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HDL cholesterol esters mediate the genetic link between sedentary behavior and urological cancers

Insights from mediation and validation analyses

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Abstract

This study explores the causal relationship between sedentary behavior and urological cancers, focusing on bladder cancer (BC), prostate cancer, and kidney cancer, using Bayesian Mendelian randomization and mediation analysis. A two-sample Mendelian randomization (MR) framework was employed, using genetic variants as instrumental variables. Bayesian and multivariate MR assessed causal effects of sedentary behaviors (TV watching, computer use, driving) on urological cancers. Sensitivity analyses (MR-Egger, MR-PRESSO, and Cochran *Q*) ensured robustness. Mediation analysis identified high-density lipoprotein (HDL) cholesterol ester levels as a primary mediator, validated through meta-analysis. Prolonged TV watching was significantly associated with increased BC risk (OR = 2.908; 95% CI = 1.221–6.930; *P* = .015). Mediation analysis showed small HDL cholesterol ester levels mediated 17.5% of this effect. No causal relationships were observed between computer use or driving and the cancers. Sensitivity analyses confirmed robust findings without heterogeneity or pleiotropy. Prolonged TV watching increases BC risk, mediated by small HDL cholesterol ester levels. Sedentary behavior is a modifiable risk factor, highlighting the importance of lifestyle interventions in prevention.

Abbreviations: BC = bladder cancer, BMI = body mass index, BMR = Bayesian Mendelian randomization, HDL = high-density lipoprotein, IVW = inverse variance weighted, KC = kidney cancer, MR = Mendelian randomization, MVMR = multivariable Mendelian randomization, ox-LDL = oxidized low-density lipoprotein, PC = prostate cancer, SB = sedentary behavior, SNP = single nucleotide polymorphism.

Keywords: Bayesian Mendelian randomization, cancer prevention, HDL cholesterol esters, sedentary behavior, urological cancers

1. Introduction

Urological cancers encompass malignant tumors that develop in various parts of the urinary system, differing in origin, cell types, characteristics, treatment approaches, and prognosis. The 3 most prevalent urological cancers are prostate cancer (PC), kidney cancer (KC), and bladder cancer (BC).

PC is the most commonly diagnosed cancer among men in the United States and is the second leading cause of cancer-related deaths.[1] In 2020, approximately 1.4 million men globally across 185 countries were newly diagnosed, and around 375,000 men were expected to die from PC.[2] KC, originating from renal tissue, accounts for 5% of all malignancies in adult males and 3% in females, ranking it seventh in men and tenth in women.[3] BC is among the top 10 most common cancers in the United States and the fourth most common cancer in men,[4,5] accounting for approximately 6% of new cancer cases and 4% of cancer-related deaths.[6] These statistics underscore the global prevalence and significant public health challenge posed by urological cancers. Rising incidence rates of KC, BC, and PC worldwide, driven by population growth and aging,[7]

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All data were sourced from the website https://gwas.mrcieu.ac.uk/. This study does not require additional ethical statements or consent.

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have a substantial impact on life expectancy due to cancer-related mortality.[8] Given the lack of highly effective curative treatments for urological cancers—treatments that are both costly and carry a risk of postoperative recurrence[9,10]—prevention, especially through lifestyle modifications, is increasingly recognized as a promising strategy to reduce cancer incidence.[11]

In recent years, research has increasingly focused on the relationship between lifestyle factors and cancer, exploring the associations between smoking, alcohol consumption, physical activity, sedentary behavior, and cancer risk. Sedentary behavior (SB), defined as any waking activity involving low energy expenditure such as sitting while working, watching TV, or using a computer, has emerged as a significant public health concern in modern society.[12] Although smoking and exposure to certain chemicals are well-established risk factors for BC, there is no consensus regarding the role of modifiable lifestyle factors, particularly SB. The epidemiological evidence linking physical activity, SB, and cancer incidence has been rapidly expanding, with substantial support for these associations.[13] Growing evidence now suggests that physical activity plays a more critical role in cancer prevention than previously thought, and SB may contribute to cancer risk.[11] Some observational studies have identified moderate evidence suggesting that high levels of SB are associated with an increased risk of cancers such as colon, endometrial, and lung cancers.[14] In the context of BC, recent prospective cohort studies have confirmed associations between moderate to vigorous physical activity, SB, and BC risk.[15] However, while many observational studies have investigated the association between SB and cancer,[16] it is challenging to establish causality due to confounding factors inherent in such studies.[17] It is noteworthy that lipid metabolism, particularly elevated cholesterol ester levels, is closely linked to sedentary behavior and urological cancers. Prolonged sitting may disrupt lipid regulation, promoting tumor growth and inflammation, thereby increasing cancer risk.

Mendelian randomization (MR) leverages genetic variants as instrumental variables to determine whether the associations observed between risk factors and outcomes are causal, providing a method that simulates randomized controlled trials using observational data.[18] Genetic variants associated with exposure are naturally assigned, unaffected by confounding factors, making differences in health outcomes between individuals with and without these variants attributable to the exposure alone. This approach, akin to randomization in controlled trials, helps overcome issues such as reverse causality and confounding, making causal inferences more reliable.[19] For diseases where observational studies show correlations but randomized controlled trials are challenging due to difficulties in eliminating confounding factors, Mendelian randomization provides an additional research approach.[20–22]

In this study, we selected genetic variants relevant to sedentary behavior as instrumental variables to explore the potential causal relationships between high-risk SB and BC, KC, and PC. Additionally, we conducted mediation analyses to quantify the mediation effects of potential mediators such as body mass index (BMI), smoking, lymphocyte indices, inflammatory markers, mental health disorders, and cholesterol ester levels in the relationship between SB and BC.

2. Materials and methods

2.1. Study design

This study employed a two-sample MR method to investigate the causal relationships between 3 types of SB—computer use, TV watching, and driving time—and the 3 most common urological tumors: BC, PC, and KC. A significant causal relationship was found only between prolonged TV watching and BC (inverse variance weighted [IVW] $P < .05$). Next, we examined potential mediating factors in the relationship between TV watching and BC. We evaluated 20 high-risk factors, including inflammatory markers, smoking, BMI, mental illness, and lipid profiles, using two-sample MR analysis, and identified 9 potential mediators. Among these, high-density lipoprotein (HDL), BMI, and smoking were found to play a causal mediating role between TV watching and BC. Sensitivity analyses showed pleiotropy in all mediators except cholesterol esters in HDL. To confirm the independent role of specific single nucleotide polymorphisms (SNPs) as mediators, we applied multivariable Mendelian randomization (MVMR) and included additional databases for HDL cholesterol esters for meta-analysis validation. This enabled more precise control over multiple variables, thereby accurately estimating the proportion of mediation effect contributed by cholesterol esters in HDL between TV watching and BC (Fig. 1).

2.2. Data sources and statistics

All data were sourced from the genome-wide association study database (https://gwas.mrcieu.ac.uk/) (Table 1). The study populations were primarily of European descent to minimize potential biases related to population heterogeneity. This study did not require additional ethical approval or informed consent.

2.3. Selection of genetic instrumental variables

In MR studies, the selection of genetic instrumental variables is based on 3 core assumptions. SNPs with genome-wide significance ($P < 5 \times 10^{-8}$) were selected, ensuring their independence ($r^2 < 0.001$, clumping window = 10,000 kb). SNPs directly associated with the outcome were excluded. Additionally, palindromic sequences and incompatible alleles were removed. The final instrumental variables were identified, and the *F*-statistic ($F = \beta^2/se^2$) was calculated, where β represents the SNPs effect on the exposure and se is the standard error. SNPs with an *F*-statistic >10 were retained to minimize bias due to weak instruments.[23]

2.4. Selection of genetic instrumental methods and sensitivity analysis

To investigate causal relationships, we employed 5 different MR methods: MR-Egger, weighted median, IVW, simple mode, and weighted mode. The IVW method served as the primary analysis tool, aggregating effect estimates from multiple genetic variants to produce a comprehensive causal effect estimate, prioritizing variants with lower variance. The other methods provided complementary validation. Specifically, MR-Egger regression assesses and corrects for horizontal pleiotropy by estimating an intercept, enhancing the precision of causal inference. The weighted median method provides reliable causal estimates even when some SNPs introduce bias, improving result consistency. The simple mode method relies on a basic linear regression framework to estimate causality, assuming no pleiotropy. Meanwhile, the weighted mode method applies advanced weighting strategies in its causal effect estimation to account for pleiotropy. All MR analyses were conducted using R (version 4.3.1) and the TwoSampleMR package (version 0.5.6).[24,25]

2.5. Heterogeneity and pleiotropy analysis

To test for heterogeneity and pleiotropy, we used Cochran *Q* statistic, MR-Egger regression, and the MR-PRESSO method to identify and exclude outlier SNPs. Cochran *Q* statistic assesses heterogeneity by measuring the variability of individual SNP effects relative to the overall effect, determining whether significant differences exist among SNPs. A significant *Q* value

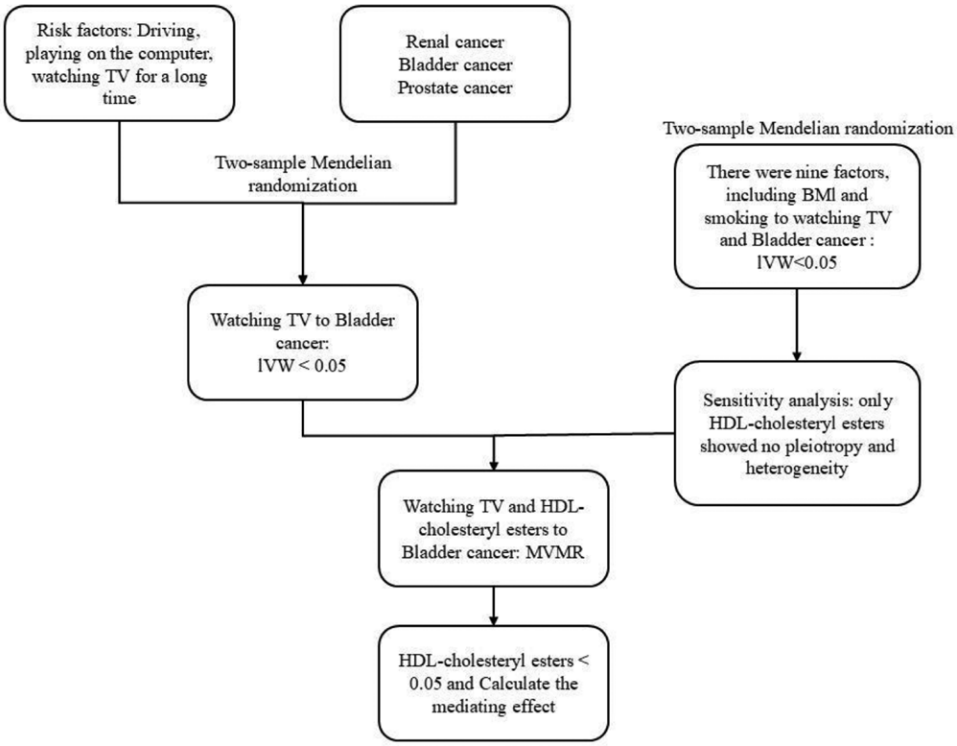

Figure 1. This flow chart illustrates the process of investigating risk factors, specifically driving, playing on the computer, and watching TV for extended periods, and their relationship with bladder cancer. The analysis uses a two-sample Mendelian randomization approach to examine the causal effect of watching TV on bladder cancer and explores the mediating effect of HDL cholesteryl esters in this relationship.

Table 1

This table provides the GWAS IDs, sample sizes, and study years for the exposures (time spent driving, watching TV, and using a computer), outcomes (bladder cancer, kidney cancer, and prostate cancer), and 9 potential mediators.

Exposure	Gwas ID	Race	Sample size	Years
Time spent driving	ukb-b-3793	European	310,555	2018
Time spent watching television	ukb-b-5192	European	437,887	2018
Time spent using computer	ukb-b-4522	European	360,895	2018
Outcome	**Gwas ID**	**Race**	**Sample size**	**Years**
Malignant neoplasm of bladder	finn-b-C3_BLADDER	European	Ncase: 1115 Ncontrol: 217,677	2021
Malignant neoplasm of kidney	finn-b-C3_KIDNEY_NOTRENALPELVIS	European	Ncase: 971 Ncontrol: 217,821	2021
Prostate cancer	ieu-b-4809	European	Ncase: 9132 Ncontrol: 173,493	2021
Nine possible intermediaries.				
Mediator	**Gwas ID**	**Race**	**Sample size**	**Years**
Lymphocyte counts	ebi-a-GCST004627	European	171,643	2016
Body mass index	ebi-a-GCST006368	European	315,347	2018
Monocyte percentage of white cells	ebi-a-GCST90002394	European	408,112	2020
Serum alkaline phosphatase levels	ebi-a-GCST90018942	European	344,292	2021
Cholesteryl ester levels in small HDL	ebi-a-GCST90092946	European	115,082	2022
Free cholesterol to total lipids ratio in small HDL	ebi-a-GCST90092949	European	115,082	2022
Concentration of small VLDL particles	ebi-a-GCST90092975	European	115,082	2022
Phospholipids to total lipids ratio in very small VLDL	ebi-a-GCST90093037	European	115,082	2022
Familial combined hyperlipidemia defined by Dutch criteria	ebi-a-GCST90104005	European	Ncase: 17,485 Ncontrol: 331,737	2021

GWAS = genome-wide association study.

indicates substantial heterogeneity, suggesting that some SNPs may have differing effects, requiring further review or adjustment. Beyond its role in causal estimation, MR-Egger regression uses its intercept to detect horizontal pleiotropy—where SNPs influence the outcome through pathways unrelated to the exposure. A significant intercept suggests pleiotropy that could

Main.outcome	Method	nSNP	P.value	OR(95%CI)	Heterogeneity.Test.P	MR.Egger.Intercept.P	MR.PRESSO.Global.Test.P
TV-BC	MR Egger	105	0.69000255	2.40(0.03 to 174.39)	0.148592152		
	Weighted median	105	0.09904136	2.82(0.82 to 9.66)			
	Inverse variance weighted	105	0.01591272	2.91(1.22 to 6.93)	0.164801827	0.928334888	0.164
	Simple mode	105	0.05250014	28.10(1.00 to 787.86)			
	Weighted mode	105	0.05005544	18.66(1.03 to 336.79)			
TV-PC	MR Egger	103	0.94422618	1.00(0.94 to 1.07)	0.189733992		
	Weighted median	103	0.21075811	0.99(0.97 to 1.01)			
	Inverse variance weighted	103	0.18103662	0.99(0.98 to 1.00)	0.205945155	0.701868514	0.195
	Simple mode	103	0.42505795	0.98(0.93 to 1.03)			
	Weighted mode	103	0.52689175	0.98(0.94 to 1.03)			
TV-KC	MR Egger	104	0.61396072	0.29(0.00 to 36.01)	0.038751009		
	Weighted median	104	0.17699729	2.47(0.67 to 9.14)			
	Inverse variance weighted	104	0.31829299	1.65(0.62 to 4.41)	0.041132423	0.470501299	0.051
	Simple mode	104	0.45134829	3.18(0.16 to 63.91)			
	Weighted mode	104	0.38908068	3.43(0.21 to 55.83)			
Driving-BC	MR Egger	6	0.85831214	40.79(0.00 to 1568450000000000000.00)	0.179515259		
	Weighted median	6	0.32572131	7.88(0.13 to 483.98)			
	Inverse variance weighted	6	0.65004397	2.27(0.07 to 78.78)	0.277206545	0.888753849	0.323
	Simple mode	6	0.35311065	27.36(0.05 to 15489.16)			
	Weighted mode	6	0.33576117	24.57(0.07 to 8915.34)			
Driving-PC	MR Egger	5	0.11804639	0.58(0.35 to 0.95)	0.972730497		
	Weighted median	5	0.89416550	0.99(0.91 to 1.08)			
	Inverse variance weighted	5	0.80286066	1.01(0.94 to 1.08)	0.269627008	0.112589904	0.309
	Simple mode	5	0.62422789	0.97(0.85 to 1.10)			
	Weighted mode	5	0.57790578	0.96(0.85 to 1.09)			
Driving-KC	MR Egger	6	0.60584752	81208.11(0.00 to 131000000000000001049826.00)	0.210404564		
	Weighted median	6	0.65221617	0.38(0.01 to 26.67)			
	Inverse variance weighted	6	0.26947448	0.11(0.00 to 5.41)	0.259628474	0.539219496	0.295
	Simple mode	6	0.93522649	0.76(0.00 to 372.86)			
	Weighted mode	6	0.98142230	0.92(0.00 to 541.91)			
Computer-BC	MR Egger	76	0.66877214	0.32(0.00 to 58.18)	0.181798149		
	Weighted median	76	0.67522645	0.76(0.21 to 2.75)			
	Inverse variance weighted	76	0.66269106	0.81(0.32 to 2.05)	0.200701055	0.721556508	0.216
	Simple mode	76	0.93115324	1.15(0.05 to 25.86)			
	Weighted mode	76	0.84562427	0.75(0.04 to 13.64)			
Computer-PC	MR Egger	78	0.88796969	1.01(0.92 to 1.10)	0.00061535		
	Weighted median	78	0.74442500	1.00(0.98 to 1.03)			
	Inverse variance weighted	78	0.24247265	1.01(0.99 to 1.03)	0.000794984	0.923736325	0.03
	Simple mode	78	0.83842303	1.01(0.95 to 1.06)			
	Weighted mode	78	0.87291153	1.00(0.96 to 1.05)			
Computer-KC	MR Egger	76	0.92155065	0.76(0.00 to 189.59)	0.227623683		
	Weighted median	76	0.03756983	0.23(0.06 to 0.92)			
	Inverse variance weighted	76	0.20771583	0.53(0.20 to 1.42)	0.252296772	0.899409665	0.265
	Simple mode	76	0.20906625	0.11(0.00 to 3.29)			
	Weighted mode	76	0.21903623	0.13(0.01 to 3.21)			

Figure 2. This figure presents the results of a Mendelian randomization analysis to evaluate the causal relationship between 3 sedentary behaviors (watching TV, driving, and using the computer) and 3 types of urinary diseases (bladder cancer, prostate cancer, and kidney cancer). It includes multiple methods like MR-Egger, weighted median, and inverse variance weighted to estimate odds ratios and 95% confidence intervals. The heterogeneity of the results is also presented with tests for pleiotropy and publication bias.

distort causal estimates, and MR-Egger adjusts for this to improve accuracy. The MR-PRESSO method aims to identify and remove outlier SNPs, refining causal estimates by minimizing their impact. Additionally, MR-PRESSO corrects for pleiotropy, further enhancing the robustness and reliability of the identified causal relationships.

2.6. Calculation of mediation effect

First, two-sample MR was used to calculate the effect of TV watching on HDL cholesterol esters (b1). Next, MVMR was applied to control for TV watching while calculating the effect of HDL cholesterol esters on BC (b2). Finally, the total effect of TV watching on BC (b3) was calculated, and the mediation effect was determined using the formula: mediation effect = (b1 × b2)/b3.[26,27]

2.7. Meta-analysis validation

To enhance the accuracy of our results, we conducted a meta-analysis using data on the same mediator (cholesterol esters in HDL) from different databases (met-d-S_HDL_CE). After performing two-sample MR analyses on HDL cholesterol esters and BC, we conducted a meta-analysis for validation.

2.8. Bayesian Mendelian randomization

Bayesian Mendelian randomization (BMR) was used to improve the accuracy of causal inference by combining Bayesian statistics with MR. BMR uses genetic variants as instrumental variables to assess causal effects between exposures and outcomes, exposures and mediators, and mediators and outcomes. By addressing the issue of weak instruments and incorporating prior knowledge to update posterior distributions, BMR provides more reliable estimates of effect sizes and enhances the robustness of causal relationships in complex settings.[28]

3. Results

The IVW method provided the most robust evidence for a causal relationship between prolonged TV watching and an increased risk of BC (Supplementary Material 2, Supplemental Digital Content, https://links.lww.com/MD/O846). No significant causal relationship was found between other SB (computer use, driving) and the 3 most common urinary system tumors (Fig. 2).

The two-sample MR analysis, using TV watching as the exposure, revealed significant causal relationships with common high-risk factors (IVW $P < .05$). When BC was analyzed as the outcome, all 9 high-risk factors were significant in the MR analysis (IVW $P < .05$) (Supplementary Material 1, Supplemental Digital Content, https://links.lww.com/MD/O847). Further sensitivity analyses confirmed that cholesterol esters in HDL exhibited no pleiotropy or heterogeneity, unlike the other 8 mediators (MR-PRESSO identified pleiotropy). This strengthens the causal relationship between TV watching and HDL cholesterol esters (Supplementary Material 2, Supplemental Digital Content, https://links.lww.com/MD/O846) and between HDL cholesterol esters and BC (IVW $P < .05$) (Supplementary Material 2, Supplemental Digital Content, https://links.lww.com/MD/O846). Although the initial MR analysis indicated possible mediation, final validation using MVMR demonstrated that HDL cholesterol esters independently mediated the relationship between TV watching and BC. The mediation

effect was quantified as 17.5% (OR = 1.194, 95% CI = 1.013–1.493), further confirming the mediating role of HDL cholesterol esters (Fig. 3). A meta-analysis of MR analyses using HDL cholesterol esters and BC data from multiple databases reinforced the significant causal relationship (common effect model OR = 1.381, 95% CI = 1.136–1.679, $P = .001$), with no publication bias (Fig. 4). Additionally, BMR validated the results of the effect of TV watching on BC through mediators, consistent with our previous findings (Supplementary Material 2, Supplemental Digital Content, https://links.lww.com/MD/O846).

4. Discussion

In modern society, many people spend long periods engaged in sedentary activities, such as watching television, working on computers, or driving long distances. Such a lifestyle may increase the risk of various diseases, including cancer. In this study, we investigated the causal relationships between 3 types of SB—driving, computer use, and television watching—and the incidence of 3 common urological cancers BC, KC, and PC using MR analysis. Our results suggest that prolonged television watching, a sedentary behavior, is associated with a higher risk of BC. However, no significant causal relationship was found between computer use, driving time, and BC risk. Further mediation analysis indicated that the causal link between television watching and BC may be mediated by elevated cholesterol ester levels in HDL.

Historically, the relationship between lifestyle factors and BC has been extensively studied. Previous research has demonstrated that long-term exposure to certain chemicals, environmental pollutants, and chronic smoking can increase BC risk.[29–31]. Additionally, observational studies have identified SB as a potential risk factor for BC, particularly in high-income countries, where sedentary lifestyles are more common.[32–34] However, the reliability of these findings is often questioned due to the potential influence of other risk factors, such as smoking and higher BMI, both of which are also associated with BC.[35]

Determining the direct link between SB and BC is challenging because these factors often overlap. However, the MR approach provides a method to address this issue by using genetic variations as instrumental variables to assess causality. MR helps overcome the confounding factors present in traditional observational studies, providing more reliable evidence for a causal relationship between sedentary behavior and BC risk.

Building on these findings, we further explored potential etiological or pathological mechanisms linking television watching to BC, focusing on high-risk factors such as smoking, BMI, lipid levels, serum alkaline phosphatase, lymphocyte count, and mental health conditions through two-sample MR analysis. This allowed us to investigate potential mediating effects. Our results indicated that television watching may mediate BC development through 9 potential mediators, including serum alkaline phosphatase, plasma lipid levels, BMI, and lymphocyte count (Supplementary Material 1, Supplemental Digital Content, https://links.lww.com/MD/O847). However, sensitivity analyses using MR-PRESSO revealed outlier SNPs in all but 1 mediator: cholesterol esters in small HDL particles. The persistence of pleiotropy after excluding outlier SNPs suggests that some genetic variants influence television watching and other pathways simultaneously, independently of the direct mechanisms involved in the observed indicators. Several factors may contribute to this pleiotropy: Composite lifestyle factors: Prolonged television watching may be closely linked to other lifestyle habits, such as diet and living environment, which can independently influence BMI and lipid metabolism.[36] A genetic variant that predisposes individuals to both sedentary behavior and unhealthy eating could affect health outcomes through multiple pathways, not solely by increasing television watching time. Complex physiological feedback mechanisms: Television watching may impact the body's metabolism and immune system through complex feedback mechanisms.[37] Genetic variants may influence multiple physiological systems, making it difficult to distinguish their effects on television watching from their impacts on other health indicators.

The relationship between SB and cancer is multifaceted, involving numerous potential biological mechanisms. Research suggests that prolonged sitting is associated with an increased risk of certain cancers, including lung,[38] breast,[39,40] colorectal,[41] ovarian,[42] and endometrial cancer.[42,43] Lipid profiles, particularly cholesterol esters, may serve as biomarkers for understanding the link between SB and cancer. Lipids in the blood, including cholesterol, triglycerides, phospholipids, and free fatty acids, play crucial roles in the body. Cholesterol exists in 2 forms: free cholesterol and cholesterol esters, the latter being a storage form transported through the bloodstream to various tissues. Several studies have demonstrated a strong relationship between lipid levels and various cancers.[44–46]

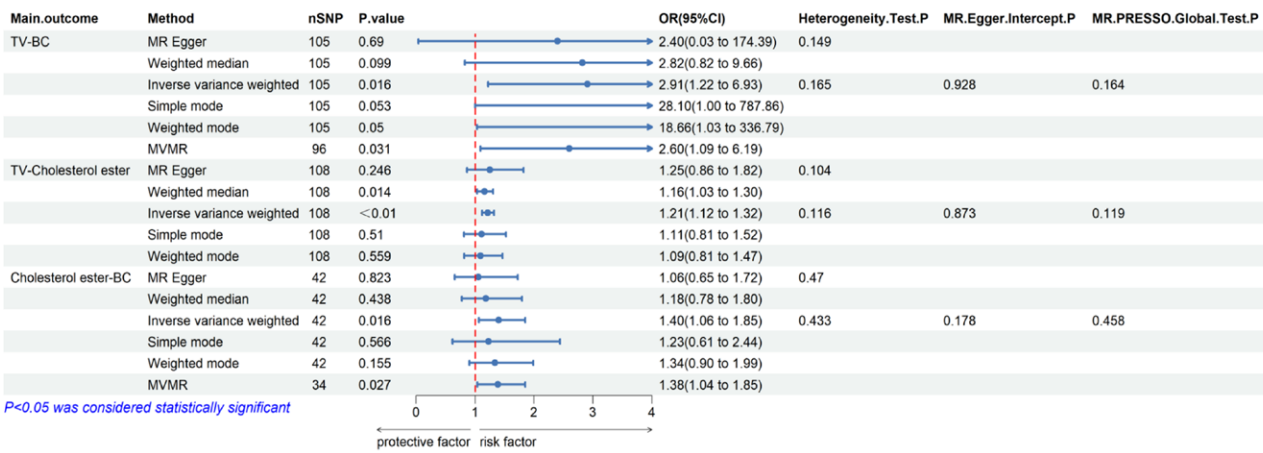

Figure 3. This figure shows the causal relationship between TV watching, HDL cholesteryl esters, and bladder cancer. The analysis uses various Mendelian randomization methods, including MR-Egger and weighted median, to explore the effects of TV watching and HDL cholesteryl esters on bladder cancer risk. The significance of the relationship is evaluated through odds ratios and *P*-values for different methods.

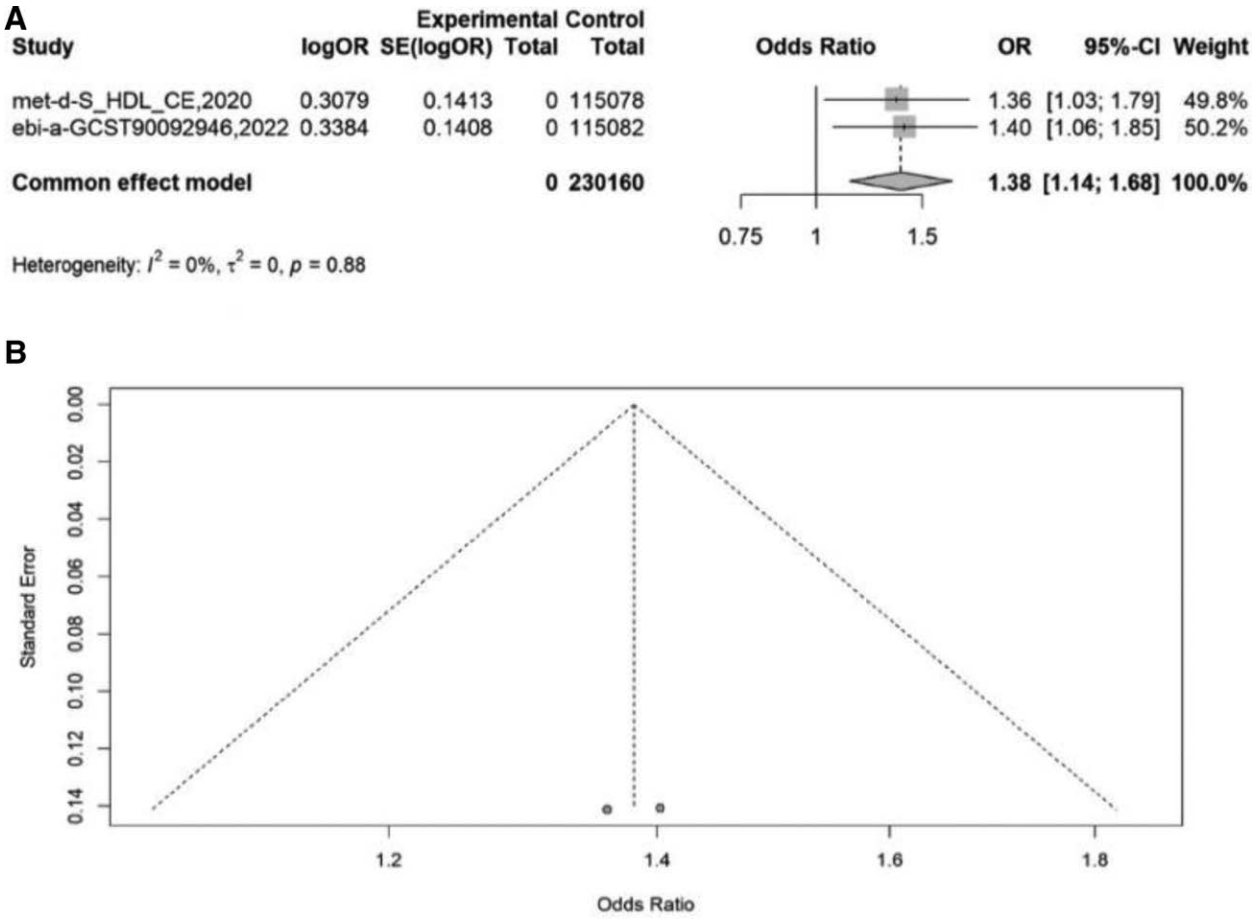

Figure 4. This figure includes the meta-analysis results for HDL cholesterol esters based on 2 studies from the MET database. It presents the odds ratios and their 95% confidence intervals, as well as the standard error for each study. (B) Additionally shows the publication bias detection for HDL cholesteryl esters included in the MET database.

Therefore, monitoring lipid levels, including cholesterol ester content, is essential for cancer risk assessment and prevention. A phenome-wide MR analysis of 378,142 patients revealed that in addition to recognized risk factors such as smoking, alcohol consumption, and obesity, steroid hormones, plasma lipids, and telomere length also significantly contribute to the risk of 8 common cancers.[47] Among adults and older individuals, prolonged leisure time characterized by low physical activity and extensive television watching increases the likelihood of abnormal lipid profiles.[48] Additional research has established a strong association between hypercholesterolemia and the aggressiveness of BC. Oxidized low-density lipoprotein (ox-LDL), induced by hypercholesterolemia, promotes BC malignancy through the CD36/STAT3 signaling pathway. Elevated ox-LDL levels could serve as a biomarker for BC prognosis, offering new perspectives for cancer diagnosis and treatment. Targeting the CD36/JAK2/STAT3 axis or reducing ox-LDL levels could offer novel therapeutic strategies for BC patients with hypercholesterolemia.[49] Thus, hypercholesterolemia may be a significant risk factor for BC, particularly among young males, although further research is required to determine if this relationship exists in females.[50] In summary, the content of various lipid components plays a critical role in BC development, progression, and metastasis.

We also found that cholesterol ester levels in small HDL particles are the only mediating factor between prolonged television watching and BC development. The lipid system includes several key markers, such as cholesterol, triglycerides, and lipoproteins (lipoprotein[a] and lipoprotein[b]).[51] Three potential explanations for this phenomenon are: Lipid system complexity: Initial two-sample MR analyses also identified lymphocyte and monocyte counts as potential mediators, but subsequent MR-PRESSO analysis revealed significant pleiotropy after excluding outlier SNPs. This may reflect the complex nature of both the immune and lipid systems, suggesting that increased levels of potential mediators are not solely caused by sedentary behavior. Biological activity of cholesteryl esters: Compared to free cholesterol and other lipids, cholesteryl esters exhibit unique biological activities.[52] Stored in the core of lipoprotein particles, cholesteryl esters may influence BC cell metabolism and proliferation during their storage and release.[53] The conversion of cholesteryl esters into free cholesterol could activate or inhibit signaling pathways related to cancer cell growth, such as hormone synthesis and cell membrane construction,[54–56] potentially impacting BC development. Metabolic homeostasis and signaling: Cholesteryl ester metabolism may influence BC cell stemness and malignancy through pathways such as JAK2/STAT3.[50] Cholesteryl esters, via the CD36/JAK2/STAT3 axis, may enhance cancer stem cell properties and promote cancer progression,[50] offering a potential mechanism that links cholesteryl esters to BC progression. In contrast to LDL, VLDL, and IDL, HDL is thought to reduce the risk of atherosclerosis and cardiovascular diseases.[57] This protective effect may also help prevent tumor development, including BC. Changes in HDL cholesteryl ester levels, which serve as indicators of HDL function, may directly reflect the strength of this protective effect. Conversely, LDL, IDL, and VLDL pathways may not be as closely associated with BC development as HDL cholesteryl esters. The differences in disease risks related to various lipoproteins further support a specific link between HDL cholesteryl esters and BC risk. Although LDL is often seen as a

major risk factor for cardiovascular disease, research suggests that variations in HDL cholesteryl ester levels may also be linked to non-cardiovascular diseases such as PC.[58] We believe the same is true for BC. HDL may influence tumor development through its roles in maintaining cell membrane integrity, regulating inflammation, and controlling cell proliferation and death—key factors in cancer development. Through MR analysis, we demonstrated that HDL cholesteryl esters mediate the relationship between prolonged television watching and BC. Leveraging this knowledge could lead to more effective BC prevention strategies. This study is significant in guiding clinical practice and informing lifestyle choices in the general population.

However, our study has several limitations that may introduce bias. First, the limited number of SNPs may not provide a comprehensive overview of the genetic architecture involved. Second, cancer heterogeneity is significant, and despite meta-analyses, the pathological types and classifications of BC vary widely, which may limit the generalizability of our findings. Further research involving higher-quality randomized controlled trials, stratified by cancer subtype and stage, is needed. Third, the study populations consisted solely of individuals of European descent, which may limit the applicability of the results to other ethnic groups. Fourth, in our study, we established a causal relationship between prolonged television watching and BC, while no significant causal relationship was found for other types of SB, such as computer use or prolonged driving. Possible explanations for these findings include the potential for recall bias or misclassification of data during manual collection. Additionally, prolonged television watching is often accompanied by other unhealthy behaviors, such as increased consumption of unhealthy snacks and reduced physical activity, which may exacerbate the health risks associated with SB. These accompanying behaviors may increase the risk of BC. Furthermore, different patterns of SB, such as continuous versus intermittent sitting, may have varying effects on health. Research has shown that breaks in sedentary time and prolonged periods of sitting have different impacts on metabolic disease risk,[59] and these differences may also apply to cancer development.

5. Conclusion

Our MR approach explored the association between sedentary behavior, cholesteryl ester levels in small HDL, and BC, finding that prolonged television viewing could potentially influence BC risk through the mediation of cholesteryl ester levels in small HDL. To prevent the onset of BC, engaging in appropriate and scientifically guided physical activity is recommended. Moreover, the MR approach requires further high-quality clinical research and exploration of underlying mechanisms to refine the relationship between SB behavior and BC.

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