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Causal effects of psychosocial factors on chronic back pain: a bidirectional Mendelian randomisation study

Frances M. K. Williams[a,*], **Elizaveta E. Elgaeva**[b,c,*], **Maxim B. Freidin**[a], **Olga O. Zaytseva**[d], **Yurii S. Aulchenko**[b,e,f], **Yakov A. Tsepilov**[b,c,**], **Pradeep Suri**[g,h,i,j,§,**]

[a]Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, London, UK

[b]Department of Natural Sciences, Novosibirsk State University, Novosibirsk, Russia

[c]Laboratory of Recombination and Segregation Analysis, Institute of Cytology and Genetics, Novosibirsk, Russia

[d]Genos Glycoscience Research Laboratory, Zagreb, 10000, Croatia

[e]PolyOmica, 's-Hertogenbosch, the Netherlands

[f]Kurchatov Genomics Center, Institute of Cytology & Genetics, Novosibirsk, Russia

[g]Division of Rehabilitation Care Services, VA Puget Sound Health Care System, USA

[h]Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Seattle, USA

[i]Department of Rehabilitation Medicine, University of Washington, Seattle, USA

[j]Clinical Learning, Evidence, and Research (CLEAR) Center, University of Washington, Seattle, USA

Abstract

Purpose: Risk factors for chronic back pain (CBP) may share underlying genetic factors, making them difficult to study using conventional methods. We conducted a bi-directional Mendelian randomisation (MR) study to examine the causal effects of risk factors (education, smoking, alcohol consumption, physical activity, sleep and depression) on CBP and the causal effect of CBP on the same risk factors.

Methods: Genetic instruments for risk factors and CBP were obtained from the largest published genome-wide association studies (GWAS) of risk factor traits conducted in individuals of European ancestry. We used inverse weighted variance meta-analysis (IVW), Causal Analysis

[§]Corresponding author: Pradeep Suri, MD, MS, VA Puget Sound Health Care System, S-152-ERIC, 1660 S. Columbian Way, Seattle, WA, 98108. pradeep.suri@va.gov, Tel: 1-206-277-1812, Fax: 1-206-764-2673.
*These authors contributed equally to this work
**These authors contributed equally to this work

CONFLICTS OF INTEREST

YSA is a cofounder and a co-owner of PolyOmica and PolyKnomics, private organizations providing services, research, and development in the field of computational and statistical genomics. OOZ is an employee of Genos Glycoscience Research Laboratory. The other authors declare that they have no competing interests.

Using Summary Effect (CAUSE) and sensitivity analyses to examine evidence for causal associations. We interpreted exposure-outcome associations as being consistent with a causal relationship if results with IVW or CAUSE were statistically significant after accounting for multiple statistical testing ($p<0.003$), and the direction and magnitude of effect estimates were concordant between IVW, CAUSE, and sensitivity analyses.

Results: We found evidence for statistically significant causal associations between greater education (OR per 4.2 years of schooling=0.54), ever smoking (OR=1.27), greater alcohol consumption (OR=1.29 per consumption category increase) and major depressive disorder (OR=1.41) and risk of CBP. Conversely, we found evidence for significant causal associations between CBP and greater alcohol consumption (OR=1.19) and between CBP and smoking (OR=1.21). Other relationships did not meet our pre-defined criteria for causal association.

Conclusion: Fewer years of schooling, smoking, greater alcohol consumption, and major depressive disorder increase the risk of CBP. CBP increases the risk of greater alcohol consumption and smoking.

Keywords

Low back pain; epidemiology; prognosis; risk factor; causation

Introduction

Chronic back pain (CBP) is the leading global cause of years lived with disability worldwide.[1] Widely accepted risk factors for CBP include higher body mass index (BMI) and smoking. [2, 3] Common co-morbidities include depression and anxiety.[4] Results of twin studies have raised the question of whether these risk factors and comorbidities have causal effects on CBP, or whether these conditions co-occur due to shared genetic predispositions (pleiotropy).[5] Conventional epidemiology provides limited tools to determine whether associations represent “true” risk factors i.e. they precede and cause back pain (BP) or whether other explanations, such as confounding, exist. Newly available genetic methods such as Mendelian randomisation (MR) allow such ambiguities to be addressed.

MR uses genetic variants as instrumental variables (“instruments”) to support causal inference about the effect of a risk factor on an outcome.[6] MR capitalises on the fact that genetic variants are allocated randomly prior to birth (conditional on parental genotype), are independent of environmental factors and temporally precede the onset of disease.[7] Thus they can be used as proxies for health conditions. MR offers advantages over other observational methods because it is less likely to be affected by reverse causation and confounding. The strength of evidence provided by MR is considered to lie between conventional observational studies and randomized trials.[6] Coronary artery disease has many putative risk factors and MR has shown low density lipoprotein cholesterol to be a true risk factor while uric acid is not.[6] This has important implications for urate-lowering treatment in cardiovascular disease prevention. Until recently it was unclear whether raised BMI is a true risk factor for BP or whether BMI increases after CBP develops. We have

recently shown using MR that elevated BMI has causal associations with CBP, indicating that weight loss may provide an important step in prevention.[8]

MR studies use genome-wide association studies (GWAS) to estimate causal effects of a risk factor. In the present study we derived multiple genetic instruments from published GWAS of possible risk factors for CBP to determine their true relationship with CBP. We conducted a bidirectional MR study to examine both possible directions of effect, specifically the causal association of risk factors on CBP and the causal association of CBP on the risk factors.

Methods

This study used summary-level GWAS data. Research approvals included the UK Biobank Research Ethics Committee (#11/NW/0382) and the VA Puget Sound Health Care System (MIRB 00903).

Overview

We hypothesized that risk factors would have causal effects on CBP and that CBP would have causal effects on risk factors. High genetic correlation between traits complicates MR analysis using inverse variance weighted meta-analysis (IVW), the most commonly used MR method, because it increases the chance of correlated horizontal pleiotropy and violates the assumptions made in MR; this may generate false positive results. Additional validation and sensitivity analyses are required in the case of a statistically significant result when using IVW.[9] In order for our findings to be robust to potential violations of MR assumptions, we used a pre-defined framework for analysis that included (1) a conventional MR approach with IVW analysis; (2) a newer method, Causal Analysis Using Summary Effect (CAUSE), which can reduce false-positive associations compared to IVW, but has less statistical power under certain scenarios;[9] and (3) sensitivity analyses to reduce confounding by excluding genetic instruments associated with possible confounders.

Data Sources

We selected the largest publicly available GWAS for 8 risk factor traits (years of schooling, ever smoking, alcohol consumption frequency, self-reported moderate physical activity, accelerometer-measured overall activity, accelerometer-measured sedentary behaviour, sleep duration hours, and major depressive disorder) across 6 risk factor categories (education, smoking, alcohol consumption, physical activity, sleep and depression) in participants of European ancestry (EA). The risk factor traits are listed in Table 1 and Supplemental Table 1, and details are reported elsewhere.[10–13] Traits were considered as exposures in forward MRs and as outcomes in reverse MRs. Additional traits implicated in CBP (blood pressure, hyperlipidemia, BMI and type 2 diabetes; and the personality traits anxiety, neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) were also considered as possible confounders in sensitivity analyses that excluded genetic instruments associated with these traits. We used the largest GWAS of CBP comprising 78,935 cases and 360,896 controls in UK Biobank including only EA participants.[8] CBP was defined as having back pain for more than 3 months.

GWAS summary statistics passing quality control were unified using tools implemented in the GWAS-MAP platform.[14, 15] Extensive details on GWAS data quality control and pre-processing can be found in the Supplementary Methods.

Statistical analysis

We examined causal relationships between the 8 putative risk factors and CBP using IVW MR and CAUSE analyses using a framework that was defined *a priori*.[9] The primary analysis consisted of forward MR analyses (putative risk factors as the exposures and CBP as the outcome) and reverse MR analyses (CBP as the exposure and risk factors as the outcomes) for each exposure-outcome pair of traits. The significance threshold for the primary analysis was defined using a Bonferroni correction as 0.003125 = 0.05/(8*2), where 8 reflects the number of trait pairs and 2 reflects each direction of the bidirectional MR analysis. Trait pairs exceeding the Bonferroni-corrected significance threshold ($p<0.003125$) in at least one of the 2 primary analysis methods (IVW and CAUSE), and having *concordance* between IVW and CAUSE methods, defined as the same direction and similar magnitude of effect estimate produced by IVW and CAUSE, were included in sensitivity analyses. In sensitivity analysis for each trait pair, the CAUSE analyses were repeated while excluding genetic instruments associated with the risk factors under study or 14 other possible confounders (Table 1), and the IVW analyses were repeated while excluding such instruments while also excluding genetic instruments identified as horizontal pleiotropy outliers using MR PRESSO.[16] The results of the sensitivity analyses were then checked for concordance with the results of primary analysis, defined as having similar direction effect estimates. We interpreted exposure-outcome associations for each trait pair as being consistent with a causal relationship if 3 pre-defined criteria were met. Criterion 1 was that the association must exceed the Bonferroni-corrected significance threshold ($p<0.003125$) in at least one of the IVW and CAUSE primary analyses. Criterion 2 was that the magnitude and direction of the effect estimates was concordant between IVW and CAUSE primary analyses, irrespective of statistical significance. Criterion 3 was that effect estimate direction must be concordant between the primary analysis and sensitivity analyses. Further details of the analytic methods, our pre-defined plan for interpretation, and sample size calculations are provided in the Supplementary Methods.

Results

Table 1 summarizes the GWAS of traits from which the SNPs used as genetic instrumental variables were drawn; further detail is provided in Supplementary Table 1.

The results of the forward MR analysis (risk factors causing CBP) are shown in Table 2 and Supplementary Tables 2, 4 and 5. Several risk factors (physical activity traits and major depressive disorder) had few SNPs available for IVW analysis but most had tens or hundreds of SNPs (Table 2). All 3 pre-defined criteria for association consistent with a causal relationship were met for years of schooling, ever smoking, alcohol consumption, and major depressive disorder, indicating these traits are likely causes of CBP (Table 2). The largest odds ratios (ORs) were for years of schooling (OR=0.54 per 4.2 years of schooling, primary IVW analysis) and major depressive disorder (OR=1.41, primary IVW analysis);

ORs for smoking (OR=1.27, primary IVW analysis) and alcohol consumption (OR=1.29 per increase in alcohol consumption category, primary IVW analysis) were smaller, and of diminished magnitude in sensitivity analyses. While analyses of sleep duration and CBP met criteria 1 and 2 for causality, they did not meet criterion 3 due to lack of concordance in effect estimates between primary and sensitivity analysis. There was no evidence of a causal relationship between the 3 physical activity traits (self-reported moderate physical activity or accelerometer-measured overall activity or sedentary behaviour) and CBP.

The results of the reverse MR analysis (CBP causing risk factors) are shown in Table 3 and Supplementary Tables 3, 6 and 7. Most risk factors had fewer SNPs available for IVW than in the forward MR, and there were fewer significant CBP-risk factor associations with significant results. The 3 pre-defined criteria consistent with a causal relationship were met for alcohol consumption, indicating causal effects of CBP on alcohol consumption (OR=1.19 in primary IVW analysis, Table 3), and smoking (OR=1.21 in primary IVW analysis, Table 3). Odds ratios for the effect of CBP on all risk factors were generally smaller than those from the forward MR. While associations of CBP with years of schooling and major depressive disorder met criteria 1 and 2 for causality, they did not meet criterion 3 due to lack of concordance in effect estimate between primary and sensitivity analysis. Noteworthy is that in sensitivity analyses of these 2 traits, all or nearly all genetic instruments were removed as horizontal pleiotropy outliers by MR PRESSO, limiting the ability to infer concordance between the results of primary and sensitivity analysis. There was no evidence of a causal relationship between CBP and sleep duration or the 3 physical activity traits.

Discussion

BP and CBP are known to be highly polygenic traits, with heritability around 40%.[17] Work to identify the genetic variants involved began with studies of lumbar disc degeneration[18, 19] and continued with recent studies of CBP in large genetic consortia and biobanks.[20–22] The biopsychosocial model of pain is supported by the findings from these studies and shows that the genetic factors involved in CBP underlie all three contributors: biological, psychological, and social.[20] That is, associations are found not only at the genes involved in the biology of the spine and musculoskeletal system, but there are significant genetic correlations between CBP and psychological factors such as depression and anxiety, and social factors such as years of schooling.[21]

Given this complex background, the current study sought to determine whether several commonly studied risk factors have strong support for causal association with CBP and vice versa (whether CBP has causal associations with these factors) using contemporary MR methods. We found evidence for causal association of fewer years of schooling, smoking, and major depressive disorder with the risk of CBP. While these findings are consistent with the results of conventional observational studies,[23–25] they differ from longitudinal twin studies which found no significant association of education,[26] smoking,[27] or depression[28] with CBP after controlling for genetic factors. These longitudinal co-twin control studies were informed by tens or at most hundreds of identical twin pairs, leading to very limited power and unclear generalizability. In contrast, the current MR analyses

were informed by more than 500,000 singleton individuals. Another notable aspect of our findings was the clear evidence that greater alcohol use causes CBP but that CBP also causes greater alcohol use - in other words, a bidirectional relationship. The separation of these two directions of effect was possible through MR because the genetic instruments that proxy risk factors are present from conception, long before the development of the outcome, providing a clear temporal sequence of risk factor preceding outcome for each direction of effect. While only one direction of effect may be relevant for some individuals, there is the possibility that alcohol use and CBP reinforce each other in another subgroup of individuals, acting in a positive feedback loop. Our demonstration of strong causal links with alcohol use is novel and makes an important contribution given the ambiguity of the alcohol-back pain relationship (outside of the context of substance abuse) according to systematic reviews on this topic.[29, 30] Our study also confirms the bidirectional nature of the smoking-CBP relationship, aspects of which have been noted before,[31, 32] but not with such clarity as we show in the current study using very large samples.

Our bidirectional MR study did not find robust support for a causal effect of sleep on CBP, or a causal effect of CBP on years of schooling or major depressive disorder. While these analyses did show significant causal associations and concordant directions and magnitudes of effect in our primary analyses, the results of sensitivity analyses were not uniformly concordant with the primary analyses. Possible explanations for this include suboptimal power, as some sensitivity analyses were informed by few genetic instruments, or no instruments were available. Alternatively, the paucity of instruments available suggests that these relationships with CBP are driven by pleiotropy – shared genetic influence on multiple conditions – and are not truly causal. Our bidirectional MR of 3 physical activity traits and CBP also did not show convincing evidence for causal relationships, a surprising finding given the long history of exercise as a treatment for CBP.[33] A possible explanation for this may be the assumption of a linear relationship between physical activity and CBP inherent in our MR methods. This linearity assumption contrasts with one view that moderate activity is beneficial for CBP but very high or low activity levels are not beneficial;[34] the results of a single meta-analysis also support this view.[35] Unfortunately, there were no existing GWAS that permitted the examination of non-linear relationships between activity and CBP in the current study.

The clinical implication of this work lies in public health and education. As with many prevalent chronic health conditions affecting Western populations, education and avoidance of excessive alcohol and smoking may have an important role in mitigating CBP. Additionally, depression may be a potentially modifiable risk factor for CBP. Our findings support the potential benefits of modifying these psychosocial factors as part of CBP prevention.

The present study has limitations. First, the risk factors considered in this study are subject to possible bias which may affect GWAS and MR estimates, so caution is needed when interpreting the results of psychosocial trait analyses; within-family MR studies are recommended to examine the findings reported here.[36] Second, while CAUSE analysis allows the use of overlapping samples, overlap is not recommended for IVW MR because it may lead to biased estimates.[37] Our use of both CAUSE and a sensitivity analysis

aimed to reduce the risk of bias due to confounding, and we required concordance of effect estimates across all methods. Moreover, our selection of genetic variants which exceeded the genome-wide significance threshold, should have reduced the potential for weak instrument bias. To estimate the relative bias of IVW MR estimates and type 1 error rate inflation due to sample overlap we conducted *post hoc* analyses using published formulae[38] and a web application (https://sb452.shinyapps.io/overlap/) (see Supplementary Methods). For all risk factors in forward and reverse IVW MR analyses, the relative bias did not exceed 0.3% and type 1 error was close to the nominal level (5%). Given this small bias and absence of inflation we conclude that our MR protocol incorporating both IVW MR and CAUSE was robust to sample overlap. Further studies using data from other biobanks may estimate the possible effects of assortative mating and other sources of bias. Third, no evidence of causation is not equivalent to evidence of no causation; it remains possible that risk factor-CBP and CBP-risk factor associations not confirmed as causal in the current analyses (such as the effect of sleep on CBP) may result from low statistical power. However, if undetected causal relationships do actually exist, their magnitude is likely smaller than the MR effects detected in the current study.

In summary, we found evidence that fewer years of schooling, smoking, greater alcohol consumption, and major depressive disorder have causal effects on CBP. Conversely, we found evidence that CBP has causal effects on greater alcohol consumption and smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

GWAS summary statistics used to study chronic back pain (CBP), risk factors, and potential confounders

Trait category	Trait name	Scale or unit used in GWAS	Sample size	Source
CBP	Self-reported back pain for 3+ months	log(OR)	439,831	doi:10.1007/s00586-019-06224-6
Risk factor GWAS used for Mendelian randomization analyses				
Education	Years of schooling	sd = 4.2 years of schooling	766,345	doi:10.1038/s41588-018-0147-3
Smoking	Ever smoker	sd = 0.499[a]	518,633	doi:10.1038/s41588-018-0309-3
Alcohol consumption	Alcohol intake frequency	1 alcohol category increment (never, special occasions only, 1–3 times per month, 1–2 times per week, 3–4 times per week, daily or almost daily	462,346	MRC-IEU[b]
Physical activity	Number of days/week of moderate physical activity 10+ minutes	days/week of moderate physical activity 10+ minutes	440,266	MRC-IEU [b]
	Overall activity[c]	sd of overall activity (units not specified)	91,105	doi:10.1038/s41467-018-07743-4
	Sedentary behaviour[c]	sd of overall activity (units not specified)	91,105	doi:10.1038/s41467-018-07743-4
Sleep	Sleep duration	hours per day	460,099	MRC-IEU [b]
Depression	Major depressive disorder	log(OR)	500,199	doi:10.1038/s41593-018-0326-7
GWAS used to identify genetic instruments associated with potential confounders [d]				
Anxiety	Anxiety disorders	Binary	361,194	Neale Lab[e]
Neuroticism	Neuroticism sum score	sd = 3.21 neuroticism sum score	380,506	doi:10.1038/s41467-018-03242-8
Extraversion	Extraversion	arbitrary score	63,030	doi:10.1007/s10519-015-9735-5
Openness to Experience	Openness to Experience	arbitrary score	17,375	doi:10.1038/mp.2010.128
Agreeableness	Agreeableness	arbitrary score	17,375	doi:10.1038/mp.2010.128
Conscientiousness	Conscientiousness	arbitrary score	17,375	doi:10.1038/mp.2010.128
Blood pressure	Diastolic blood pressure	sd = 10.52 mmHg	436,424	MRC-IEU[b]
	Systolic blood pressure	sd = 19.31 mmHg	436,419	MRC-IEU [b]
Hyperlipidemia	LDL cholesterol	mg/dL	173,082	doi:10.1038/ng.2797
	HDL cholesterol	mg/dL	187,167	doi:10.1038/ng.2797
	Triglycerides	mg/dL	177,861	doi:10.1038/ng.2797
	Total cholesterol	mg/dL	187,365	doi:10.1038/ng.2797

Trait category	Trait name	Scale or unit used in GWAS	Sample size	Source
Type 2 diabetes	Type 2 diabetes	log(OR)	898,130	doi:10.1038/s41588-018-0241-6
Obesity	Body mass index	sd = 4.77 Kg/m^2	322,154	doi:10.1038/nature14177

log(OR) = natural logarithm of odds ratio, sd = standard deviation, LDL = low-density lipoproteins, HDL = high-density lipoproteins

[a] GWAS scale was transformed to log(OR) (see Table S1 and Supplementary methods for details)

[b] gwas.mrcieu.ac.uk

[c] GWAS data without adjustment for covariates

[d] Genetic instruments associated with potential confounders were excluded in Mendelian randomization sensitivity analyses

[e] nealelab.is/uk-biobank

Table 2.

Mendelian randomization estimates for the causal effect of risk factors on chronic back pain (CBP)

		IVW analysis				CAUSE analysis						
Exposure	**Analysis type**	**# of SNPs**	**Beta**	**SE**	**p-value**	**# of SNPs**	**Gamma**	**p-value**	**OR[f]**	**Criterion 1[a]**	**Criterion 2[b]**	**Criterion 3[c]**
Years of schooling	Primary	304	−0.612	0.040	3.0E-53	972	−0.547	2.2E-08	0.54(0.50,0.59)	Yes	Yes	Yes
	Sensitivity[d]	118	−0.547	0.055	6.7E-23	486	−0.462	2.0E-05	0.58(0.52,0.65)			
Ever smoker[e]	Primary	133	0.238	0.031	7.0E-15	809	0.227	0.0001	1.27(1.19,1.35)	Yes	Yes	Yes
	Sensitivity[d]	39	0.132	0.047	4.9E-03	350	0.164	0.013	1.14(1.04,1.25)			
Alcohol intake frequency	Primary	94	0.254	0.051	7.2E-07	773	0.261	0.029	1.29(1.17,1.43)	Yes	Yes	Yes
	Sensitivity[d]	21	0.074	0.067	2.7E-01	312	0.145	0.069	1.08(0.94,1.23)			
# of days/week of moderate physical activity 10+ minutes	Primary	16	−0.030	0.083	7.2E-01	579	0.007	0.99	0.97(0.82,1.14)	No	-	-
Overall activity	Primary	6	−0.130	0.167	4.4E-01	541	−0.104	0.39	0.88(0.63,1.22)	No	-	-
Sedentary behavior	Primary	5	−0.149	0.093	1.1E-01	490	0.040	0.88	0.86(0.72,1.03)	No	-	-
Sleep duration	Primary	65	−0.322	0.116	5.4E-03	715	−0.373	0.002	0.72(0.58,0.91)	Yes	Yes	No
	Sensitivity[d]	14	0.037	0.157	8.1E-01	310	−0.409	0.026	1.04(0.76,1.41)			
Major depressive disorder	Primary	46	0.347	0.055	2.5E-10	662	0.291	0.017	1.41(1.27,1.58)	Yes	Yes	Yes
	Sensitivity[d]	6	0.402	0.092	1.3E-05	279	0.263	0.002	1.49(1.25,1.79)			

IVW=inverse variance weighted meta-analysis, CAUSE= Causal Analysis Using Summary Effect, SNP=single nucleotide polymorphism, OR = odds ratio

Results highlighted in red are statistically significant (p-value<0.003125 = 0.05/(8*2)); further details of Mendelian randomization results are provided in Supplemental Tables S2, S4, S5

[a]Criterion 1: significant (p <0.003125) associations in IVW or CAUSE

[b]Criterion 2: magnitude and direction of the effect estimates is concordant between IVW and CAUSE

[c]Criterion 3: direction of the effect estimates is concordant between primary analysis and both sensitivity analyses

[d]For CAUSE sensitivity analyses, SNPs associated with other risk factors with p < 5E-7 (22 risk factors, see Table S1) were excluded. For IVW sensitivity analyses, SNPs associated with other risk factors with p < 5E-7 (22 risk factors, see Table S1) were excluded, as were SNPs identifed by MR PRESSO as horizontal pleiotropy outliers.

[e]Mendelian randomization estimates both for IVW and CAUSE were transformed using scaling coefficient (see Table S2 and Supplementary methods)

[f] Odds ratio estimates were obtained from Beta IVW, lower and upper estimates of OR are provided in brackets (95% CI). Of note, ORs reflect 95% CI and therefore do not correlate with the Bonferroni-corrected threshold for statistical significance ($p < 0.003125$).

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Table 3.

Mendelian randomization estimates for the causal effect of chronic back pain (CBP) on risk factors

		IVW analysis				CAUSE analysis						
Outcome	**Analysis type**	**# of SNPs**	**Beta**	**SE**	**p-value**	**# of SNPs**	**Gamma**	**p-value**	**OR[f]**	**Criterion 1[a]**	**Criterion 2[b]**	**Criterion 3[c]**
Years of schooling	Primary	21	−0.145	0.043	6.87E-04	611	−0.126	2.97E-06	0.86(0.80,0.94)	Yes	Yes	No
	Sensitivity[d]	0	-	-	-	292	−0.081	1.09E-02	-			
Ever smoker[e]	Primary	21	0.191	0.067	4.53E-03	609	0.243	1.79E-05	1.21(1.06,1.38)	Yes	Yes	Yes
	Sensitivity[d]	1	0.015	0.134	9.09E-01	263	0.121	6.78E-02	1.02(0.78,1.32)			
Alcohol intake frequency	Primary	21	0.178	0.048	2.16E-04	609	0.124	2.05E-04	1.19(1.09,1.31)	Yes	Yes	Yes
	Sensitivity[d]	3	0.055	0.050	2.72E-01	259	0.083	6.13E-02	1.06(0.96,1.17)			
# of days/week of moderate physical activity 10+ minutes	Primary	21	−0.020	0.046	6.64E-01	609	0.051	2.97E-01	0.98(0.90,1.07)	No	-	-
Overall activity	Primary	20	−0.101	0.034	3.13E-03	620	−0.038	2.89E-01	0.90(0.84,0.97)	No	-	-
Sedentary behavior	Primary	20	0.052	0.036	1.46E-01	620	−0.007	9.99E-01	1.05(0.98,1.13)	No	-	-
Sleep duration	Primary	21	−0.044	0.020	2.79E-02	609	−0.039	1.00E-01	0.96(0.92,1.00)	No	-	-
Major depressive disorder	Primary	18	0.227	0.070	1.22E-03	608	0.233	9.76E-05	1.26(1.09,1.44)	Yes	Yes	No
	Sensitivity[d]	1	−0.124	0.145	3.91E-01	254	0.170	1.03E-02	0.88(0.67,1.17)			

IVW=inverse variance weighted meta-analysis, CAUSE= Causal Analysis Using Summary Effect, SNP=single nucleotide polymorphism, OR = odds ratio

Results highlighted in red are statistically significant (p-value<0.003125 = 0.05/(8*2)); further details of Mendelian randomization results are provided in Supplemental Tables S3, S6, S7

[a]Criterion 1: significant (p <0.003125) associations in IVW or CAUSE

[b]Criterion 2: magnitude and direction of the effect estimates is concordant between IVW and CAUSE

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[f]Odds ratio estimates were obtained from Beta IVW, lower and upper estimates of OR are provided in brackets (95% CI). Of note, ORs reflect 95% CI and therefore do not correlate with the Bonferroni-corrected threshold for statistical significance (p <0.003125).