

Sedentary behaviour increases the risk of infection and death: a two-sample Mendelian randomisation study

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Abstract

Background

Observational studies associate physical activity and sedentary behaviour with infection risk, but confounding and reverse causation remain concerns. We used Mendelian randomisation (MR) to investigate associations of genetically proxied sedentary behaviour and moderate-to-vigorous physical activity (MVPA) with bacterial infection outcomes.

Methods

We conducted two-sample MR analyses using summary-level genetic data. Associations with any infection, infection-related mortality, pneumonia, and urinary tract infection (UTI) were estimated separately in the new GWAS performed in the Merged Anaesthesia and Intensive Care Cohort of Sweden (MAICS) and UK Biobank (UKBB). Inverse-variance weighting was the primary method, followed by common-effect meta-analysis. Sensitivity analyses assessed robustness.

Results

The analyses included up to 466,087 participants. Per 1-standard deviation increase in genetically proxied leisure sedentary behaviour, pooled odds ratios (OR) were 1.43 (95% CI 1.33–1.53) for any infection, 1.55 (95% CI 1.29–1.87) for infection-related mortality, 1.54 (95% CI 1.38–1.71) for pneumonia, and 1.28 (95% CI 1.15–1.42) for UTI. Associations with any infection and pneumonia were observed in both cohorts, whereas the other associations were more pronounced in UKBB. In pooled analyses, genetic liability to higher MVPA was inversely associated with any infection (OR 0.81, 95% CI 0.71–0.93) and UTI (OR 0.72, 95% CI 0.55–0.95). Sensitivity analyses indicated SNP-level heterogeneity in several television-watching analyses and possible directional horizontal pleiotropy for MVPA associations with pneumonia and UTI in UKBB.

Conclusions

Higher genetically proxied sedentary behaviour was associated with higher odds of all studied infectious outcomes, whereas genetic liability to higher MVPA was associated with lower odds of several infection outcomes. These findings support a possible role of activity-related behaviours in infection susceptibility, but pleiotropy, heterogeneity, and sample overlap limit causal interpretation.

Background

Bacterial infections are among the leading causes of death worldwide.⁽¹⁾ The risk of developing an infection and of dying from infection is influenced by multiple factors, including age, comorbidity, and

pre-existing health status.(2) Physical activity may affect these risks through its associations with cardiovascular and metabolic health, immune function, systemic inflammation, and physiological reserve. (3, 4) Since a large proportion of the population does not achieve even the recommended levels of physical activity, physical activity may represent a potentially modifiable determinant of infection risk. (5)

Observational studies have associated higher levels of physical activity with a lower risk of developing infection(6–8) and of infection-related mortality.(8, 9) Physical activity and sedentary behaviour, however, are associated with socioeconomic position, smoking, other health-related behaviours and pre-existing health status.(10) These factors may confound observational associations, while underlying disease may reduce physical activity and thereby introduce reverse causation. Residual confounding by unmeasured or inadequately measured factors is also likely.

Mendelian randomisation (MR) uses genetic variants associated with an exposure as instrumental variables to assess whether the exposure may have a causal effect on an outcome. Because genetic variants are assigned at conception, MR may reduce bias from conventional confounding and reverse causation, provided that the instrumental-variable assumptions are satisfied. (11) In a two-sample MR design, associations between genetic variants and sedentary behaviour or physical activity are obtained from an exposure genome-wide association study (GWAS), while associations between the same variants and infection outcomes are obtained from a separate outcome GWAS. Previous MR studies have examined sepsis and COVID-19, and a recent hypothesis-free phenome-wide effort screened several infection-related diagnoses. However, evidence specifically addressing multiple bacterial infections and infection-related mortality remains limited.(12–14)

The aim of this study was to investigate whether genetically proxied sedentary behaviour and physical activity were associated with the risk of developing bacterial infection and with infection-related mortality, using two-sample MR analyses across large population-based datasets.

Methods

We conducted two-sample MR analyses to investigate the potential causal effects of genetically proxied sedentary behaviour and physical activity on the risk of developing bacterial infection and on infection-related mortality. MR uses genetic variants, typically single-nucleotide polymorphisms (SNPs), as instrumental variables for an exposure. Because genetic variants are randomly assigned at conception, MR may reduce bias from conventional confounding and reverse causation and support causal inference, provided that three instrumental-variable assumptions are satisfied: (1) the genetic variants are associated with the exposure; (2) the genetic variants are independent of confounders of the exposure–outcome association; and (3) the genetic variants affect the outcome exclusively through the exposure and not through alternative pathways, including horizontal pleiotropy. Genetic associations with physical activity and sedentary behaviour were obtained from exposure GWASs, and associations with infection outcomes were obtained from separate outcome datasets. The study adhered to the

Instrumental variables

The National Human Genome Research Institute–European Bioinformatics Institute (NHGRI-EBI) GWAS Catalog(16) was searched on 1 March 2025 for genome-wide association studies of physical activity and sedentary behaviour. We selected two large GWASs with publicly available genetic association data: a GWAS of leisure television watching as a domain-specific measure of sedentary behaviour and a meta-GWAS of moderate-to-vigorous physical activity during leisure time (MVPA).(17, 18)

Van de Vegte et al. conducted GWASs of three self-reported leisure sedentary behaviours (television watching, computer use, and driving) among 422,218 participants of European ancestry from the UK Biobank. 54.3% of these were women and the mean age was 57.4 years. (17) The analysis of leisure television watching included 408,815 participants. Participants reported the number of hours spent watching television on a typical day, and the phenotype was inverse-rank normalised before analysis. The original study identified 152 independent SNPs in 145 loci associated with leisure television watching at $p < 1 \times 10^{-8}$, after LD-clumping using an r^2 threshold of 0.005 within a 5-Mb window. These SNPs were considered candidate instrumental variables (GWAS Catalog accession GCST010084). 150 SNPs were available in the UK Biobank (UKBB, described below) outcome summary statistics, of which 145 were retained after harmonisation and included in the MR analyses. In the Merged Anaesthesia and Intensive Care Cohort of Sweden (MAICS, described below), 106 SNPs were available in the outcome summary statistics, of which 100 were retained after harmonisation. The same sets of SNPs were used for all four infection outcomes within each cohort.

Wang et al. performed a meta-analysis of GWASs from 51 studies to identify genetic variants associated with several self-reported physical activity and sedentary behaviour phenotypes.(18) MVPA was harmonised across the contributing studies as a dichotomous, cohort-specific phenotype reflecting participation in moderate-to-vigorous physical activity during leisure time. In most cohorts, including UKBB, participants reporting at least 20 minutes of MVPA per week were classified as active, although the exact definitions varied between cohorts. Accordingly, the MR estimates were interpreted as reflecting genetic liability to higher MVPA rather than the effect of a specific increase in minutes of physical activity. The primary European-ancestry meta-analysis included up to 606,820 participants, while the corresponding multi-ancestry analysis included up to 636,924 participants. Eight lead SNPs associated with MVPA at $p < 5 \times 10^{-9}$ were extracted from Supplementary Table 3 of the original publication and selected as instrumental variables: six originated from the European-ancestry meta-analysis (GWAS Catalog accession GCST90104341) and two from the multi-ancestry meta-analysis (GCST90104342). No additional LD-clumping was performed because the selected variants represented independent lead signals identified in the original GWASs. All eight MVPA variants were available, retained after harmonisation, and included in the UKBB analyses. In MAICS, rs142601240 was unavailable in the outcome summary statistics; the remaining seven variants were retained after

harmonisation and included in the MR analyses. The same sets of variants were used for all four infection outcomes within each outcome cohort.

Outcome data

Genetic associations with the infection outcomes were estimated separately in two cohorts: the Merged Anaesthesia and Intensive Care Cohort of Sweden (MAICS) and the UK Biobank (UKBB).

MAICS was assembled from genotyped participants in two Swedish cohorts and biobanks. EpiHealth comprises 25,104 individuals aged 45–75 years who were recruited in Uppsala and Malmö between 2010 and 2016.⁽¹⁹⁾ SIMPLER comprises two prospective population-based cohorts: the Swedish Mammography Cohort (SMCC), originally including 61,433 women from Uppsala and Västmanland counties who were enrolled in 1987–1990, and the Cohort of Swedish Men (COSM), originally including 45,906 men from Västmanland and Örebro counties who were enrolled in 1997.⁽²⁰⁾ After genotyping, quality control, and removal of duplicate individuals across the source cohorts, MAICS included 57,423 unique participants. Participants were linked through their personal identity numbers to nationwide health registers, including the National Patient Register and the Cause of Death Register

UKBB is a prospective population-based cohort of 502,271 participants aged 40–69 years at recruitment between 2006 and 2010.⁽²¹⁾ Genome-wide genotype data were available for approximately 488,000 participants. After genetic quality control and application of the study-specific inclusion criteria, 408,664 participants were included in the present analyses. Phenotypic data were obtained through linkage to national hospital and mortality records.

Bacterial infection outcomes were identified using prespecified International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10), codes recorded in hospital and mortality registers. Complete code lists with mapping between ICD-9 and ICD-10 are provided in Supplementary Table 1. Four outcomes were analysed: (1) any infection, defined as at least one recorded diagnosis included in the composite infection phenotype; (2) infection-related mortality, defined as an underlying or contributing cause of death corresponding to any code included in the composite phenotype; (3) pneumonia; and (4) urinary tract infection

Statistical analyses

Genome-wide association analyses of the four binary outcomes (any infection, pneumonia, urinary tract infection, and infection-related mortality, as defined above) were performed separately in UKBB and MAICS. Binary-trait association testing was performed for both, using mixed models to control for relatedness and population structure in the data. Variants with a minor allele frequency of 0.5% or lower or genotype missingness greater than 10% were excluded. Variants were additionally excluded if INFO score was below 0.8.

UKBB GWAS was performed using Regenie (version 3.4.1), including only Caucasians. Approximate Firth likelihood ratio test was used for variants with a p-value below 0.01. Covariates included sex, age, and

the first ten genetic principal components.

MAICS was created using both cases and controls from the two genotyped Swedish cohorts EpiHealth and SIMPLER including sub-cohorts SMCC and COSM. Each cohort was imputed separately by the respective data provider. Imputation to Genome Reference Consortium Human Build 37 (GRCh37) was performed using the Haplotype Reference Consortium (HRC 1.1) reference panel on the Michigan Imputation Server. Genotyping was performed on Illumina Infinium Global Screening Array Multiple Disease (GSA-MD) for EpiHealth and SMCC, and Illumina Infinium Global Screening Array version 3 (GSAv3) for SIMPLER and COSM.

MAICS GWAS was performed using fastGWA-GLMM(22) (GCTA version 1.94.1), excluding subjects born outside Europe. Covariates included sex, age, the first ten genetic principal components, and genotyping batch.

For infection cases, age was defined as age at the first recorded diagnosis of the corresponding infection outcome. For controls, age was calculated at the median calendar date of the first recorded diagnosis among cases for the corresponding outcome and cohort. Mendelian randomisation analyses were conducted in R (version 4.3.1) using the TwoSampleMR package(23, 24) (version 0.5.7). Exposure and outcome associations were harmonised to align effect alleles. Palindromic variants with intermediate allele frequencies, for which allele orientation could not be determined reliably, were excluded. For each SNP, a Wald ratio was calculated by dividing the SNP–outcome association by the corresponding SNP–exposure association. SNP-specific Wald ratios were combined using the inverse-variance weighted (IVW) method, which was the primary analysis for all exposure–outcome combinations. The IVW method assumes that the genetic variants are valid instrumental variables or, under a random-effects formulation, that horizontal pleiotropic effects are balanced and independent of instrument strength.

Robustness was assessed using weighted-median and MR-Egger regression. The weighted-median estimator can provide a consistent estimate if at least 50% of the total weight is contributed by valid instrumental variables. MR-Egger regression was used to estimate the association while allowing for directional horizontal pleiotropy. The MR-Egger intercept was used to test for evidence of directional pleiotropy.

Heterogeneity among the SNP-specific estimates was assessed using Cochran's Q statistic. Leave-one-out analyses were performed to identify variants that disproportionately influenced the IVW estimate.

Instrument strength was assessed using the approximate F statistic, calculated as β_x^2/SE_x^2 for each SNP, where β_x and SE_x denote the SNP–exposure association and its standard error. The mean, range, and number of SNPs with an F statistic below 10 were determined separately for each harmonised instrument set. For the binary MVPA exposure, these values were regarded as approximate or pseudo-F statistics.

MR analyses were initially performed separately in MAICS and UKBB. Cohort-specific IVW estimates were subsequently combined using common-effect meta-analysis using the meta package(25) (version 6.5.0). Between-cohort heterogeneity was assessed using Cochran's Q and I^2 .

MR estimates for infection outcomes were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Estimates for television watching were expressed per one-standard-deviation increase in the exposure. Because MVPA was defined as a binary phenotype in the source GWAS, MR estimates were expressed as odds ratios for the outcome per one-unit increase in the genetically predicted log odds of being classified as physically active. All statistical tests were two-sided. The study protocol and details were not preregistered.

OpenAI's ChatGPT was used to improve grammar and readability and to assist with developing and refining the analytical code. All AI-generated outputs were reviewed and verified by the authors.

Results

GWAS

At the prespecified genome-wide significance threshold of 5×10^{-8} , the GWAS of any infection identified 273 independent loci in UKBB, whereas no genome-wide significant loci were identified in MAICS. The corresponding analyses identified 61 loci for pneumonia and 7 loci for urinary tract infection in UKBB, but none in MAICS. No genome-wide significant loci were identified for infection-related mortality in either cohort. (Supplementary Fig. 1, A-H) The numbers of cases and controls included in each GWAS are presented in Table 1.

Table 1
Baseline data for outcome GWAS.

Total sample size, n	MAICS	UKBB
	57,423	408,664
Sex, n (%)	33,594 (58.5)	187,710 (45.9)
Men	23,829 (41.5)	220,954 (54.1)
Women		
Age, median (min, max)	68 (19, 103)	62 (15, 86)
Any infection, n (%)	21,206 (36.9)	147,855 (36.2)
Cases	36,217 (63.1)	260,809 (63.8)
Controls		
Infection-related mortality, n (%)	2,951 (7.5)	7,237 (1.8)
Cases	36,217 (92.5)	401,427 (98.2)
Controls		
Pneumonia, n	7,698 (13.4)	29,353 (7.2)
Cases	49,725 (86.6)	379,311 (92.8)
Controls		
UTI, n	6,851 (11.9)	29,296 (7.2)
Cases	50,572 (88.1)	379,368 (92.8)
Controls		
GWAS, Genome wide association study; MAICS, Merged Anaesthesia and Intensive Care Cohort of Sweden; UKBB, United Kingdom BioBank; UTI, urinary tract infection.		

The GWAS of any infection in UKBB showed two significant peaks on chromosome 2, and one on chromosome 10. The lead variant for the main peak on chromosome 2 was rs75331444 (2:44069772:G:A, EAF = 0.065, $P = 5.5e-18$), an intron variant associated with the ABCG8 gene. The second peak on chromosome 2 has rs1559068778 (2:144349506:ACT:A, EAF = 0.821, $P = 1.8e-16$) as lead SNP, which has no annotation, and neither does the secondary lead SNP rs6430037 (2:144356694:T:A, EAF = 0.821, $P = 2.5e-16$). rs7894565 (10:21872913:T:C, EAF = 0.309, $P = 4.2e-11$) is an intron variant associated with the MLLT10 gene.

Additionally, there are several smaller peaks identified on chromosomes 1 (lead variant rs10910384 (1:234353053:A:C, EAF = 0.164, $P = 4.4e-09$), an intron variant associated with the SLC35F3 gene), 6 (lead variant rs148844907 (6:31628397:T:A, EAF = 0.013, $P = 8.2e-09$), a 5' UTR variant associated with

the C6orf47), 9 (lead variant rs4743923 (9:96251061:T:C, EAF 0.359, $P = 2.2 \times 10^{-8}$), which has no annotation, and neighbouring variant rs7864396 (9:96251318:A:C, EAF = 0.359, $P = 2.8 \times 10^{-8}$), an intron variant associated with the FAM120A gene), 15 (lead variants rs112761061 (15:76851548:T:A, EAF = 0.487, $P = 1.5 \times 10^{-8}$), no annotation, and rs146660740 (15:43796307:A:AC, EAF = 0.242, $P = 2.5 \times 10^{-8}$), an intron variant associated with the TP53BP1 gene), 16 (lead variant rs79501485 (16:84939983:G:C, EAF = 0.088, $P = 3.03 \times 10^{-9}$), no annotation), and 19 (lead variant rs660745 (19:49219459:T:C, EAF = 0.545, $P = 2.7 \times 10^{-8}$), and intron variant associated with the MAMSTR gene).

The pneumonia GWAS in UKBB identified a main peak at chromosome 15 and some individually significant variants on chromosome 1, 5, and 7. The lead SNP on chromosome 15 was rs2568489 (15:78737483:T:A, EAF = 0.387, $P = 1.4 \times 10^{-10}$), which has no annotation, unlike the second peak rs72738736 (15:78765122:G:T, EAF = 0.327, $P = 1.6 \times 10^{-10}$), which is an intron variant associated with the IREB2 gene.

The urinary tract infection GWAS in UKBB only had a peak at chromosome 19, with lead variant rs157592 (19:45424514:A:C, EAF = 0.186, $P = 3.5 \times 10^{-9}$), an intergenic variant associated with the APOC1 gene. This variant has previously been associated with Alzheimer's disease,(26) and increased VLDL measurements.(27)

Associations with previous infectious disease GWASs are presented in Supplementary Table 2.(28)

Genetic instruments and instrument strength

Harmonized SNP-specific associations with the exposures and outcomes, including effect and other alleles, effect estimates, standard errors, and effect allele frequencies, are provided in Supplementary Tables 3–18.

The genetic instruments were strong. For leisure television watching, the 145 SNPs included in the UKBB analyses had a mean approximate F statistic of 44.7, while the 100 SNPs retained in the MAICS analyses had a mean F statistic of 45.9 (range 32.9–144.2 in both cohorts). No television-watching SNP had an F statistic below 10. The corresponding mean pseudo-F statistic for the MVPA instruments was 43.0 in UKBB and 44.1 in MAICS (range 34.6–81.4 in both cohorts) with no SNPs below 10.

Sedentary behaviour

A 1-SD increase in genetically proxied leisure television watching was associated with higher odds of any infection in both MAICS (OR 1.27, 95% CI 1.07–1.51) and UKBB (OR 1.46, 95% CI 1.36–1.57). Similar associations were observed for pneumonia in MAICS (OR 1.54, 95% CI 1.19–2.00) and UKBB (OR 1.54, 95% CI 1.37–1.73). In UKBB, higher genetically proxied television watching was also associated with infection-related mortality (OR 1.69, 95% CI 1.38–2.09) and urinary tract infection (OR 1.34, 95% CI 1.20–1.50). The corresponding MAICS analyses were not statistically significant for infection-related mortality (OR 1.10, 95% CI 0.73–1.67) or urinary tract infection (OR 1.00, 95% CI 0.77–1.30) (Fig. 1; Supplementary Fig. 2).

Weighted-median estimates were directionally consistent with the IVW estimates. MR-Egger estimates were also generally directionally consistent, although several were imprecise and had confidence intervals that included the null. The MR-Egger intercept provided no evidence of average directional horizontal pleiotropy in television-watching analyses except for the UKBB pneumonia analysis where the intercept was nominally different from zero (intercept = 0.009, $p = 0.049$), suggesting possible directional horizontal pleiotropy (Table 2).

Table 2
MR results for the effect of leisure sedentary behaviour on the risk of infections including test for horizontal pleiotropy

Outcome	MR Egger				
	Method	OR (95% CI)	p-value	Intercept	p-value
Any infection (MAICS)	IVW	1.27 (1.07–1.51)	0.007	-0.000	0.947
	MR-Egger		0.508		
	WM	1.30 (0.60–2.83)	0.066		
		1.28 (0.98–1.66)			
Any infection (UKBB)	IVW	1.46 (1.36–1.57)	< 0.001	-0.001	0.718
	MR-Egger		0.011		
	WM	1.55 (1.11–2.17)	< 0.001		
		1.45 (1.33–1.58)			
Infection-related mortality (MAICS)	IVW	1.10 (0.73–1.67)	0.648	0.004	0.797
	MR-Egger		0.881		
	WM	0.87 (0.13–5.60)	0.297		
		1.37 (0.76–2.49)			
Infection-related mortality (UKBB)	IVW	1.69 (1.38–2.09)	< 0.001	-0.009	0.239
	MR-Egger		0.026		
	WM	2.94 (1.15–7.54)	0.043		
		1.37 (1.01–1.86)			
Pneumonia (MAICS)	IVW	1.54 (1.19–2.00)	0.001	0.006	0.526
	MR-Egger		0.917		
	WM	1.06 (0.33–3.44)	0.016		
		1.55 (1.09–2.22)			

Odds ratios representing the effect of one standard deviation increase in sedentary behaviour on the risk of the outcome. MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; MAICS, Merged Anaesthesia and Intensive Care cohort from Sweden; IVW, inverse-variance weighted meta-analysis; WM, weighted median meta-analysis; UKBB, UK biobank; UTI, urinary tract infection.

Outcome	MR Egger				
	Method	OR (95% CI)	p-value	Intercept	p-value
Pneumonia (UKBB)	IVW	1.54 (1.37–1.73)	< 0.001	-0.009	0.049
	MR-Egger		< 0.001		
	WM	2.60 (1.53–4.42)	< 0.001		
		1.60 (1.38–1.85)			
UTI (MAICS)	IVW	1.00 (0.77–1.30)	0.990	-0.000	0.976
	MR-Egger		0.975		
	WM	1.02 (0.32–3.27)	0.540		
		1.12 (0.78–1.62)			
UTI (UKBB)	IVW	1.34 (1.20–1.50)	< 0.001	-0.004	0.340
	MR-Egger		0.042		
	WM	1.71 (1.03–2.85)	< 0.001		
		1.38 (1.19–1.59)			
Odds ratios representing the effect of one standard deviation increase in sedentary behaviour on the risk of the outcome. MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; MAICS, Merged Anaesthesia and Intensive Care cohort from Sweden; IVW, inverse-variance weighted meta-analysis; WM, weighted median meta-analysis; UKBB, UK biobank; UTI, urinary tract infection.					

In UKBB, Cochran's Q indicated heterogeneity among the SNP-specific estimates for any infection (IVW: Q = 283, df = 144, p < 0.001; MR-Egger: Q = 283, df = 143, p < 0.001), pneumonia (IVW: Q = 213, df = 144, p < 0.001; MR-Egger: Q = 207, df = 143, p < 0.001), and urinary tract infection (IVW: Q = 192, df = 144, p = 0.004; MR-Egger: Q = 191, df = 143, p = 0.004). No statistically significant heterogeneity was detected for infection-related mortality in UKBB or for any outcome in MAICS. The observed heterogeneity indicates variation among the SNP-specific estimates. The MR-Egger intercept being different from zero in the UKBB pneumonia analysis, suggesting possible average directional horizontal pleiotropy in this analysis; no corresponding evidence was observed for the other outcomes.

In leave-one-out analyses, exclusion of individual SNPs slightly changed the magnitude of the IVW estimates. No individual SNP changed the direction of an estimate or altered the overall conclusions (Supplementary Fig. 3).

Common-effect meta-analysis of the cohort-specific IVW estimates supported associations between higher genetically proxied leisure television watching and all four infection outcomes (Fig. 2, A-D).

Pooled estimates were OR 1.43 (95% CI 1.33–1.53) for any infection, OR 1.55 (95% CI 1.29–1.87) for infection-related mortality, OR 1.54 (95% CI 1.38–1.71) for pneumonia, and OR 1.28 (95% CI 1.15–1.42) for urinary tract infection (all $p < 0.001$). There was no evidence of between-cohort heterogeneity for pneumonia (Cochran's $Q = 0.00$, $df = 1$, $p = 0.979$; $I^2 = 0.0\%$). Between-cohort heterogeneity was detected for urinary tract infection ($Q = 4.06$, $df = 1$, $p = 0.044$; $I^2 = 75.4\%$). For any infection ($Q = 2.12$, $df = 1$, $p = 0.146$; $I^2 = 52.8\%$) and infection-related mortality ($Q = 3.32$, $df = 1$, $p = 0.069$; $I^2 = 69.9\%$), the Q tests did not reach statistical significance, although the I^2 estimates suggested possible between-cohort inconsistency.

Physical Activity

In UKBB, higher genetically proxied MVPA was associated with lower odds of any infection in the primary IVW analysis (OR 0.81, 95% CI 0.70–0.95). No statistically significant associations were observed for the other three outcomes in the UKBB analyses or for any outcome in MAICS (Fig. 3; Supplementary Fig. 4).

Weighted-median point estimates were generally directionally consistent with the IVW estimates, although none were statistically significant (Table 3). In contrast, the MR-Egger point estimates were generally in the opposite direction and were highly imprecise. The MR-Egger intercepts provided nominal evidence of average directional horizontal pleiotropy in the UKBB analyses of pneumonia (intercept -0.038 , $p = 0.038$) and UTI (intercept -0.035 , $p = 0.049$). These findings suggest that the corresponding IVW estimates may be affected by directional horizontal pleiotropy. No evidence of average directional horizontal pleiotropy was detected in the remaining analyses.

Table 3

MR results for the effect of moderate to vigorous intensity physical activity on the risk of infections including test for horizontal pleiotropy

Outcome	MR Egger				
	Method	OR (95% CI)	p-value	Intercept	p-value
Any infection (MAICS)	IVW	0.80 (0.54–1.17)	0.249	-0.043	0.147
	MR-Egger		0.210		
	WM	3.87 (0.61–24.45)	0.889		
		0.96 (0.58–1.60)			
Any infection (UKBB)	IVW	0.81 (0.70–0.95)	0.007	-0.017	0.069
	MR-Egger		0.209		
	WM	1.48 (0.86–2.56)	0.309		
		0.91 (0.77–1.09)			
Infection-related mortality (MAICS)	IVW	0.85 (0.35–2.06)	0.717	-0.014	0.819
	MR-Egger		0.879		
	WM	1.42 (0.02–99.92)	0.767		
		0.85 (0.30–2.44)			
Infection-related mortality (UKBB)	IVW	0.76 (0.46–1.24)	0.272	0.023	0.471
	MR-Egger		0.374		
	WM	0.34 (0.04–2.76)	0.644		
		0.86 (0.44–1.66)			
Pneumonia (MAICS)	IVW	0.96 (0.54–1.68)	0.876	-0.029	0.486
	MR-Egger		0.512		
	WM	2.77 (0.16–47.11)	0.804		
		1.09 (0.54–2.20)			

Odds ratios representin one-unit increase in the genetically predicted log odds of being classified as physically active. MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; MAICS, Merged Anaesthesia and Intensive Care cohort from Sweden; IVW, inverse-variance weighted meta-analysis; WM, weighted median meta-analysis; UKBB, UK biobank; UTI, urinary tract infection.

Outcome	MR Egger				
	Method	OR (95% CI)	p-value	Intercept	p-value
Pneumonia (UKBB)	IVW	0.80 (0.61–1.04)	0.095	-0.038	0.038
	MR-Egger		0.076		
	WM	3.03 (1.10–8.36)	0.620		
		0.92 (0.67–1.27)			
UTI (MAICS)	IVW	0.61 (0.34–1.08)	0.087	-0.017	0.653
	MR-Egger		0.915		
	WM	1.17 (0.07–18.53)	0.684		
		0.86 (0.40–1.81)			
UTI (UKBB)	IVW	0.76 (0.56–1.04)	0.083	-0.035	0.049
	MR-Egger		0.112		
	WM	2.62 (0.95–7.22)	0.589		
		0.92 (0.66–1.26)			
Odds ratios representin one-unit increase in the genetically predicted log odds of being classified as physically active. MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; MAICS, Merged Anaesthesia and Intensive Care cohort from Sweden; IVW, inverse-variance weighted meta-analysis; WM, weighted median meta-analysis; UKBB, UK biobank; UTI, urinary tract infection.					

Cochran's Q tests did not provide evidence of heterogeneity among the SNP-specific estimates in any of the MVPA analyses ($p = 0.109–0.945$). Leave-one-out estimates were generally stable, and exclusion of individual variants did not materially alter the overall conclusions. In the analysis of MVPA and pneumonia in MAICS, exclusion of either rs1625595 or rs1160545 shifted the point estimate from below to above the null. Except for the analysis on any infection in UKBB, all leave-one-out estimates were imprecise, with confidence intervals that included the null (Supplementary Fig. 5).

Common-effect meta-analysis of the cohort-specific IVW estimates showed statistically significant inverse associations between higher genetically proxied MVPA and any infection (OR 0.81, 95% CI 0.71–0.93; $p = 0.003$) and urinary tract infection (OR 0.72, 95% CI 0.55–0.95; $p = 0.020$), but not infection-related mortality (OR 0.78, 95% CI 0.51–1.20; $p = 0.256$) or pneumonia (OR 0.82, 95% CI 0.65–1.05; $p = 0.115$) (Fig. 4A–D). There was no statistical evidence of between-cohort heterogeneity for any infection (Cochran's $Q = 0.01$, $df = 1$, $p = 0.924$; $I^2=0\%$), pneumonia ($Q = 0.33$, $df = 1$, $p = 0.565$; $I^2=0\%$), urinary tract infection ($Q = 0.46$, $df = 1$, $p = 0.496$; $I^2=0\%$) or infection-related mortality ($Q = 0.05$, $df = 1$, $p = 0.829$; $I^2=0\%$).

Discussion

In this two-sample Mendelian randomisation study, higher genetically proxied sedentary behaviour was associated with higher odds of acquiring and dying from infection in pooled analyses, with consistent cohort-specific associations for any infection and pneumonia. Conversely, genetic liability to higher MVPA was associated with lower odds of any infection and urinary tract infection in the pooled analyses. These associations however, did not reach statistical significance in the separate cohorts. Together, these complementary findings suggest that activity-related behaviours may influence susceptibility to infection, while pleiotropy, heterogeneity, and sample overlap warrant cautious causal interpretation.

Despite differences in how infection groups were defined, several of our lead variants overlapped with loci reported by Tängdén et al.(28) The clearest overlap was on chromosome 2, where one of our lead signals for any infection in UK Biobank was strongly correlated with a Tängdén abdominal-infection lead SNP at the same locus, and that variant was itself genome-wide significant in our any-infection GWAS. A comparable but weaker overlap was seen on chromosome 1, where one of our lead variants, a modest signal rather than a well-defined peak, was correlated with a Tängdén abdominal-infection SNP that was likewise significant in our data. On chromosome 16, a weakly significant variant from our analysis showed only slight correlation with a further Tängdén abdominal-infection SNP.

For other regions the signals appeared to be independent. On chromosome 6, our any-infection variant was in linkage equilibrium with both of Tängdén's signals in that region, one respiratory and one abdominal, indicating distinct associations despite the shared locus. Similarly, our chromosome 15 any-infection variant was in linkage equilibrium with Tängdén's bacterial-pneumonia signal, which was not significant in our studies. Two comparisons could not be completed. Tängdén's bacterial-pneumonia signal lies close to the lead SNP from our pneumonia GWAS, but the latter is absent from the 1000 Genomes reference panel, so linkage disequilibrium could not be calculated. Finally, our chromosome 10 lead variant for any infection was not reported by Tängdén et al.

Our findings are broadly consistent with observational studies reporting associations between higher physical activity and lower risks of community-acquired pneumonia, sepsis, other bacterial infections, and infection-related mortality. (6–9) They also align with previous MR studies linking sedentary behaviour and physical activity to lower risks of sepsis and severe COVID-19, although these studies were restricted to specific infectious outcomes.(12, 13) A recent MR-Phenome Wide Association Study similarly found directionally concordant estimates for unspecified bacterial infection, influenza/pneumonia, and cystitis, although these associations did not meet Bonferroni-corrected threshold. Unlike this hypothesis-free screen, our study prespecified bacterial infection outcomes including infection-related mortality, and assessed outcome in two different cohorts.(14)

The associations were more consistent and more precisely estimated for leisure television watching than for MVPA. However, the magnitudes of these associations cannot be compared directly because the two exposures were measured on different scales and represented distinct behavioural constructs. Moreover, the television-watching instrument included 100–145 variants, whereas only seven or eight

variants were available for MVPA. The apparent difference may therefore reflect differences in instrument strength and statistical precision rather than a stronger biological effect of sedentary behaviour. Physical activity and sedentary behaviour are not direct opposites either, as individuals may meet recommendations for physical activity while spending substantial time sedentary.

The sensitivity analyses provided differing levels of support for the two exposures. For television watching, weighted-median estimates were directionally consistent with the IVW estimates. The MR-Egger generally provided no evidence of average directional horizontal pleiotropy; however, the intercept was nominally different from zero in the UKBB pneumonia analysis, suggesting possible directional horizontal pleiotropy. Substantial heterogeneity among SNP-specific estimates was also observed for several UKBB outcomes. This heterogeneity may reflect variation in SNP-specific effects or balanced horizontal pleiotropy and, together with the borderline MR-Egger intercept finding for pneumonia, warrants caution when interpreting the corresponding IVW estimates. For MVPA, weighted-median estimates were directionally consistent with IVW but less precise, whereas the MR-Egger estimates were generally in the opposite direction and highly imprecise. In addition, MR-Egger intercept tests provided nominal evidence of directional horizontal pleiotropy for pneumonia and UTI in UKBB. These findings weaken the robustness of the corresponding IVW estimates, although the limited number of MVPA instruments also resulted in low precision and limited power for MR-Egger regression.

Several biological and behavioural pathways could potentially explain the observed associations. Physical inactivity and prolonged sedentary behaviour contribute to obesity, type 2 diabetes and cardiovascular disease, all of which are associated with susceptibility to infection and adverse outcomes. If these conditions arise downstream of sedentary behaviour or physical activity, they may mediate part of the total effect estimated by MR rather than act as conventional confounders. Conversely, genetic variants that influence infection through cardiometabolic, behavioural, or socioeconomic pathways independently of the studied exposure would violate the exclusion-restriction assumption through horizontal pleiotropy.

Modulation of immune function represents another possible pathway. Observational and experimental studies suggest that regular physical activity may affect inflammatory signalling, immune-cell metabolism, mucosal immunity, and components of innate and adaptive immune function.(29–33) The present MR analyses did not evaluate immune mediators and therefore cannot establish whether altered immune function explains the observed associations.

This study has several strengths. It evaluated four clinically relevant infection outcomes using large, genotyped datasets from the United Kingdom and Sweden. The use of separate outcome datasets provided an opportunity to examine the consistency of the estimates across populations and healthcare systems. We also evaluated two related but distinct lifestyle phenotypes and applied complementary MR estimators and sensitivity analyses to assess the robustness of the findings.

Some limitations should be considered. First, exposure was based on self-reported behaviour and thus susceptible to measurement error and reporting bias.(34) Physical activity is commonly overreported,

whereas sedentary behaviour may be underreported. Such reporting patterns may attenuate differences between exposure levels and could therefore contribute to underestimation of the associations, although the direction of bias in the MR estimates is uncertain. Leisure television watching is a domain-specific behaviour and should not be interpreted as a comprehensive measure of total sedentary time. MVPA was defined using cohort-specific dichotomous measures, with some variation in the thresholds and questionnaires used. Consequently, the MVPA estimates reflect genetic liability to higher activity rather than the effect of a specified increase in physical activity duration. Second, the MVPA analyses included few variants, limiting the precision of the sensitivity analyses and the ability to detect horizontal pleiotropy. Although the television-watching analyses included substantially more variants, heterogeneity among SNP-specific estimates was present for several outcomes. Neither the absence of an MR-Egger intercept nor directional agreement between MR methods can definitively establish that all instruments satisfy the exclusion-restriction assumption. Third, there was substantial sample overlap in some analyses. UKBB provided both the exposure data for the television-watching GWAS and the outcome data for the UKBB infection analyses. UKBB also contributed to the MVPA meta-GWAS, resulting in partial overlap for the corresponding analyses. Sample overlap can bias two-sample MR estimates towards confounded observational associations and may lead to underestimated uncertainty, particularly when instruments are weak. However, the point estimates for analyses in the independent MAICS cohort were in the same direction as in UKBB which support our findings. Fourth, infection outcomes were identified from diagnostic and cause-of-death codes. Misclassification is therefore possible, and differences in coding practices and register coverage may have contributed to differences between MAICS and UKBB. The considerably smaller MAICS cohort resulted in wide confidence intervals, particularly for infection-related mortality, and absence of statistical significance should not be interpreted as evidence of no association. Moreover, the common-effect meta-analyses included only two outcome cohorts, making estimates of between-cohort heterogeneity imprecise. Finally, the study populations consisted predominantly of individuals of European ancestry and were generally middle-aged or older. The findings may therefore not be generalisable to younger populations or to populations with other genetic ancestries.

Conclusions

Higher genetically proxied leisure television watching was associated with higher odds of infection and infection-related mortality, whereas higher genetically proxied MVPA was associated with lower odds of several, but not all, infection outcomes. The television-watching findings were more consistent across methods and cohorts, while the MVPA findings were less precise and potentially affected by directional horizontal pleiotropy. These results support further investigation of sedentary behaviour and physical activity as potentially modifiable determinants of infection.

Abbreviations

CI; confidence interval

COSM; the Cohort of Swedish Men

GWAS; genome-wide association study

HRC; Haplotype Reference Consortium

ICD; International Classification of Diseases

IVW; inverse-variance weighted

MAICS; Merged Anaesthesia and Intensive Care Cohort of Sweden

MR; Mendelian randomisation

MVPA; moderate-to-vigorous physical activity

NHGRI-EBI; The National Human Genome Research Institute–European Bioinformatics Institute

OR; odds ratio

SD; standard deviation

SMCC; the Swedish Mammography Cohort

SNPs; single-nucleotide polymorphisms

STROBE-MR; Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization

UKBB; United Kingdom Biobank

UTI; urinary tract infection

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and applicable national ethical regulations. It was approved by the National Ethical Review Agency, Stockholm, Sweden (DNR 2021-05478-01 with amendments 2021-06705-02, 2022-05728-02, Ö11-2023/3.1, 2023-02342-02, 2023-04512-02 and 2024-02090-02), which waived the requirement for individual informed consent.

Consent for publication

Not applicable

Availability of data and materials

Exposure data are available in the studies by Van de Vegte (17) and Wang et al. (18). Outcome data from the new GWASs are uploaded to the European Genome-phenome Archive (EGA; <https://ega-archive.org>). Coding is available upon request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in the conceptualisation of the study which was planned in detail by KS and ME. BB, MMH and ML performed initial data handling. BB, ME and MMH performed the analyses. KS and ME wrote the first manuscript draft. All authors read and approved the final manuscript.

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Figures

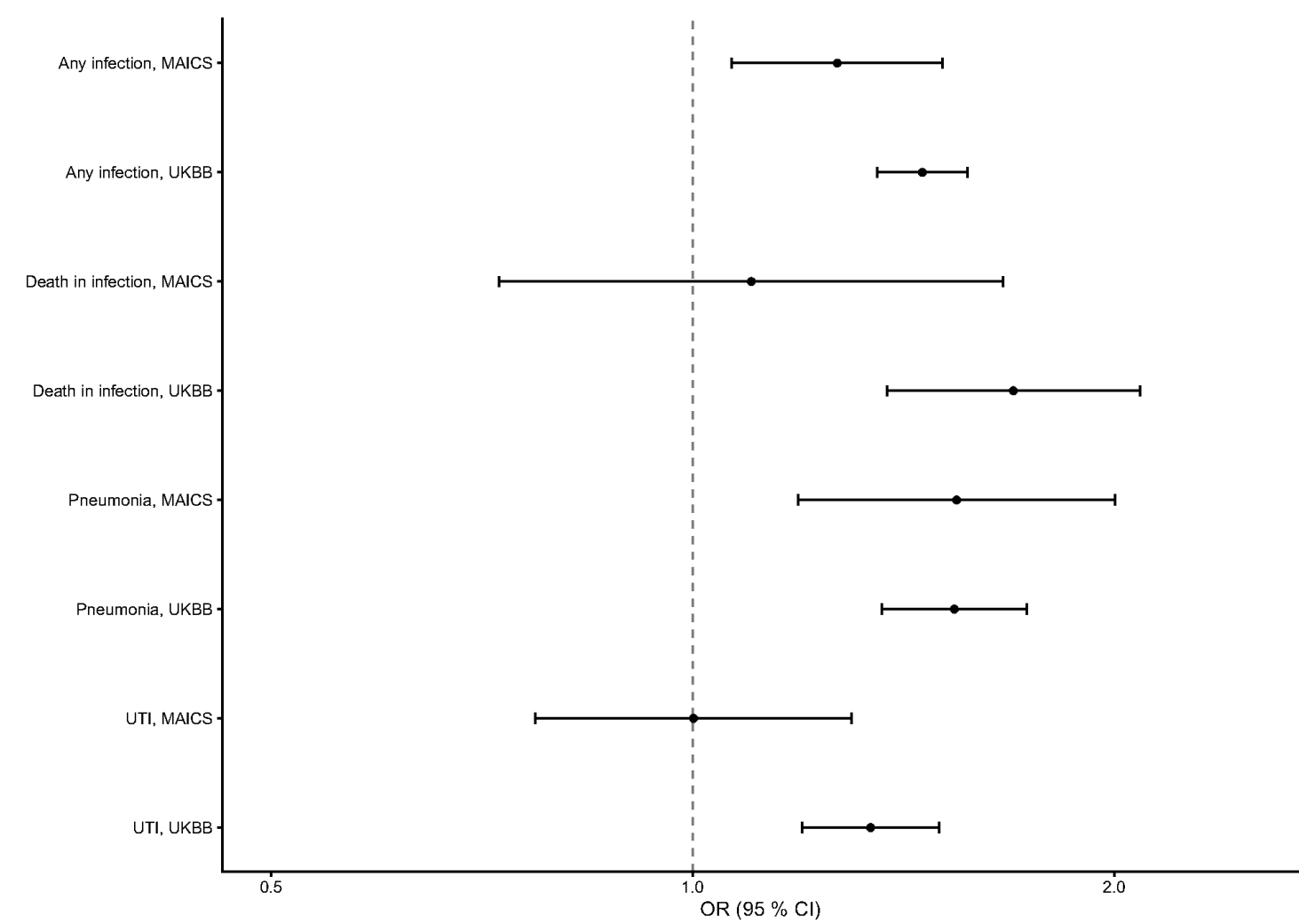
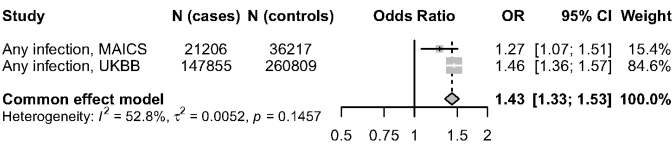


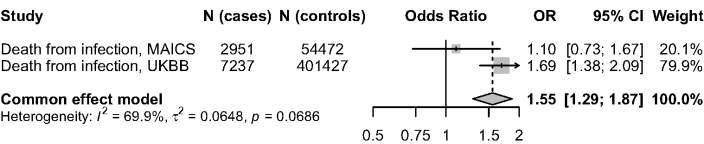
Figure 1

Inverse-variance weighted MR estimates of the effect of sedentary behaviour (television watching) on risk of infectious outcomes in MAICS and UKBB. Estimates expressed as the increase in odds ratio (OR) with 95 % confidence interval (CI) per one-standard-deviation increase in the exposure.

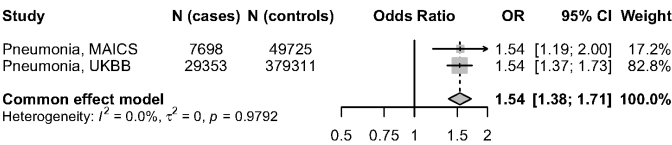
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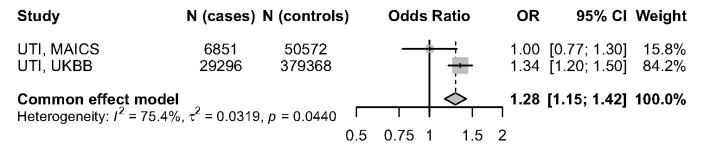


Figure 2

Causal inference meta-analysis of sedentary behaviour (television watching) and risk of A) any infection B) death from infection C) pneumonia and D) UTI in MAICS and UKBB. Odds ratios with 95% confidence intervals are displayed.

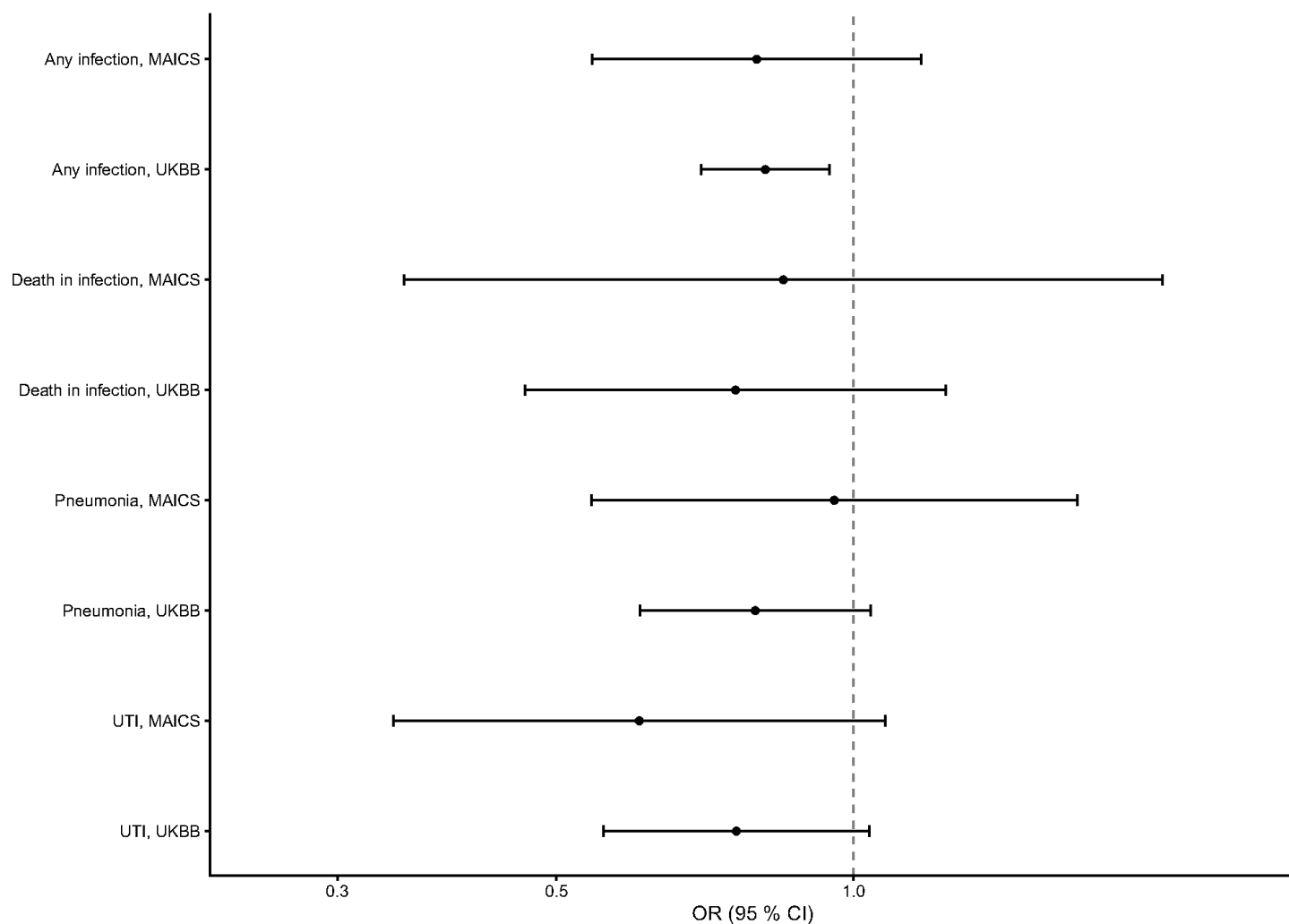


Figure 3

Inverse-variance weighted MR estimates of the effect of moderate-to-vigorous physical activity on risk of infectious outcomes in MAICS and UKBB. Estimates expressed as the increase in odds ratio (OR) with 95 % confidence interval (CI) for the outcome per one-unit increase in the genetically predicted log odds of being classified as physically active.

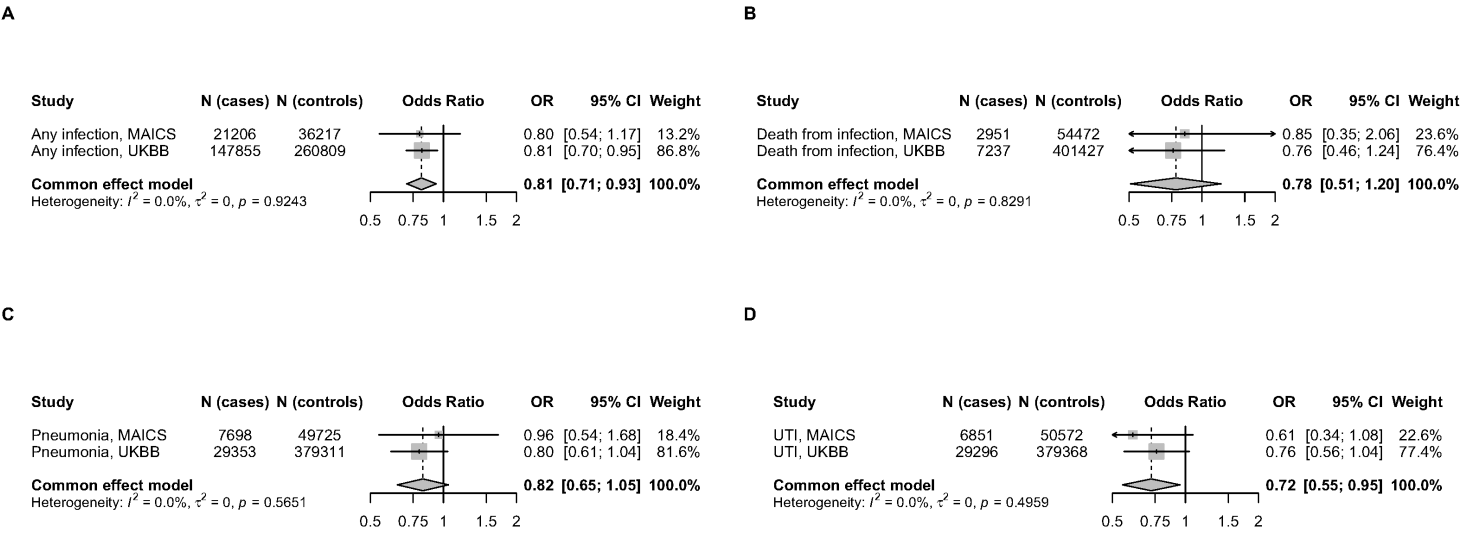


Figure 4

Causal inference meta-analysis of moderate-to-vigorous physical activity and risk of A) any infection B) death from infection C) pneumonia and D) UTI in MAICS and UKBB. Odds ratios with 95% confidence intervals are displayed.

Supplementary Files

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