] MR-Egger method,[27] and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method[28] were employed in the follow-up sensitivity analyses. The weighted median method could provide valid estimates if at least 50% of the weight came from valid SNPs.[26] The MR-Egger method and MR-PRESSO method could detect and correct for the potential pleiotropy and outliers, respectively.[27, 28] Moreover, a leave-one-out analysis was implemented to determine whether the overall estimate was disproportionately affected by a single SNP. In addition, funnel plot was generated to visually inspect the pleiotropic effect, in which symmetry indicated no evidence of pleiotropy.[29]

Multivariable MR Analysis And Mediation Analysis

The results for association between of sedentary behaviors and potential confounding or mediating traits were presented in Table S6. The results for association between television watching and the risk of type 2 diabetes after adjustment for potential confounder or mediator were presented in Table 2. Adjusting the physical activity, SBP, smoking and drinking did not have a large effect on the estimate, respectively. By contrast, adjusting BMI or WHR substantially attenuated the relationship between television watching and the risk of type 2 diabetes (adjusting BMI: OR = 1.35, 95% CI = 1.17–1.57, $P = 4.1 \times 10^{-5}$; adjusting WHR: OR = 1.26, 95% CI = 1.09–1.45, $P = 1.4 \times 10^{-3}$). In addition, this association was also attenuated after adjusting the educational attainment (OR = 1.49, 95% CI = 1.16–1.91, $P = 1.7 \times 10^{-3}$). Mediation analysis indicated that the association between television watching and the risk of type 2 diabetes was partially mediated by BMI (proportion mediated = 50%, 95% CI = 24% − 75%) or WHR (proportion mediated = 62%, 95% CI = 22% − 101%), also this association was partially explained by the educational attainment (proportion mediated = 34%, 95% CI = 12% − 57%).

Table 2
Multivariable Mendelian randomization analysis of the association between television watching and type 2 diabetes.

Adjusted factor	OR (95% CI)	*P*
Physical activity	1.84 (1.62, 2.09)	1.2E-20
Body mass index	1.35 (1.17, 1.57)	4.1E-05
Waist-to-hip ratio	1.26 (1.09, 1.45)	1.4E-03
Educational attainment	1.49 (1.16, 1.91)	1.7E-03
Systolic blood pressure	1.76 (1.55, 2.00)	7.3E-18
Smoking	1.76 (1.54, 2.00)	3.3E-17
Drinking	1.78 (1.57, 2.02)	2.7E-19
All the above	1.12 (0.93, 1.46)	0.20

OR, odds ratio; CI, confidence interval.

Results

Sedentary behaviors and risk of type 2 diabetes

The MR analysis results for association between sedentary behaviors and the risk of type 2 diabetes were presented in Fig. 2. In brief, prolonged genetically predicted television watching time was significantly associated with increased risk of type 2 diabetes (odds ratio (OR) = 1.82, 95% confidence interval (CI) = 1.61–2.07, $P = 3.2 \times 10^{-21}$, using the IVW method). However, it was not the case for computer use and driving behavior. In the sensitivity analyses, similar results were observed for television watching (except the MR-Egger analysis) and computer use, while the results for driving behavior were inconsistent. The leave-one-out analyses indicated that the overall estimate was not disproportionately driven by any specific SNP (Figure S1-S3). The almost symmetrical graphics in the funnel plots suggested no evidence of pleiotropy in the primary analysis (Figure S4-S6). The statistical power for television watching and driving behavior was strong, while it was relevantly limited for computer use (Table S5).

The results for reverse association between sedentary behaviors and the risk of type 2 diabetes were presented in Fig. 3. Though type 2 diabetes was significantly associated with prolonged time of television watching and driving behavior using the IVW method, it was inconsistent in the sensitivity analyses. No significant association of type 2 diabetes with computer use was observed in the MR analyses.

Discussion

To the best of our knowledge, this is the first study using the MR method to investigate the potential causal association between domain-specific sedentary behaviors and the risk of type 2 diabetes. Our study clarified the directionality of the association between television watching and type 2 diabetes, supporting that prolonged television watching time increases the risk of type 2 diabetes. However, no evidence was observed for the association of computer use and driving behavior with the risk of type 2 diabetes. Furthermore, our study suggested that the association between television watching and the risk of type 2 diabetes may be mainly mediated by BMI or WHR and partially explained by educational attainment.

Our findings are in line with the results of previous studies, which also suggested that prolonged time spent on television watching was a risk factor of type 2 diabetes. For instance, an American prospective cohort study with 68,497 women, 6 years of fellow-up and adjustment for other covariates indicated that each 2 hours per day increment in television watching was associated with a 14% increased risk for type 2 diabetes.[34] In addition, another European study with 23,855 individuals and 7.8 years of follow-up found that the amount of time spent on television watching was positively associated with incident diabetes, but this association was largely attenuated after adjusting for anthropometric measures.[35] Furthermore, one cross-sectional study conducted among older people suggested that excessive television watching was associated with higher risk of type 2 diabetes (OR = 1.56, 95% CI = 1.10–2.21), but this was not the case for other domain-specific sedentary behaviors including computer use and transport.[36]

Actually, television watching is the most commonly used proxy for sedentary behavior in observational studies, as it is easier to recall and shows considerable accuracy.[37, 38] In addition, television is almost solely performed at home, which is more modifiable by intervention.[39, 40] Based on our findings and previous literature, several hypotheses have been put forward as to why prolonged television watching seems to increase the risk of type 2 diabetes. A commonly acknowledged mechanism is that excessive television watching increases obesity, a major risk factor for type 2 diabetes. Specifically, long-term leisure television watching is related to a lower expenditure of energy, as well as a higher energy intake and a relatively unhealthy dietary pattern, leading to obesity and weight gain, which in turn increases the risk of type 2 diabetes.[41–43] Our study found that the association between television watching and the risk of type 2 diabetes attenuated larger when adjusting WHR than BMI, which suggested that abdominal obesity might be a more proper mechanistic element for this association. Second, since physical activity was an established protective factor for type 2 diabetes, several studies suggested that the association between television watching and type 2 diabetes may be explained by lack of physical activity.[44, 45] However, some other studies indicated poor correlation between television watching and physical activity, supporting that television watching was associated with type 2 diabetes independently of physical activity.[46, 47] Consistent with this finding, the association was little attenuated after adjustment for physical activity in our study. Third, the attenuation of the association between television watching and type 2 diabetes after adjustment for education attainment may represent another explanatory mechanism. In line with this, previous study indicated that higher educational attainment was negatively associated with incident diabetes.[48]

Previous studies have reported null association between computer use and the risk of type 2 diabetes.[36, 49] Energy expenditure for computer use might be greater than that for television watching.[50] Interestingly, negative association between computer use and type 2 diabetes was observed in our study though not significant. This potential association may be possibly explained by the confounding bias of television watching and educational attainment. First, in the original UK Biobank study, from which we obtained summary dataset, television watching was inversely correlated with computer use.[17] Second, significant association between computer use and educational attainment was observed in our study, and education was reported negatively related to incident diabetes in previous study.[48] Further studies are warranted to explore the nature association between computer use and type 2 diabetes.

The major strength of present study was the MR design, which could reduce the bias of confounding and reverse causation. In addition, bidirectional MR analysis and multivariable MR analysis was used to further minimize the bias of reverse causation and confounding, respectively. Mediation analysis was performed to investigate the proportion mediated via specific potential mediator. Another strength was the large sample sizes for the both data sources used for genetic associations with sedentary behaviors and the type 2 diabetes. A further strength was the large number of SNPs identified as IVs for television watching. This two together resulted in high precision of the results in our study. However, the estimates calculated by MR-Egger analysis were imprecise and must be interpreted with caution.

There were potential limitations to current study. First, the pleiotropic effect could not be completely ruled out, which was an established limitation to the MR analysis. However, symmetrical graphics were observed in the funnel plot, and robust results were observed in the analyses using multiple methods. In addition, multivariable MR analysis was used to adjust for other traits. Second, dietary energy and diet quality were not adjusted in our multivariable MR analysis, since the genetic association with dietary factors was not available. Dietary factor was a potential mediator for the association between television watching and type 2 diabetes, thus further studies are needed to determine the effect of dietary factors on this association. Third, the number of SNPs identified as IVs for computer use and driving behavior were relevantly small, which may lead to low power of the analyses. Thus, the corresponding results might be imprecise and must be interpreted with caution. Forth, because our study was limited to individuals of European ancestry, it was unclear whether our results could be generalized to other ancestral populations. Fifth, individual-level data were not available, which precluded us from the sex-specific analyses. Finally, we only clarified the association between sedentary behaviors with the risk of type 2 diabetes from a genetic perspective, further investigations are warranted.

Conclusions

In summary, this MR study found evidence for a causal association between prolonged television watching time and increased risk of type 2 diabetes, which was partially explained by educational attainment and obesity to a considerable extent. This finding may have public health and clinical implications as motivating individuals to decrease their pursuit of television watching can be part of the

comprehensive efforts to prevent incident diabetes. The importance of this topic is amplified by the ongoing sedentary epidemic around the world.

Abbreviations

MR: Mendelian randomization; IV: instrumental variable; GWAS: genome-wide association study; DIAGRAM: DIAbetes Genetics Replication And Meta-analysis; BMI: body mass index; WHR: waist-to-hip ratio; SSGAC: Social Science Genetic Association Consortium; SBP: systolic blood pressure; SNP: Single nucleotide polymorphism; LD: linkage disequilibrium; IVW: inverse variance-weighted; SE: standard error; MR-PRESSO: MR Pleiotropy Residual Sum and Outlier; OR: odds ratio; CI: confidence interval.

Declarations

Ethics approval and consent to participate

All the original studies that provided data for our analyses had received ethics approval, and all participants had provided written informed consent. No additional ethics approval was required since we only re-analyzed the publicly available data.

Consent for publication

Not applicable.

Availability of data and materials

All the datasets used in our study are publicly available; the summary statistics for sedentary behaviors can be downloaded from https://doi.org/10.17632/mxjj6czsrd.1; the summary statistics for type 2 diabetes can be downloaded from the DIAGRAM consortium website http://diagram-consortium.org/; the summary statistics for physical activity can be downloaded from https://doi.org/10.5287/bodleian:yjp6zzmdj; the summary statistics for BMI and WHR can be downloaded from https://github.com/lindgrengroup/fatdistnGWAS; the summary statistics for educational attainment can be downloaded from www.thessgac.org/data; the summary statistics for SBP can be downloaded from https://grasp.nhlbi.nih.gov/FullResults.aspx; the summary statistics for smoking and drinking can be downloaded from https://conservancy.umn.edu/handle/11299/201564. All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SC, FY and WZ designed the study, and wrote the analysis plan. SC, FY undertook analyses and all authors interpreted the results in the study. SC wrote the first draft of the manuscript with critical revisions from TX, YW and GF. All authors gave final approval of the version to be published.

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Figures

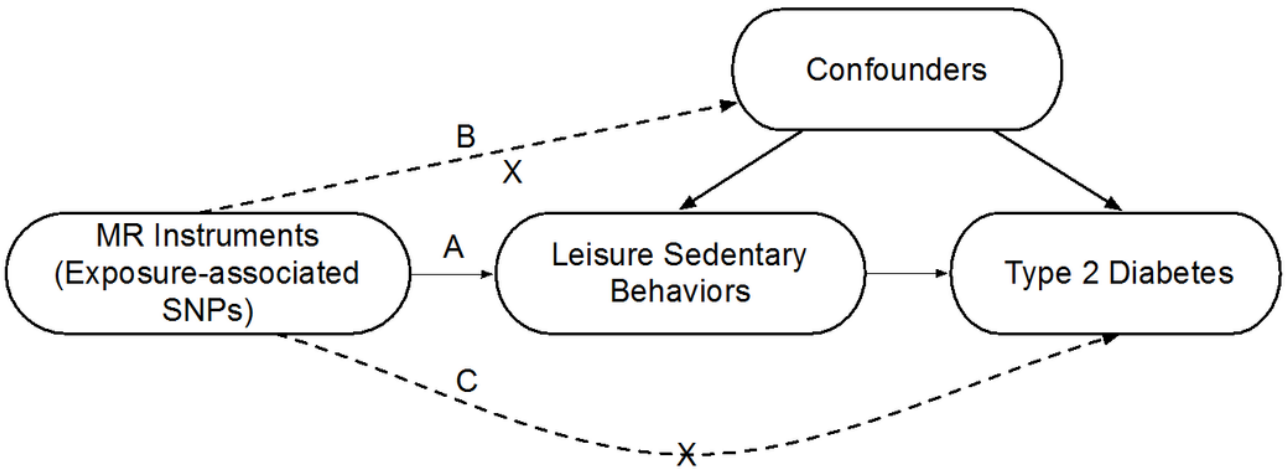

Figure 1

Schematic representation of the two-sample Mendelian randomization analysis of the association between leisure sedentary behaviors and type 2 diabetes. Three core assumptions are as follows: (A) the genetic instrumental variables (IVs) are strongly associated with the exposure; (B) the IVs are independent of any possible confounders; (C) the IVs influence the outcome only via the exposure.

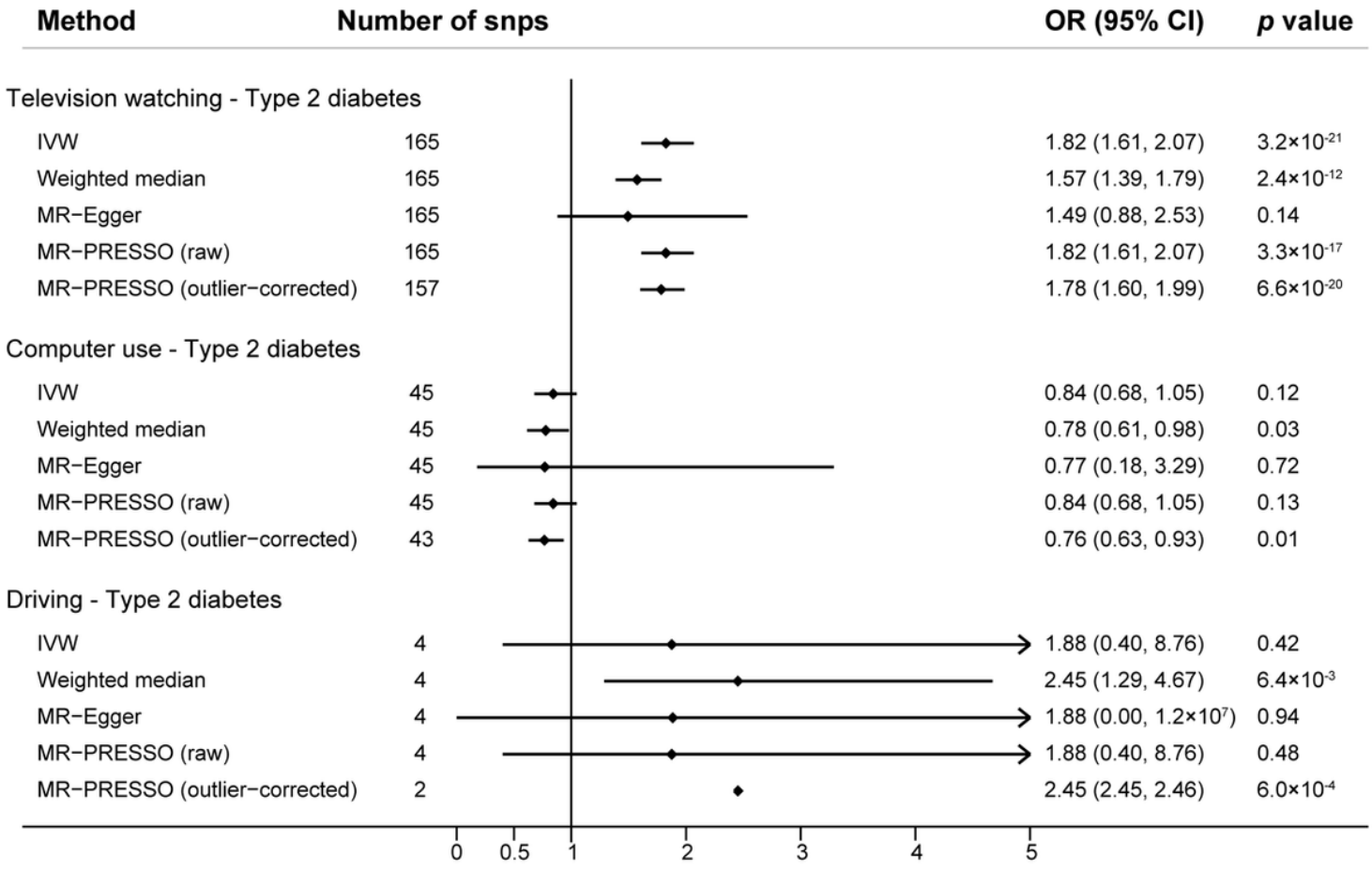

Figure 2

Summary Mendelian randomization estimates of the association of three types of sedentary behaviors with the risk of type 2 diabetes. OR, odds ratio; CI, confidence interval; IVW, inverse variance-weighted; MR, Mendelian randomization; MR-PRESSO, MR Pleiotropy Residual Sum and Outlier.

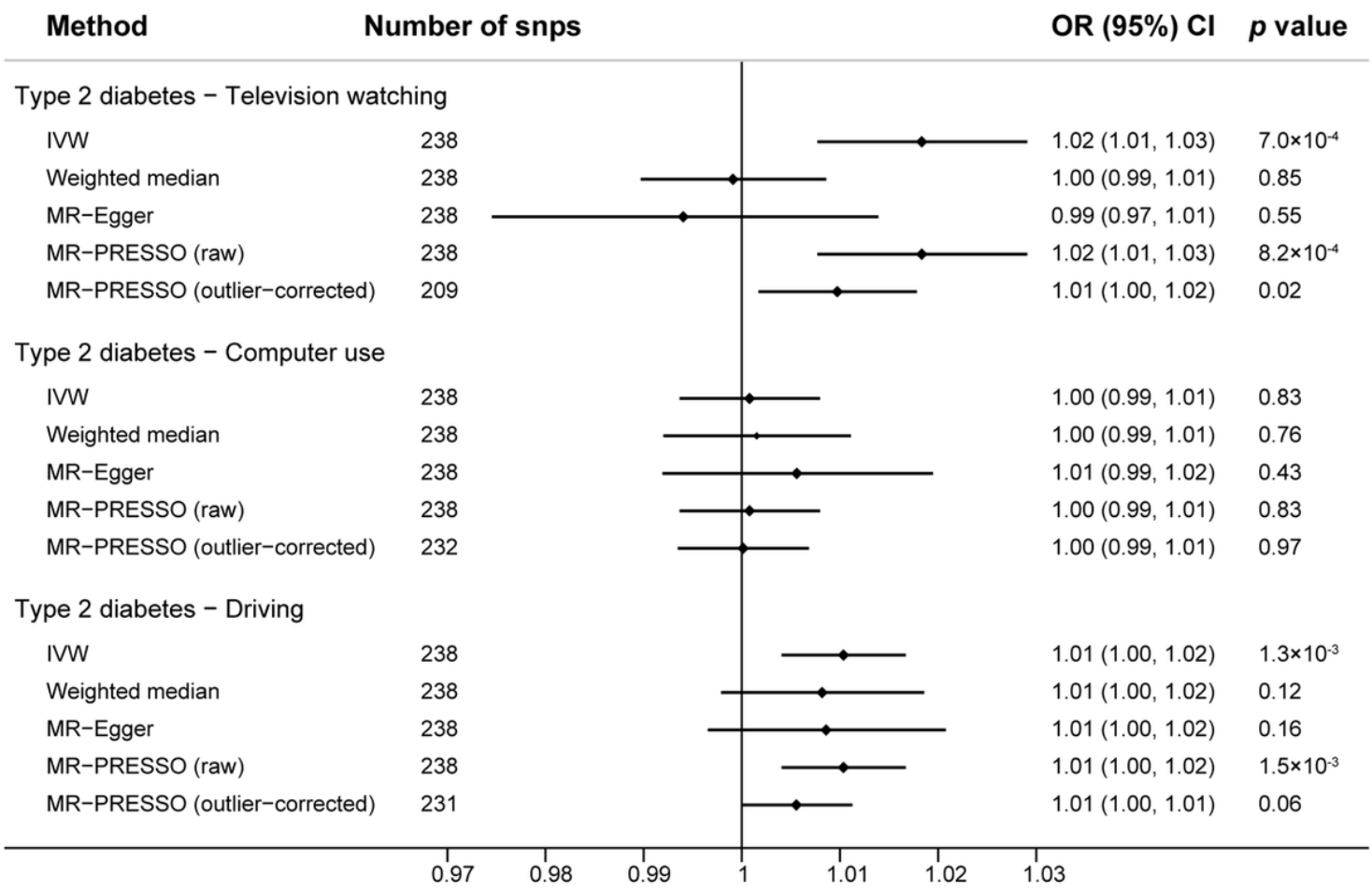

Figure 3

Summary Mendelian randomization estimates of the association of type 2 diabetes and three types of sedentary behaviors. OR, odds ratio; CI, confidence interval; IVW, inverse variance-weighted; MR, Mendelian randomization; MR-PRESSO, MR Pleiotropy Residual Sum and Outlier.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx