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Original Article

Physical activity, sedentary behaviour, and exocrine and endocrine pancreatic diseases: results from a prospective cohort study and Mendelian randomization

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Abstract

Background: **Whether physical activity and restricted sedentary behaviour can maintain pancreas health remains inconclusive. We aimed to comprehensively investigate the associations of physical activity and sedentary behaviour with exocrine and endocrine pancreatic diseases in a prospective cohort study and further verify these associations by using Mendelian randomization (MR).**

Methods: **The prospective study included 437,131 UK Biobank participants free of pancreatic diseases at baseline. We used moderate-to-vigorous physical activity (MVPA) to indicate physical activity and leisure screen time (LST) to indicate sedentary behaviour. Outcomes included five diseases related to pancreatic secretory functions. We conducted Cox proportional hazards regression and mediation analyses to examine the mediating role of body mass index (BMI). MR analysis was used to assess the robustness of the observational findings.**

Results: **During a mean follow-up of 14 years, we identified 2,548 acute pancreatitis (AP), 638 chronic pancreatitis (CP), 1,711 pancreatic cancer (PC), 1,705 type 1 diabetes mellitus (T1DM), and 19,371 type 2 diabetes mellitus (T2DM) cases. Increasing MVPA was associated with AP, CP, T1DM, and T2DM risk in a U-shaped manner, with the lowest risk at ∼3,000 metabolic equivalent tasks-minutes/week (all *P*-nonlinearity < 0.05). BMI partially mediated associations of MVPA with AP, T1DM, and T2DM. LST was associated with an increased risk of AP, CP, PC, T1DM, and T2DM, with significant linear trends for CP, PC, and T1DM (all *P*-nonlinearity > 0.05). BMI partially mediated the associations of LST with AP, PC, T1DM, and T2DM. MR confirmed the associations of MVPA with AP and CP and of LST with AP, CP, and T2DM.**

Conclusion: **Moderate MVPA and strict restriction of LST can serve as effective and practical strategies for preventing AP, CP, and T2DM.**

Keywords acute pancreatitis, chronic pancreatitis, diabetes mellitus, pancreatic cancer, physical activity, sedentary behaviour.

Introduction

The pancreas, an endocrine and exocrine gland, is essential for facilitating digestion and regulating glucose homeostasis [1]. Dysfunctions of the pancreas can lead to multiple life-threatening or chronic diseases including pancreatitis, pancreatic cancer (PC), and diabetes mellitus that pose substantial burdens on affected individuals [2–5]. For instance, the incidence of acute pancreatitis (AP) and chronic pancreatitis (CP) causes a range of symptoms and complications that are

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challenging to manage and can lead to long-term disability [6]. PC (primarily pancreatic ductal adenocarcinoma) remains one of the most lethal types of cancers, with an overall 5-year survival rate of 9% [7]. Diabetes mellitus, including type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), affects ≤529 million people worldwide [8]. The increasing complexity and burden of these pancreatic diseases worldwide warrant more effective and practical prevention.

Some preclinical evidence suggests that physical activity confers potential benefits for pancreatic health, while sedentary behaviour adversely affects it. Specifically, by mitigating ultrastructural abnormalities in the exocrine pancreas and enhancing beta-cell function, physical activity improves overall pancreatic health, resulting in more favourable glucose and insulin profiles [9, 10]. In contrast, sedentary behaviour (i.e. physical inactivity) increases insulin resistance and impairs glucose metabolism [11]. According to the World Health Organization guideline on physical activity, moderate-to-vigorous physical activity (MVPA) (e.g. weightlifting, bicycling, and swimming) is recommended for adults to maintain general health [12]. It provides better benefits for various health outcomes compared with light physical activity in the same total physical activity volume (intensity × duration) [13–15]. Due to the higher-intensity characteristic of MVPA compared with light physical activity, better benefits can be achieved in a shorter time, making it a more time-efficient preventive strategy against diseases.

Although the World Health Organization recommendation emphasizes the importance of MVPA, current epidemiological evidence on its benefits for some pancreatic diseases remains inconsistent or scarce. Prior large cohort studies have mainly focused on the effects of MVPA on T2DM [16], while the potential benefits of MVPA on other pancreatic diseases have been overlooked. A review of systematic reviews and meta-analyses from the 2018 PAGAC Scientific Reporter suggested a preventive effect of physical activity on PC [17]. However, the limited number of studies included in these reviews and their methodological heterogeneity [18–21] make it premature to draw definite conclusions on the benefits of physical activity for PC. Moreover, a latest pooled analysis of 12 prospective cohorts from the USA and Europe including >1.4 million people, among whom 4,186 PC cases were identified, reported a non-significant association between MVPA (comparing the 90th and 10th percentiles) and PC incidence [22]. Except for T2DM and PC, the relationships of MVPA with the risk of AP, CP, and T1DM have not been well studied. The deleterious impact caused by sedentary behaviour cannot be fully offset by physical activity [23], indicating the limiting sedentary behaviour instead of just increasing the amount of physical activity is essential for maintaining general health. While the positive association between sedentary behaviour and T2DM risk has been well established [24], few studies have explored the associations of sedentary behaviour with the risk of AP, CP, PC, and T1DM.

In the present study, we aimed to comprehensively investigate the associations of MVPA and sedentary behaviour with the incidence of major exocrine and endocrine pancreatic diseases in a prospective cohort study. As confounding and reverse causality are potential issues in observational data [25], Mendelian randomization (MR), which uses genetic variants as proxies for exposure, has been increasingly employed to mitigate confounding and avoid reverse causality [26, 27]. Therefore, MR was further utilized to validate the observational associations and enhance the causal inference.

Materials and methods

Study population

UK Biobank is a large cohort study that enrolled >500,000 participants aged 40–69 years between 2006 and 2010 from 22 assessment centres across the UK [28]. Participants completed touchscreen questionnaires, interviews, physical measurements, and sample collection at baseline. The study was approved by the North West-Haydock Research Ethics Committee (REC reference: 21/NW/0157). In the current study, we excluded participants without data on physical activity and sedentary behaviour and with any pancreatic diseases at baseline. The final analysis included 437,131 participants (Figure 1). All participants provided written informed consent before the study began, with access to UK Biobank data approved by the UK Biobank Access Committee (application number 79612). This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [29].

Assessment of exposures

MVPA was derived from the short form of the International Physical Activity Questionnaire [30] and converted into the metabolic equivalent task (MET) minutes per week, subsequently categorized into tertiles based on the sample distribution: low (<360 MET-min/week, medium (360–1,520 MET-min/week), and high (>1,520 MET-min/week). Sedentary behaviour was indicated as leisure screen time (LST) estimated via the question: 'How many hours do you spend watching TV or using a computer outside of work in a typical day?' [31]. The weekly screen time was calculated by multiplying the daily screen time by seven and categorized into tertiles: low (<21 h/week), medium (21–28 h/week), and high (>28 h/week) [32]. Further details on MVPA and LST are provided in Supplementary Table S1.

Ascertainment of outcomes

AP, CP, PC, T1DM, and T2DM were identified by using the International Classification of Diseases (ICD) 9 and 10 codes, derived from related data including primary care records, inpatient data, and death registries (Supplementary Table S2). Participants were followed up until the date of first diagnosis of these outcomes, death, loss to follow-up (e.g. migration out of the UK), or the end of follow-up (31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales).

Assessment of covariates

Potential covariates were determined based on previous literature and represented in a directed acyclic graph to guide the modelling strategy (Supplementary Figure S1). Relevant covariates included age (continuous, in years), gender (categorical; female and male), ethnicity (categorical; white and others), education level (categorical; college and below college),

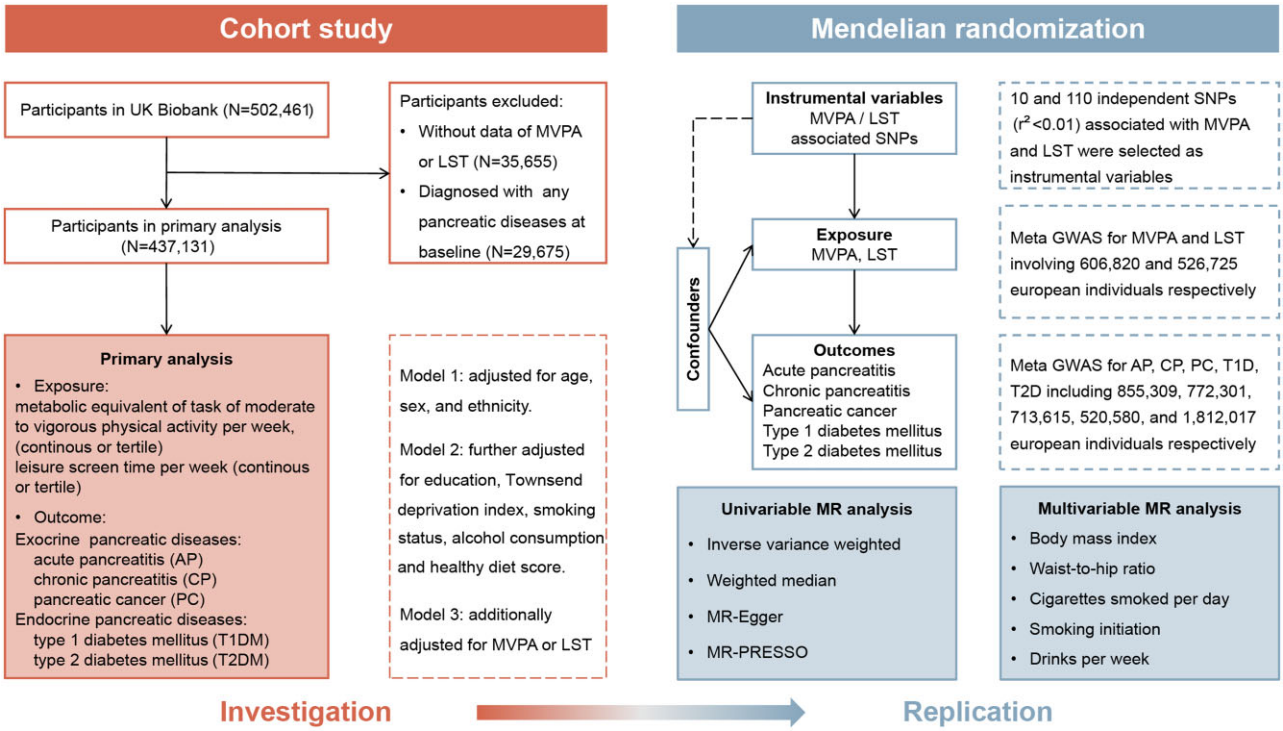


Figure 1 Study design. BMI = body mass Index, GWAS = genome-wide association study, LST = leisure screen time, MR = Mendelian randomization, MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier, SNPs = single nucleotide polymorphisms.

Townsend deprivation index (continuous), smoking status (categorical; never, previous, and current), alcohol consumption (categorical; never, previous, and current), healthy diet score (categorical; healthy and unhealthy), body mass index (BMI, continuous, kg/m^2), and Charlson Comorbidity Index. The healthy diet score was calculated based on the frequency of consumption of seven food groups (fruits, vegetables, processed meats, unprocessed red meat, fish, whole grains, and refined grains). These food groups were selected according to the American Heart Association's recommendations to define food intake as beneficial to cardiometabolic health and have been shown to be inversely associated with the risk of inflammatory bowel disease [33–38]. As recommended by these studies, a diet with a score of ≥4 was considered healthy. The Charlson Comorbidity Index was calculated via summing the weighted scores of 17 comorbidities based on ICD-10 codes to assess the severity of the underlying comorbidities [39]. Less than 2% of values were missing for each covariate. Missing values in continuous variables (e.g. BMI) were imputed by the median and those in categorical variables (e.g. ethnicity, education) were imputed by the mode. More details on these covariates are shown in Supplementary Table S1.

Statistical analyses

The baseline characteristics of participants are presented as tertiles of the MVPA levels. Descriptive statistics are shown as mean (standard deviation, SD) for continuous variables and percentages for categorical variables.

Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of MVPA and LST with AP, CP, PC, T1DM, and T2DM. The proportional hazards assumptions were tested via the Schoenfeld residuals method and were found to be met (all $P > 0.05$). MVPA and LST were analysed both as continuous variables (to estimate HRs per SD increase) and as categorical variables (with the lowest group set as the reference). Three sequential models were applied: Model 1 was adjusted for age, sex, and ethnicity; Model 2 included additional adjustments for education, Townsend deprivation index, smoking status, alcohol consumption, and healthy diet; Model 3 was further adjusted as MVPA for LST and LST for MVPA. Restricted cubic splines were employed to describe dose–response associations with three knots at the 10th, 50th, and 90th percentiles. Mediation analysis was further conducted to examine the mediating effects of BMI in the association of MVPA/LST with AP, CP, PC, T1DM, and T2DM.

Subgroup analyses were conducted by stratifying participants by age, gender, smoking status, and alcohol consumption, Townsend deprivation index, healthy diet, BMI, and either MVPA or LST to explore potential effect modification. Several sensitivity analyses were performed to test the robustness of our findings. First, missing values were refilled by using multiple imputation through chained equations to explore the potential impact of missing values. Second, cases of any pancreatic diseases occurring within the first 1, 2, and 3 years were excluded to address reverse causality. Third, the model was further adjusted for Charlson Comorbidity Index. Fourth, a binary classification of MVPA (active vs inactive) was used in the observational analysis to align with the categorization used in the genome-wide association study (GWAS) from which the genetic instruments for the MVPA were derived.

MR analyses

Two-sample MR analyses were performed to strengthen the causal inference. A total of 17 single nucleotide polymorphism (SNPs) for MVPA and 132 SNPs for LST at genome-wide significance ($P < 5 \times 10^{-8}$) and with independence ($r^2 < 0.01$) were selected from a GWAS meta-analysis of 51 studies involving individuals of European ancestry [40], in which MVPA was self-reported, with >20 minutes per week categorized as active (Supplementary Table S3). As these selected SNPs, located within specific gene loci, serve as instrumental variables representing the exposures, they were referred to as 'genetically proxied MVPA' or 'genetically proxied LST' in the MR analyses. Summary-level data for the pancreatic diseases, derived from European ancestry populations, were obtained from UK Biobank [28], the FinnGen study [41], the PanScan1 study [42], and several GWAS meta-analyses [43–45] (Supplementary Table S4). The inverse variance weighted method was used in the primary analysis to estimate the odds ratios (ORs) and corresponding 95% CIs [46], with the Cochran's Q test used to evaluate heterogeneity between the SNP estimates. Analyses using the weighted median, MR-Egger regression, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods were performed to examine the robustness of the results and to address potential horizontal pleiotropy [46–48]. The MR Steiger test was applied to evaluate potential bias from reverse causation. Multivariable MR analyses were used to adjust for pleiotropic effects from smoking, alcohol drinking, BMI, and waist-to-hip ratio, with SNPs extracted from the corresponding GWASs [49, 50]. Given the strong genetic correlation between MVPA and LST, mutual adjustments through multivariable MR were performed to assess the independent effects of MVPA and LST on pancreatic diseases. Full details of the MR analyses are presented in Supplementary Tables S3–S5.

Observational analyses were conducted by using the survival R package and the Two-Sample MR, Mendelian Randomization, and MR-PRESSO R packages were utilized for the MR analyses. All statistical analyses were performed in R software (version 4.2.0). A false discovery rate correction using the Benjamini–Hochberg method was applied with a significance threshold of 0.05.

Results

Baseline characteristics

During the follow-up period, 23,254 participants of UK Biobank developed an exocrine or endocrine pancreatic disease, including 2,548 with AP (mean follow-up: 14.2 years), 638 with CP (14.2 years), 1,711 with PC (14.2 years), 1,705 with T1DM (14.2 years), and 19,371 with T2DM (13.9 years). Participants in the highest tertile of the MVPA levels were more likely to be male and had higher educational levels, higher alcohol intake, a healthier diet, and lower BMI compared with those in the lowest tertile of the MVPA levels (Table 1).

Observational analyses

After adjustment for important sociodemographic and lifestyle factors (Model 3), MVPA was inversely associated with the risk of AP, CP, T1DM, and T2DM, while LST was positively associated with the risk of AP, CP, PC, T1DM, and T2DM (Table 2 and Supplementary Figure S2). Participants in the highest tertile of MVPA had a lower risk of AP (HR 0.77, 95% CI 0.70–0.84), CP (HR 0.78, 95% CI 0.65–0.95), T1DM (HR 0.67, 95% CI 0.60–0.75), and T2DM (HR 0.69, 95% CI 0.67–0.72) compared with those in the lowest tertile (Table 2). U-shaped associations were observed between MVPA and these outcomes, with the lowest risk observed at ~3,000 MET-min/week (P-nonlinearity < 0.05, Supplementary Figure S3). Mediation analysis demonstrated that BMI accounted for 38.5% (25.5%–64.2%) of the association between MVPA and AP, 53.3% (36.2%–84.5%) for T1DM, and 60.0% (52.7%–67.1%) for T2DM (Supplementary Figure S4). In contrast, the highest tertile of LST was associated with an elevated risk of AP (HR 1.33, 95% CI 1.21–1.45), CP (HR 1.44, 95% CI 1.20–1.72), PC (HR 1.22, 95% CI 1.09–1.36), T1DM (HR 1.49, 95% CI 1.33–1.66), and T2DM (HR 1.51, 95% CI 1.46–1.56) compared with the lowest tertile (Table 2). Non-linear associations were found for LST with CP, PC, and T1DM (P-nonlinearity > 0.05, Supplementary Figure S3). The proportion of the association explained via BMI was 47.5% (37.1%–68.4%) for AP, 25.8% (12.8%–85.1%) for PC, 47.6% (39.3%–62.0%) for T1DM, and 61.4% (57.7%–66.5%) for T2DM (Supplementary Figure S4).

Subgroup and sensitivity analyses

Subgroup analyses indicated consistent results across most subgroups. However, notable subgroup differences emerged in the specific contexts. For MVPA, stronger inverse associations were observed among younger individuals (<60 years) for AP, among those with sub-college education for T1DM, and among younger and white people for T2DM (Supplementary Tables S6–S10). In contrast, longer LST appeared to increase the PC risk in males and T2DM risk in younger, female, or white individuals, as well as in those with a college education and never smokers (Supplementary Tables S6–S10). Results were consistent when we repeated the analyses after refilling missing values by using multiple imputation through chained equations, excluding participants with a pancreatic disease diagnosis within the first 1, 2, or 3 years of follow-up, additionally adjusting analyses for Charlson Comorbidity Index, and using MVPA as a binary exposure (Supplementary Tables S11 and S12).

MR analyses

The inverse variance weighted (IVW) method verified the associations of genetically predicted MVPA with AP (OR 0.62, 95% CI 0.43–0.90) and CP (OR 0.48, 95% CI 0.29–0.80) as well as the associations of genetically predicted LST with AP (OR 1.37, 95% CI 1.20–1.56), CP (OR 1.32, 95% CI 1.09–1.60), and T2DM (OR 1.34, 95% CI 1.23–1.46) (Supplementary Table S13). Most associations were directionally consistent across other MR methods, except for the associations of MVPA with AP and CP for the MR-Egger method. Notably, the association between genetically predicted MVPA and T2DM became significant after the removal of six outliers in the MR-PRESSO method (Supplementary Tables S13 and S14). The MR Steiger test confirmed the directionality of the identified associations for both MVPA and LST (Supplementary Tables S13 and S14). For MVMR (Multivariable MR)-IVW, most associations remained consistent (Figure 2). However, the associations of genetically predicted MVPA with AP and CP became non-significant after adjustment for genetically

Table 1 Baseline characteristics of participants in UK Biobank by MVPA levels.

Variable	Overall	MVPA			*P*
		Low	Medium	High	
Number of cases	437,131	151,598	141,319	144,214	
Age, years, mean ± SD	56.27 ± 8.1	56.16 ± 7.9	56.10 ± 8.2	56.56 ± 8.3	**<0.001**
Age, *n* (%)					
<60	253,669 (58.0)	90,851 (59.9)	83,046 (58.8)	79,772 (55.3)	**<0.001**
≥60	183,462 (42.0)	60,747 (40.1)	58,273 (41.2)	64,442 (44.7)	
Sex, *n* (%)					
Female	241,050 (55.1)	87,029 (57.4)	80,125 (56.7)	73,896 (51.2)	**<0.001**
Male	196,081 (44.9)	64,569 (42.6)	61,194 (43.3)	70,318 (48.8)	
Ethnicity, *n* (%)					
Not white	20,666 (4.7)	7,684 (5.1)	6,783 (4.8)	6,199 (4.3)	**<0.001**
White	415,104 (95.3)	143,393 (94.9)	134,157 (95.2)	137,554 (95.7)	
Education, *n* (%)					
Below college	283,187 (65.5)	99,127 (66.6)	86,904 (61.9)	97,156 (67.9)	**<0.001**
College	148,941 (34.5)	49,682 (33.4)	53,420 (38.1)	45,839 (32.1)	
Townsend deprivation index, mean ± SD	−1.42 (3.02)	−1.27 (3.10)	−1.54 (2.97)	−1.47 (2.98)	**<0.001**
Townsend deprivation index, *n* (%)					
Low	145,532 (33.3)	48,458 (32.0)	48,748 (34.5)	48,326 (33.5)	**<0.001**
Medium	145,533 (33.3)	49,503 (32.7)	47,387 (33.6)	48,643 (33.8)	
High	145,530 (33.3)	53,432 (35.3)	45,012 (31.9)	47,086 (32.7)	
Smoking, *n* (%)					
Never	241,673 (55.5)	82,891 (54.9)	80,012 (56.8)	78,770 (54.8)	**<0.001**
Previous or current	194,135 (44.5)	68,178 (45.1)	60,924 (43.2)	65,033 (45.2)	
Alcohol consumption, *n* (%)					
None to moderate	318,523 (72.9)	112,675 (74.4)	102,777 (72.8)	103,071 (71.5)	**<0.001**
Heavy	118,347 (27.1)	38,796 (25.6)	38,478 (27.2)	41,073 (28.5)	
Healthy diet score, *n* (%)					
Unhealthy	200,611 (45.9)	81,228 (53.6)	61,442 (43.5)	57,941 (40.2)	**<0.001**
Healthy	236,512 (54.1)	70,364 (46.4)	79,877 (56.5)	86,271 (59.8)	
BMI, kg/m^2, mean ± SD	27.13 (4.57)	27.82 (5.00)	26.94 (4.42)	26.58 (4.14)	**<0.001**
BMI group, *n* (%)					
≤25	151,239 (34.8)	45,680 (30.3)	50,553 (35.9)	55,006 (38.3)	**<0.001**
>25	283,907 (65.2)	104,972 (69.7)	90,241 (64.1)	88,694 (61.7)	
Charlson Comorbidity Index, mean ± SD	0.23 (0.8)	0.27 (0.9)	0.22 (0.8)	0.21 (0.8)	**<0.001**
LST per week, hours, mean ± SD	26.57 (14.6)	28.24 (15.9)	26.06 (14.0)	25.33 (13.4)	**<0.001**
LST, *n* (%)					
Low	207,139 (47.4)	65,824 (43.4)	68,741 (48.6)	72,574 (50.3)	**<0.001**
Medium	93,912 (21.5)	32,208 (21.2)	30,543 (21.6)	31,161 (21.6)	
High	136,080 (31.1)	53,566 (35.3)	42,035 (29.7)	40,479 (28.1)	

Low MVPA: <360 MET-min/week; medium MVPA: 360–1,520 MET-min/week; high MVPA: >1,520 MET-min/week.
MET = metabolic equivalent task.

predicted LST (Figure 2 and Supplementary Table S15). The association between genetically predicted LST and CP was diminished and became null with adjustments for genetically predicted alcoholic drinks per week and MVPA (Figure 2 and Supplementary Table S15).

Discussion

Principal findings

The key findings for MVPA in the observational and MR analyses can be summarized as follows: higher MVPA levels were associated with a lower risk of AP and CP. Maintaining an MVPA level of 360–1,520 MET-min/week (the medium tertile) was associated with a 23% reduction in AP risk and a 22% risk reduction in CP risk compared with individuals at <360 MET-min/week (the lowest tertile) in the observational analyses. Further increasing MVPA levels beyond 1,520 MET-min/week (the highest tertile) resulted in minimal additional risk changes, suggesting that, for the general population, sustaining an MVPA level of 360–1,520 MET-min/week—equivalent to ∼10–35 minutes per day of bicycling (16–19 km/h) [51]—is sufficient to achieve substantial clinical benefits and may offer better long-term compliance [52]. For LST, both the observational and the MR analyses

Table 2. Association of MVPA and LST with exocrine and endocrine pancreatic diseases in the observational analysis.

Exposure	Case/person-years	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
MVPA-AP							
MET per week (SD)	2,548/19,385	**0.90 (0.86, 0.94)**	**<0.001**	**0.91 (0.87, 0.95)**	**<0.001**	**0.92 (0.88, 0.96)**	**<0.001**
MVPA							
Low	1,073/7,964	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	722/5,586	**0.71 (0.65, 0.79)**	**<0.001**	**0.76 (0.69, 0.84)**	**<0.001**	**0.77 (0.70, 0.85)**	**<0.001**
High	753/5,835	**0.71 (0.65, 0.78)**	**<0.001**	**0.75 (0.68, 0.83)**	**<0.001**	**0.77 (0.70, 0.84)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**
MVPA-CP							
MET per week (SD)	638/4,685	0.93 (0.86, 1.01)	0.095	0.94 (0.87, 1.02)	0.112	0.96 (0.88, 1.03)	0.263
MVPA							
Low	272/1,896	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	169/1,267	**0.66 (0.54, 0.80)**	**<0.001**	**0.72 (0.59, 0.87)**	**0.001**	**0.73 (0.60, 0.88)**	**0.001**
High	197/1,522	**0.71 (0.59, 0.86)**	**<0.001**	**0.76 (0.63, 0.91)**	**0.004**	**0.78 (0.65, 0.95)**	**0.011**
P for trend			**0.003**		**0.017**		**0.039**
MVPA-PC							
MET per week (SD)	1,711/14,146	1.01 (0.96, 1.05)	0.755	1.01 (0.96, 1.06)	0.667	1.02 (0.97, 1.06)	0.484
MVPA							
Low	601/4,994	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	533/4,426	0.93 (0.83, 1.05)	0.235	0.94 (0.84, 1.06)	0.336	0.95 (0.85, 1.07)	0.398
High	577/4,726	0.93 (0.83, 1.05)	0.239	0.95 (0.84, 1.06)	0.346	0.96 (0.86, 1.08)	0.488
P for trend			0.329		0.437		0.592
MVPA-T1DM							
MET per week (SD)	1,705/9,156	**0.88 (0.83, 0.93)**	**<0.001**	**0.88 (0.84, 0.93)**	**<0.001**	**0.90 (0.85, 0.95)**	**<0.001**
MVPA							
Low	756/3,949	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	475/2,554	**0.67 (0.60, 0.75)**	**<0.001**	**0.71 (0.63, 0.80)**	**<0.001**	**0.72 (0.64, 0.81)**	**<0.001**
High	474/2,653	**0.63 (0.56, 0.71)**	**<0.001**	**0.65 (0.58, 0.73)**	**<0.001**	**0.67 (0.60, 0.75)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**
MVPA-T2DM							
MET per week (SD)	19,371/145,982	**0.88 (0.87, 0.90)**	**<0.001**	**0.89 (0.87, 0.90)**	**<0.001**	**0.90 (0.89, 0.92)**	**<0.001**
MVPA							
Low	8,436/62,360	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	5,525/41,933	**0.69 (0.67, 0.72)**	**<0.001**	**0.74 (0.72, 0.77)**	**<0.001**	**0.76 (0.73, 0.78)**	**<0.001**
High	5,410/41,689	**0.64 (0.62, 0.66)**	**<0.001**	**0.67 (0.65, 0.70)**	**<0.001**	**0.69 (0.67, 0.72)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**
LST-AP							
LST per week (SD)	2,548/19,384	**1.19 (1.15, 1.23)**	**<0.001**	**1.14 (1.10, 1.18)**	**<0.001**	**1.13 (1.09, 1.17)**	**<0.001**
LST							
Low	962/7,515	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	587/4,416	**1.28 (1.16, 1.42)**	**<0.001**	**1.23 (1.11, 1.36)**	**<0.001**	**1.22 (1.10, 1.35)**	**<0.001**
High	999/7,453	**1.50 (1.37, 1.64)**	**<0.001**	**1.35 (1.24, 1.48)**	**<0.001**	**1.33 (1.21, 1.45)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**0.001**
LST-CP							
LST per week (SD)	638/4,685	**1.28 (1.22, 1.36)**	**<0.001**	**1.20 (1.13, 1.28)**	**<0.001**	**1.20 (1.12, 1.28)**	**<0.001**
LST							
Low	231/1,760	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	121/900	1.07 (0.86, 1.33)	0.544	1.01 (0.81, 1.26)	0.981	1.01 (0.81, 1.26)	0.948
High	286/2,025	**1.69 (1.42, 2.01)**	**<0.001**	**1.47 (1.23, 1.75)**	**<0.001**	**1.44 (1.20, 1.72)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**
LST-PC							
LST per week (SD)	1,711/14,146	**1.09 (1.04, 1.14)**	**<0.001**	**1.08 (1.03, 1.13)**	**0.002**	**1.08 (1.03, 1.13)**	**0.002**
LST							

(continued)

Table 2. (continued)

Exposure	Case/person-years	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Low	666/5,422	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	391/3,324	1.13 (1.00, 1.28)	0.051	1.13 (1.00, 1.28)	0.057	1.13 (1.00, 1.28)	0.058
High	654/5,400	**1.25 (1.12, 1.39)**	**<0.001**	**1.22 (1.09, 1.36)**	**<0.001**	**1.22 (1.09, 1.36)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**0.001**
LST-T1DM							
LST per week (SD)	1,705/9,156	**1.27 (1.22, 1.32)**	**<0.001**	**1.23 (1.18, 1.27)**	**<0.001**	**1.22 (1.17, 1.26)**	**<0.001**
LST							
Low	599/3,438	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	374/2,074	**1.30 (1.15, 1.48)**	**<0.001**	**1.25 (1.10, 1.43)**	**0.001**	**1.24 (1.09, 1.42)**	**0.001**
High	732/3,644	**1.68 (1.50, 1.87)**	**<0.001**	**1.53 (1.37, 1.71)**	**<0.001**	**1.49 (1.33, 1.66)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**
LST-T2DM							
LST per week (SD)	19,371/145,981	**1.26 (1.25, 1.28)**	**<0.001**	**1.21 (1.19, 1.22)**	**<0.001**	**1.20 (1.18, 1.21)**	**<0.001**
LST							
Low	6,707/51,514	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium	4,222/31,784	**1.31 (1.26, 1.36)**	**<0.001**	**1.24 (1.19, 1.29)**	**<0.001**	**1.23 (1.19, 1.28)**	**<0.001**
High	8,442/62,683	**1.74 (1.69, 1.80)**	**<0.001**	**1.55 (1.50, 1.60)**	**<0.001**	**1.51 (1.46, 1.56)**	**<0.001**
P for trend			**<0.001**		**<0.001**		**<0.001**

Estimates with $P < 0.05$ in observational analysis are reported in bold.
Model 1: adjusted for age, sex, and ethnicity.
Model 2: adjusted for age, sex, ethnicity, education, Townsend deprivation index, smoking status, alcohol consumption, and healthy diet score.
Model 3: adjusted for age, sex, ethnicity, education, Townsend deprivation index, smoking status, alcohol consumption, healthy diet score, and LST/MVPA.

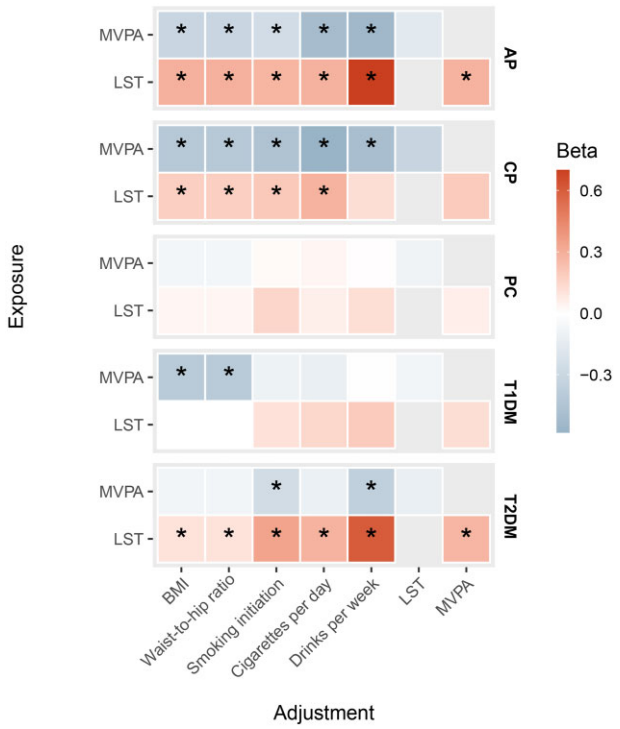


Figure 2. Heat map for multivariable MR analysis. $^{*}P < 0.05$.

support positive associations of LST with the risk of AP, CP, and T2DM. Hence, minimizing screen time as much as possible is more effective for the prevention of these diseases. Notably, BMI demonstrated substantial mediating effects in the associations of MVPA/LST with AP and T2DM, which indicates that the effects (protective/harmful) of MVPA and LST are largely attributable to BMI changes.

Comparisons with other studies

For pancreatitis, we found inverse associations of AP and CP with MVPA, as well as positive associations with LST in the observational and MR analyses. Similarly to our findings, a prospective study based on China Kadoorie Biobank involving 512,891 adults demonstrated that higher physical activity levels were associated with a decreased risk of AP [53]. Furthermore, a case–control study involving 17 CP patients and 15 controls without the disease found that participants with CP had lower physical activity levels [54]. A previous MR study, which also explored the relationships of physical activity and sedentary behaviour with AP and CP risk, only found that genetically predicted LST was positively associated with AP risk, while it did not find causal associations between physical activity or sedentary behaviour [55]. In contrast, the results from another large-sample MR study examining the associations of MVPA and LST with 24 gastrointestinal diseases (including AP and CP) were in line with ours completely [56]. Some potential evidence in line with our findings is noteworthy. Specifically, recent studies demonstrated that high physical activity levels and limited sedentary behaviour were associated with decreased inflammatory biomarkers [57, 58] and a lower risk of the common causes of AP and CP, such as gallstone and hyperlipidaemia [59–61].

There remains a need for further research to confirm our findings.

Existing evidence suggests robust relationships of physical activity and LST with T2DM. It has been well documented that high physical activity levels and limited sedentary behaviour were associated with a lower risk of T2DM in a meta-analysis of multiethnic populations [16, 24], which was consistent with the results in our observational analyses. Two previous two-sample MR studies involving individuals of European ancestry demonstrated causal associations of genetically proxied MVPA and LST with T2DM [62, 63]. However, our MR analysis only confirmed causal interference between genetically proxied LST and T2DM, while it did not support the association between genetically predicted MVPA and T2DM. The results from our study may have been affected by potential heterogeneity, as demonstrated by the outliers in the MR-PRESSO method. After removing these outliers, we observed a significant association between MVPA and T2DM. Our observational analyses revealed associations of T1DM with LST and MVPA but were not further supported by MR analyses. Some experimental studies implied that physical activity and limited LST appeared to preserve beta-cell function in animal models and healthy individuals, as well as modify the function of immune system [64–67], which may affect T1DM risk. Future studies are needed to clarify our findings.

Regarding PC, the results from our observational and MR analyses did not support MVPA and limited LST as preventive strategies for this fatal malignancy. Previous studies examining the association between physical activity and PC yielded heterogeneous findings, with some indicating a protective effect while others found no such association or even a risk increase. Previous case–control and cohort studies across Minnesota, Europe, and the USA showed that the clinical benefits of physical activity on PC risk appeared to be confined to low/moderate physical activity, with no benefits observed with vigorous physical activity [68–70]. Evidence from the BCDDP cohort and NIH-AARP Diet and Health cohort similarly showed no significant association between vigorous physical activity and PC risk [71, 72]. Furthermore, a landmark pooled analysis of 12 prospective cohorts, including $>$1.4 million people from the USA and Europe (with 4,186 PC cases), showed that, compared with individuals at the 10th percentile of MVPA, those at the 90th did not exhibit a significant reduction in PC incidence [22]. However, some other cohort studies from China and Korea demonstrated that MVPA was associated with a reduced PC risk, especially in males [73, 74]. Further research is required to better understand these discrepancies. Supporting our results, a two-sample MR study found that genetically predicted MVPA was not associated with PC risk [75]. Notably, this MR study identified longer television-watching time as a risk factor for PC, partially mediated by BMI, which is in line with the results from our observational analyses but not our MR analyses. In contrast to this study, our MR analysis included additional data from UK Biobank, in which the population had healthier lifestyles and a relatively lower number of PC cases, potentially leading to an underestimation of the PC risk.

Possible interpretations

MVPA and sedentary behaviour influence chronic disease risk and overall health, often with opposite effects, by impacting the circulatory, respiratory, musculoskeletal, and immune systems and metabolic status [76]. Interrupting sedentary behaviour with regular participation in MVPA confers additional benefits on adiposity, cardiovascular health, and so on compared with light physical activity according to the World Health Organization guidelines. As for exocrine and endocrine pancreatic diseases, several mechanisms could explain the associations in our study. First, physical activity and limited sedentary behaviour can reduce intra-pancreatic fat content [77], which has been indicated as a risk factor for pancreatic diseases [78]. Second, physically active individuals have better immune function and lower levels of inflammatory biomarkers [79]. Third, physical activity and limited sedentary behaviour reduced the incidence of causes of AP or CP such as gallstones and hyperlipidaemia [59–61]. Fourth, physical activity has been associated with enhanced beta-cell function and a better glucose and insulin profile [80].

Strengths and limitations

The strength of this study lies in the employment of observational and MR analyses, which mutually reinforce the robustness of our findings. The observational analyses provide an epidemiological perspective on the associations of MVPA and LST with pancreatic diseases. MR analyses mitigate the inherent biases from residual confounding (which includes reverse causality) and measurement in the observational analyses [25]. However, several limitations in our study should be noted. First, the data on physical activity and sedentary behaviour in the observational analyses and relevant GWAS, derived from questionnaires, may have been prone to recall bias. However, the measurement methods for physical activity and sedentary behaviour have been well validated in previous studies [81]. Second, selection bias was inevitable in both the observational and the MR analyses, although differing in form [25, 82]. Third, the small number of CP and PC cases in our MR analyses should be noted, as it may have limited the statistical power. Fourth, the inclusion of participants solely of European ancestry may have limited the generalizability of our findings to other populations. Fifth, the overlap in the sample populations between the exposure and outcome datasets could have caused the MR estimates to closely resemble observational estimates. Nevertheless, this bias is likely mitigated by the good strength of the genetic instrumental variables used for the exposures (F-statistic $>$ 10). Sixth, the SNP-heritability estimate for MVPA in the original GWAS was 8%, indicating that only a small proportion of the variance in MVPA can be explained by genetic variants, which may have led to low statistical power in our MR analyses [40]. Seventh, some SNPs for MVPA are pleiotropic and have previously been associated with LST and some obesity-related traits [83, 84]. Nevertheless, through MVMR analysis, we adjusted for the genetically predicted levels of these traits to mitigate genetic confounding.

Conclusion

Findings from this study support the protective causal effects of MVPA on AP and CP risk, and the detrimental causal effects of

LST on AP, CP, and T2DM risk. These findings highlight the importance of moderate MVPA and strictly limiting sedentary behaviour as strategies to prevent AP, CP, and T2DM. Future studies are warranted to verify the reliability of our results and explore the underlying mechanisms.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Authors' contributions

C.Z., X.W., and J.C. conceptualized, designed, and supervised the study. T.C., S.Y., and L.D. performed the data analysis. T.C., Z.W., and S.Y wrote the manuscript. X.R. and S.C.L. were responsible for revising the manuscript. L.D., Y.Z., X.W., T.C., and S.Y. contributed to the methodology of the study. All authors reviewed the manuscript.

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Conflicts of interest

None declared.

Data availability

Data for this study are available from UK Biobank at www.ukbiobank.ac.uk.

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