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Original Article

Physical Activity, Sedentary Behavior, and Osteoarthritis: A Two-Sample Mendelian Randomization Analysis

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Abstract

Background: Sedentary behavior and physical activity are still ambiguous in their effects on osteoarthritis. We aimed to evaluate the effects of physical activity and sedentary behavior on osteoarthritis to provide a reference for the prevention of osteoarthritis.

Methods: This study was conducted in Changchun, China in 2022. We used two-sample Mendelian randomization with the SNP as an instrumental variable to investigate the effect of physical activity and sedentary behavior on osteoarthritis. In addition, a two-step Mendelian randomization method was used to test whether mediating factors (BMI, smoking, Apolipoprotein B) were involved in mediating the effects of exposure factors on osteoarthritis.

Results: TV watching was causally related to knee osteoarthritis and spine osteoarthritis, and they were positively correlated (knee osteoarthritis: OR=1.162,95 %CI: 1.027-1.315, *P*=0.017; spine osteoarthritis: OR=1.208,95 %CI: 1.033-1.413, *P*=0.018). BMI played a mediating role in the process of TV watching with knee osteoarthritis and spine osteoarthritis. ((The proportion of BMI mediating effect: knee osteoarthritis: 47.1% (95% CI: 36.7%~63.2%); spine osteoarthritis: 29.5% (95% CI: 19.3%~40.8%)). The proportion of Smoking mediating effect in the process of TV watching with spine osteoarthritis was 16.1% (95% CI: 3.7% ~ 31.6%).

Conclusion: TV watching is a potential risk factor for osteoarthritis and plays a role through modifiable factors such as BMI and smoking, therefore, interventions on these factors have the potential to reduce the burden of osteoarthritis caused by longer TV watching times.

Keywords: Osteoarthritis; Sedentary behavior; Mendelian randomization; Lifestyle

Introduction

Arthritis is a disease characterized by joint pain, swelling, and restricted joint movement (1). Its global prevalence is high and there are many types, the most common of which is osteoarthri-

tis(OA) (2). OA mainly involves the hands, hips, and knees, and the risk of all-cause death in patients with hip and knee OA is too high, which brings a great burden to patients and society (3). At present, there is no radical treatment for OA (3), and the risk factors and preventive measures for osteoarthritis are still under study, and the pathogenesis of arthritis is still inconclusive(4), but changeable lifestyles such as physical activity and sedentary behavior may be important factors affecting OA(5).

Physical activity has long been regarded as a crucial component of overall bodily health. Exercise can lower the risk of metabolic illnesses and cardiovascular disorders. (6). In addition, physical activity is closely related to OA. Although some studies (7, 8) have shown the protective effect of physical activity in OA, other studies revealed the negative effects of exercise in promoting the development of OA. Sedentary behavior includes sedentary computer use, watching television, and driving (9). An increase in leisure and sedentary behavior is associated with a higher risk of mental illness (10) and cancer (11). There was a link between a sedentary lifestyle and symptomatic OA, as well as a correlation between the degree of sitting and the severity of the OA symptoms (12). Although there is evidence for a connection between physical activity and sedentary behavior and OA, it is unclear if this connection is causal. Moreover, the majority of studies are observational studies, provide the potential for bias due to confounders and reverse causality.

Mendelian randomization(MR) is one method that uses genetic variants to ascertain whether there is a causal relationship between risk factors and outcomes (13). Genetic variations are randomly assigned at conception, MR analysis can eliminate potential unmeasured confounders and reverse causality, which is a major drawback of observational study evidence (14). It incorporates genetic information into standard epidemiology and provides new ideas for studying the association between factors.

By utilizing Mendelian randomization analysis, this study sought to offer light on the potential correlation between physical activity, sedentary behavior, and OA in order to offer fresh insights into novel treatments and preventative strategies (15).

Methods and Design

Research design

Figure 1 shows the research design and MR hypothesis. Using GWAS summary data, a two-sample MR analysis was utilized in our study to investigate the causative relationships between physical activity, sedentary behavior and all OA, hand OA, hip OA, knee OA, and spine OA.

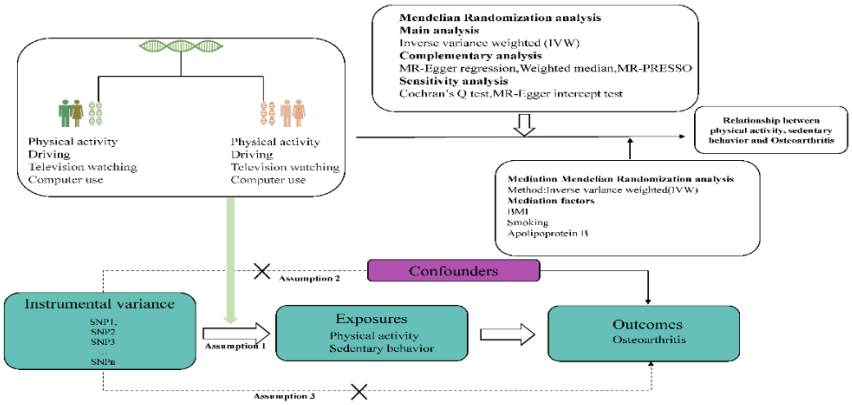

Fig.1: Overview and assumptions of the Mendelian randomization study design

In order to discuss the impacts of mediating variables, a two-step MR analysis was performed (BMI, Smoking, Apolipoprotein B). Mendelian randomized design must fulfill three assump-

tions: 1): instrumental variables are connected to exposure factors ($P<5\times10^{-8}$); 2) instrumental variables are independent of possible confounding factors; 3) Instrumental variables impact outcomes solely through exposure factors.

Data sources

Exposure

For physical activity, we used the latest GWAS data from the UK Biobank. Single Nucleotide Polymorphisms (SNPs) associated with self-reported moderate to severe physical activity (MVPA), accelerometer-based average physical activity (AccAve), and accelerometer-assessed fraction accelerations >425 milligravities (Acc425) were used as instrumental variables for physical activity. The self-reported moderate to severe physical activity data were derived from the GWAS summary data published by Klimentidis et al. (16), which included 377,234 European participants. The MVPA was calculated by multiplying the total number of minutes per week of moderate physical activity (MPA) by 4 and the total number of minutes per week of vigorous physical activity (VPA) by 8 to correspond to their metabolic equivalents. Data on average accelerometer-based physical activity (AccAve) and accelerometer-assessed fraction accelerations > 425 milligravities (Acc425) were derived from a prospective study of large-scale physical activity assessments conducted by Doherty A et al. The study was conducted on 500,000 subjects between the ages of 40 and 69, and finally received data on 103,712 subjects wearing Axivity AX3 triaxial accelerometers. Details on this PA phenotype can be found in the original article by Doherty Aiden et al. (17).

The data related to leisure sedentary behavior came from summary-level GWAS results based on previous publications (18) in the UK Biobank, including 422,218 European samples. The average daily TV watching, computer use, and driving time reported in the data were 2.8 hours (SD 1.5), 1.0 hours (SD 1.2), and 0.9 hours (SD 1.0), respectively.

Outcome

The phenotype of OA was divided into all OA, hand OA, hip OA, knee OA, and spine OA. The data on osteoarthritis is derived from the latest GWAS data of the Genetics of Osteoarthritis (GO) Consortium (19). The database contains 826,690 samples, including 177,517 patients with OA, all of which were European samples.

Mediator factors

Mediator GWAS data comes from the IEU GWAS database, where body mass index (BMI) data contains 461,460 samples, smoking GWAS data (20) contains 607,291 samples, and the Apolipoprotein B GWAS data (21) contains 439,214 European samples. The fundamental aspects of the relevant GWAS study and data sources are displayed in Supplementary Table 1 (Not published).

Selection of instrumental variables

The selection process of instrumental variables is shown in Fig. 2. According to the standard proposed by Martin Bahls et al. (22), we first select the genome-wide significant level of SNP($P<5\times10^{-8}$) (Since only 2 SNPs were associated with genome-wide activity with a significant acceleration fraction >425 milligrams, we set the threshold to a significant level $P<5\times10^{-7}$); Subsequently, the linkage disequilibrium was removed, and the genetic distance was set to 10000 kb, and the linkage disequilibrium parameter r^2 threshold=0.001; Third, a coordination process was undertaken to exclude ambiguous and palindromic SNP; Fourth: F statistics were used to evaluate whether the included SNPs were affected by weak instrumental variables, and if F<10, the corresponding SNPs were removed. Fifth: PhenoScanner V2 database (23) was used to further verify whether the above SNPs were associated with other confounding factors (BMI, smoking, apolipoprotein B). Finally, the included SNPs were subjected to MR analysis.

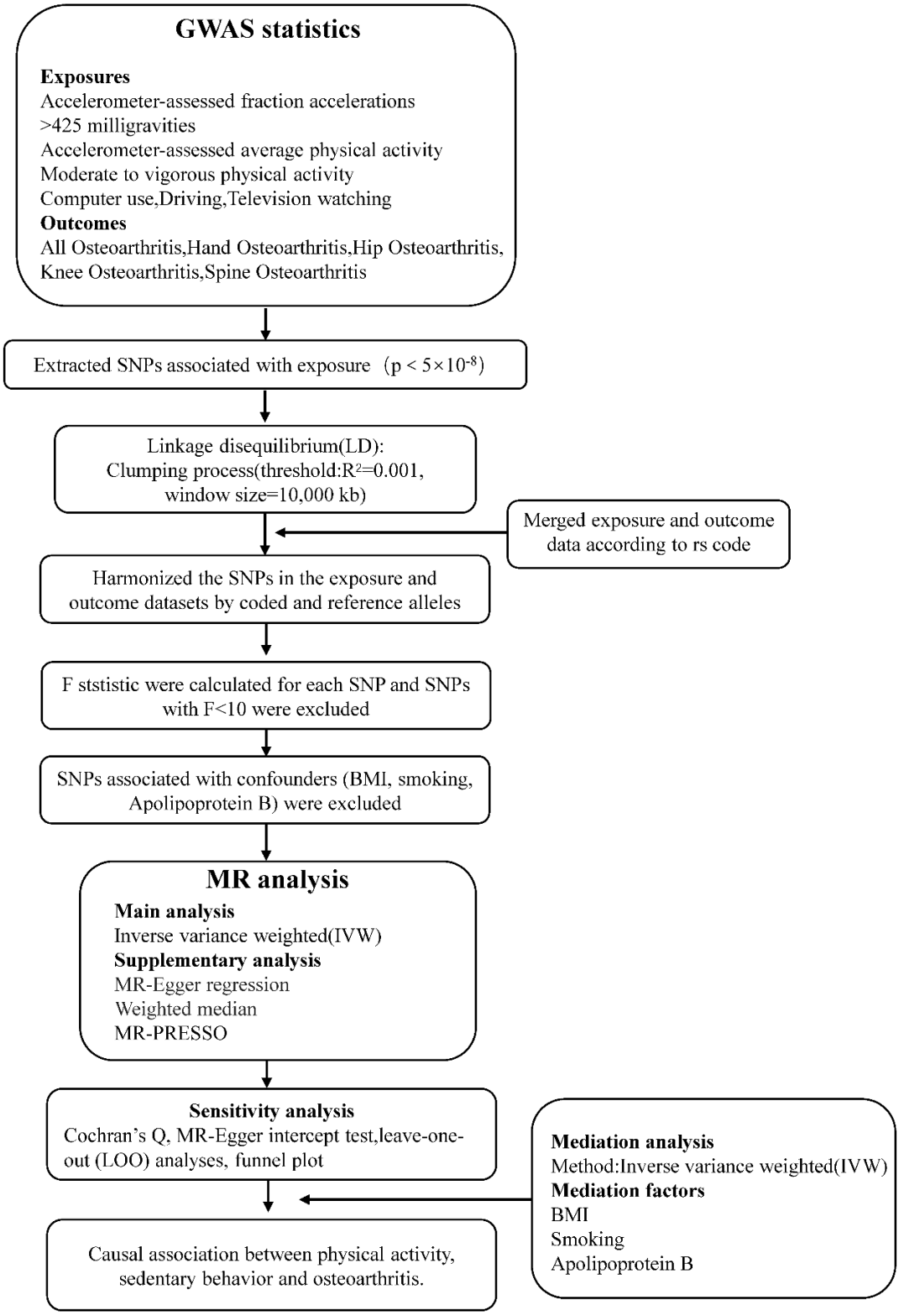

Fig. 2: Flow chart about the analytical methods and how the MR analysis was performed step-by-step

Statistical analysis

The major causal impact estimate in this research was calculated using the inverse variance weighting (IVW) method, which integrates the Wald ratio of each SNP to the outcome and accounts for overdispersion. MR-Egger regression and the weighted median estimator (WME) method can also be used in addition to IVW since they can generate more reliable estimates in a wider variety of circumstances. The MR-PRESSO method was utilized in this study to find outliers. The removal and reanalysis of any outliers occurred. Heterogeneity was identified using Cochran's Q statistic. If $P>0.05$, there is no substantial heterogeneity in the analysis's findings. Gene pleiotropy bias may be assessed using MR-Egger intercept analysis. Pleiotropy was deemed significant when $P<0.05$. IVW-MR estimation also uses the online MR power calculation tool (24) to generate power values for each MR analysis.

The TwoSampleMR (Version 0.5.6) package was used to calculate the coefficient of determination (R^2) for exposure to genetic variation based on the total allele score.

We used univariate Mendelian randomization analysis to estimate the impact of positive exposure factors on each mediation and used IVW as our main estimation method. To determine the impact of each medium on the risk of OA, we estimated the effect using regression-based multivariate Mendelian randomization (MVMR) (25). The coefficient product technique was primarily employed to evaluate the indirect effect (the influence of exposure factors on osteoarthritis through mediation) for each mediating component individually (BMI, Smoking, Apolipoprotein B) (26). This involves first estimating the impact of exposure factors on each mediator separately(β1) and then multiplying the exposure-mediation effect by the exposure-adjusted effect of the mediator on the outcome(β2) (27). By dividing the indirect effect by the total effect, it was calculated what proportion of the overall exposure factor influence on OA was mediated by each risk factor. The following equation was used to estimate the percentage of the effect mediated by any of the candidate mediators (28):

$$E\ (\%) = \frac{\sum_{k=1}^{k} \beta 1 * \beta 2_k}{\sum_{k=1}^{k} \beta 3 + \beta 1 * \beta 2_k}$$

(β3 was the MR effect of TV watching on OA adjusted for genetically determined potential mediator)

All analyses in this study were based on R (Version 4.2.1) and the MR-PERESSO (Version 1.0.0), TwosampleMR (Version 0.5.6) packages. $P<0.05$ was considered significant.

Ethical approval

This work uses publicly available GWAS meta-analysis results and therefore does not require ethical approval. All procedures comply with the ethical standards of the Institutional Research Council. Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Results

Instrumental variables

After screening, 7, 4, 17, 42, 5, and 110 SNPs were used as IVs of Acc425, AccAve, MVPA, computer use, driving, and TV watching, respectively. The detailed information on SNPs used as IVs is shown Supplementary Table 2. The F values of the selected SNPs were > 23, excluding the possibility of weak instrumental variables. In addition, the selected SNPs explained 0.17%, 9.44%, 0.15%, 0.39%, 0.05%, and 1.1% of the variance of Acc425, AccAve, MVPA, computer use, driving, and TV watching behavior, respectively. Acc425 and hip OA, TV watching and all OA, TV watching and knee OA, TV watching and spine OA analysis showed high statistical efficiency (Power>80%), and the rest of the MR analysis showed low statistical efficiency. The above results are detailed in Supplementary Table 3.

MR analysis results

The results of MR analysis of different methods are detailed in Supplementary Table 4. In general, there was a link between TV watching and OA. The primary findings of IVW demonstrated that watching TV was related to an increased risk of spine OA (OR=1.208,95% CI: 1.033-1.413, *P*=0.018). Other analysis methods also showed consistent directions, among which the WME method showed significant directionality (OR=1.244,95% CI: 1.000-1.546, *P*=0.049). Among the main results of IVW, no causal relationship was found between Acc425, AccAve, MVPA, computer use, driving, and OA. Significant results were observed only in the WME analysis of computer use and knee OA (OR=0.175,95% CI 0.037-0.825; *P*<0.05). P=0.033).

MR-PRESSO analysis

In the MR-PRESSO analysis (Supplementary Table 5), after removing the outliers, TV Watching significantly increased the risk of developing knee OA. (OR=1.162,95% CI: 1.027-1.315, *P*=0.017). This relationship was also directionally consistent and significantly validated in the WME method (OR=1.180,95% CI: 1.009-1.380, *P*=0.038). There were no outliers in the MR PRESSO analysis of TV watching and spine OA, and the analysis results were consistent with the above results. IVW result analysis is shown in Fig. 3.

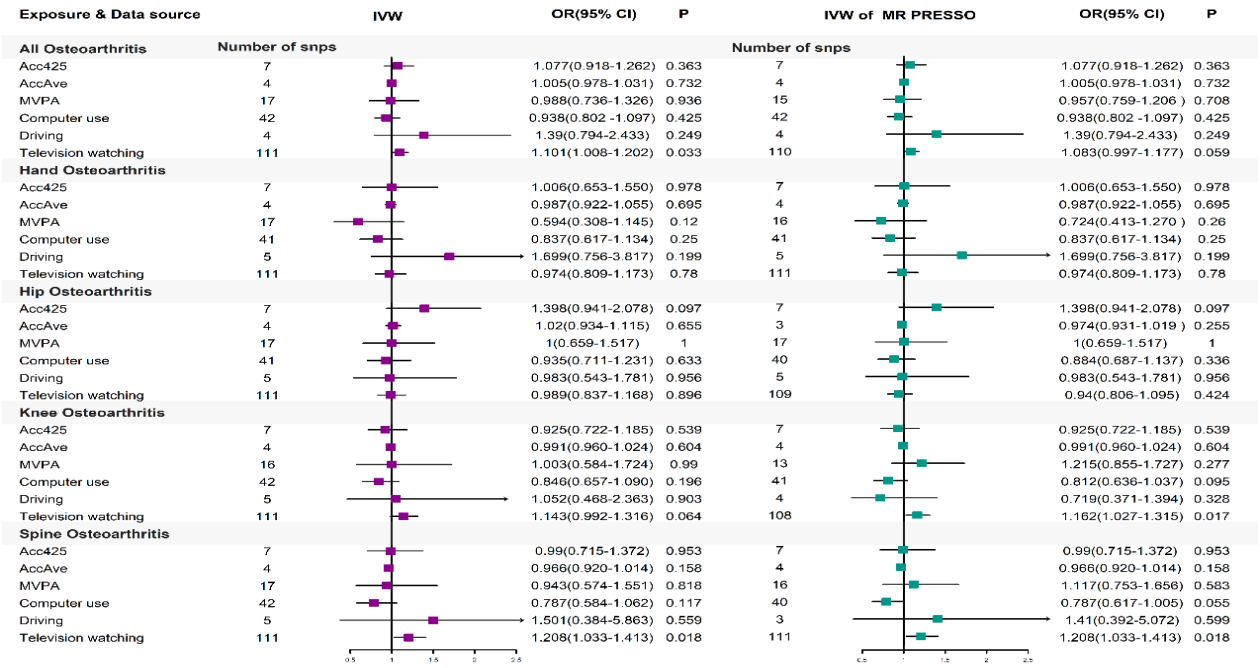

Fig.3: Associations of genetically Physical Activity, Sedentary Behavior with Osteoarthritis using random effect inverse-variance weighted method.

SNP, single nucleotide polymorphism;IVW, inverse-variance weighted; OR, odds ratio; CI,confidence interval

Sensitivity analysis

In sensitivity analysis, only horizontal pleiotropy was found between MVPA and hip OA (intercept:0.315, *P*=0.041). No horizontal pleiotropy was found in other MR analyses. Cochran's Q test results showed that AccAve, MVPA, computer use, driving, and all OA showed widespread heterogeneity (Supplementary Table 6). In addition, TV watching and all OA (Cochrane's Q value=188.1, *P*=3.8e-06), TV watching and knee OA (Cochrane's Q value=217.8, *P*=4.2e-09) showed heterogeneity, because we used random effect IVW as the main result. Heterogeneity is acceptable (29).

Analysis of mediating effect

Figure 4 displays the findings of the mediating MR analysis of confounding factors. There was a significant correlation between TV watching and BMI, smoking, and apolipoprotein B (P<0.05) (Supplementary Table 4). MVMR analysis of mediating factors and outcome OA showed that BMI and Apolipoprotein B were significantly correlated with knee OA (Supplementary Table 5)(BMI: OR=1.863,95% CI: 1.726-2.011; apo B: OR=0.927, 95% CI: 0.880~0.977), BMI, smoking were significantly associated with spine OA (BMI: OR=1.397, 95% CI: 1.272~1.534; smoking: OR=1.227,95% CI: 1.060~1.420), indicating that BMI and apolipoprotein B mediate the effect of TV watching on knee OA, and BMI and smoking mediate the effect of TV watching on spine OA.

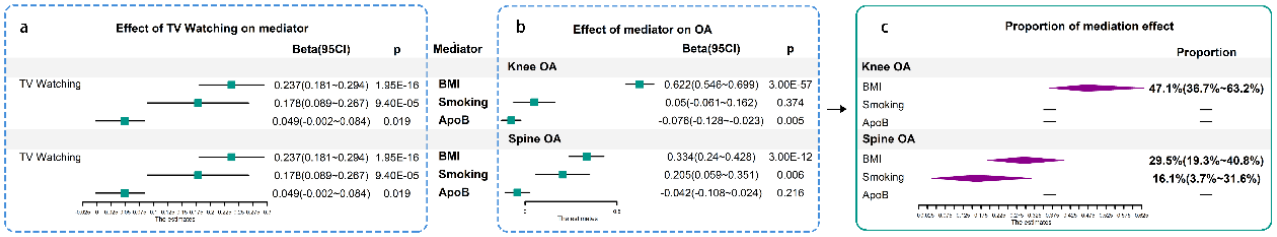

Fig.4: (a) MR-estimated effects of TV watching on each mediator separately, presented as β with 95% CI. (b) MR-estimated effects of each mediator separately on Osteoarthritis after MVMR adjustment for TV watching, presented as β with 95% CI. (c) MR-estimated proportions mediated (%) are presented with 95% CIs. OA, Osteoarthritis; TV, television; CI, confidence interval

In the proportion of mediating effect, BMI explained 47.1% (95% CI: 36.7%~63.2%) of the effect of TV watching on knee OA. In the analysis of the effect of Apo B-mediated TV watching on knee OA, the Apo B-mediated effect may be an incomplete mediating effect, so the proportion of mediating effect was not calculated. BMI explained 29.5% (95% CI: 19.3%-40.8%) of the effect of television watching on spine OA and smoking explained 16.1% (95% CI: 3.7%-31.6%) of the effect of television watching on spine OA (Fig. 4).

Discussion

Our study uncovered a correlation between TV watching and OA, with each one standard deviation (SD) increase in TV watching time associated with a 16% increase in knee OA and 20% increase in spine OA risk. Additionally, BMI had the most significant proportion of the mediating effect, whether for knee OA or spine OA. These results offer new insights at the gene level for mitigating OA risk.

Television watching is commonly considered the primary leisure activity associated with sedentary behavior and is frequently used in studies of sedentary behavior (30, 31). Patients with knee OA exhibit less activity and more sedentary behavior than the general population (32) , and a lack of physical activity may increase the risk of OA (33). Sedentary behavior-induced muscle weakness may also be a significant cause of knee osteoarthritis (34). Moreover, reducing sedentary behavior is thought to decrease functional limitations in patients with knee OA (35) and alleviate barriers to functional exercise (32).

Our study also revealed that BMI and smoking mediate the effects of modifiable lifestyle factors on OA. Increased TV watching time in healthy individuals is linked to unhealthy habits such as obesity and smoking (36). Furthermore, previous studies have extensively examined the negative impact of obesity on OA (37). Other studies have suggested that watching TV adversely affects glucose and lipid metabolism, increasing the risk of obesity (38). Overweight individuals face increased joint load, hastening degenerative changes in joint cartilage and raising the risk of OA

(39). While some studies suggest that smoking behavior has a negative impact on OA (44, 45), others have reported the opposite (40). Although some scholars (41) have suggested that the evidence supporting smoking's protective effect on OA is unconvincing, further research is required to explore the conflicting conclusions.

Our study has several limitations. Firstly, a two-way Mendelian randomization (MR) analysis was not conducted, which precluded the exclusion of the possibility of OA leading to BMI or smoking behavior. Secondly, the study samples were exclusively from the European population, and the potential confounding impact of racial factors on the mediating effect of the aforementioned factors on OA was not investigated (42). Finally, the presence of significant heterogeneity among the SNPs in this study may have resulted in some degree of bias in the findings. However, since our study employs a random effects model, heterogeneity is deemed acceptable.

Conclusion

The genetic evidence generated by MR analysis in this study indicated that TV watching increases the risk of OA and may be mediated by modifiable risk factors such as BMI and smoking. Therefore, intervention in these factors may significantly reduce the burden of OA caused by sedentary behavior.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data Availability Statements

The data used in this article are included in the supplementary files (Readers may contact the corresponding author, if needed). GWAS data of osteoarthritis can be found in Genetics of Osteoarthritis (GO) Consortium.(https://www.genetics-osteoarthritis.com), GWAS data of intermediary factors can be found in IEU Open GWAS.(https://gwas.mrcieu.ac.uk/), GWAS data about physical activity can be found in (https://drive.google.com/drive/folders/1p2-aKT6GgOv4425yaIcvO0nN30O4mpPh), GWAS data of sedentary behavior can be found in (https://data.mendeley.com/datasets/mxjj6czsrd/1).

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