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Association of physical activity and sedentary behavior with type 2 diabetes and glycemic traits: a two-sample Mendelian randomization study

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ABSTRACT

Introduction Observational studies suggest that physical activity lowers and sedentary behavior increases the risk of type 2 diabetes. Despite of some supportive trial data for physical activity, it is largely unresolved whether these relations are causal or due to bias.

Objective We investigated the associations between accelerometer-based physical activity and sedentary behavior with type 2 diabetes and several glycemic traits using two-sample Mendelian randomization analysis.

Research design and methods Single nucleotide polymorphisms (SNPs) associated at $p<5\times10^{-8}$ with accelerometer-based physical activity average accelerations, vigorous physical activity (fraction of accelerations >425 milligravities), and sedentary behavior (metabolic equivalent task ≤1.5) in a genome-wide analysis of the UK Biobank served as instrumental variables.

Outcomes Type 2 diabetes, hemoglobin A1c (HbA1c), fasting glucose, homeostasis model assessment of beta-cell function (HOMA-B), and homeostasis model assessment of insulin resistance (HOMA-IR).

Results Physical activity and sedentary behavior were unrelated to type 2 diabetes, HbA1c, fasting glucose, HOMA-B, and HOMA-IR. The inverse variance weighted ORs per SD increment for the association between average accelerations and vigorous physical activity with type 2 diabetes were 1.00 (95% CI 0.94 to 1.07, p=0.948) and 0.83 (95% CI 0.56 to 1.23, p=0.357), respectively. These results were confirmed by sensitivity analyses using alternative MR-methods to test the robustness of our findings.

Conclusions Based on these results, genetically predicted objectively measured average or vigorous physical activity and sedentary behavior is not associated with type 2 diabetes risk or with glycemic traits in the general population. Further research is required to deepen the understanding of the biological pathways of physical activity.

Significance of this study

What is already known about this subject?

- Based on randomized controlled trials mostly conducted in people with high risk for diabetes, there is no clear evidence that physical activity alone or diet alone compared with standard treatment influences the risk for type 2 diabetes.

What are the new findings?

- In a two-sample Mendelian randomization study, neither genetically predicted objectively measured average and vigorous physical activity nor sedentary behavior were significantly associated with type 2 diabetes and glycemic traits in the general population.

How might these results change the focus of research or clinical practice?

- Further investigation is necessary to deepen the understanding of the biologic pathways of physical activity.

INTRODUCTION

Type 2 diabetes is one of the most frequent non-communicable diseases, with an estimated 463 million cases worldwide in 2019; this number is projected to increase to 578 million by 2030.[1] A variety of observational cohort studies found an inverse association between physical activity (PA) and type 2 diabetes, while only a few investigations reported no association.[2] Studies showed a reduced risk with greater moderate and vigorous activity, but data were less consistent for low intensity activity such as walking.[2] Subsequent studies focused on specific types of PA and possible dose–response relationships.[2] In addition, meta-analyses of intervention studies revealed that exercise programs induce changes in glycemic traits such as fasting blood glucose and glycated hemoglobin levels.[3] However, the beneficial effect of PA seems to depend on the duration of exercise and not on the type and intensity of activity.[3]

Previous observational studies have relied on self-report measures of PA, which are

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prone to recall and response biases and may attenuate 'true' associations with the outcome.[4 5] There is evidence that self-reported and objective measures of PA can yield discrepant estimates.[4 6–8] Large epidemiologic studies usually lack objective measurements of PA; however, the UK Biobank is an exception. In approximately 100 000 study participants, PA was measured using a wrist accelerometer that study participants wore for 7 days.[9] Although objective methods to measure PA help address measurement error, observational studies can be subject to other biases including residual confounding and reverse causality.

Mendelian randomization (MR) may provide another line of evidence concerning the roles of PA and sedentary behaviors (SBs) in type 2 diabetes. MR tests the effects of PA on type 2 diabetes using genetic variants as instruments that are explicitly associated with the exposure PA and exert an effect on type 2 diabetes only via the exposure. Because variants are randomly allocated from parents to offspring at conception, they are less susceptible to environmental confounding and reverse causation than traditional observational studies.[10] Because genetic variants instrument for long-term levels of PA, regression dilution bias is less likely in MR studies.[11] Moreover, objectively measured PA is more heritable[12] than self-reported PA and thus more powerfully instrumented by single nucleotide polymorphism (SNPs) in the MR context.[13] We performed two-sample MR analyses to investigate the relationship between accelerometer-based average accelerations, vigorous PA (fraction of accelerations >425 milligravities), and SB with type 2 diabetes and glycemic traits, namely hemoglobin A1c (HbA1c), fasting blood glucose, homeostasis model assessment of beta-cell function (HOMA-B), and homeostasis model assessment of insulin resistance (HOMA-IR).

METHODS

The study design had five components: (1) identification of genetic variants to serve as instrumental variables for PA and SB; (2) acquisition of instrumenting SNP outcome summary data from genome-wide association studies of type 2 diabetes, HbA1c levels, fasting glucose levels, HOMA-B, and HOMA-IR; (3) harmonization of SNP exposure and SNP outcome datasets; (4) statistical analysis; and (5) evaluation of MR analysis assumptions and sensitivity analyses.

Assessment of PA in UK Biobank

Data regarding different types of PA were gathered in the UK Biobank, a large prospective cohort study including approximately 500 000 men and women (ages 40–69 years) living in the UK. Recruitment from 22 centers across the UK was performed between 2006 and 2010.[14] All study participants provided written informed consent.

In approximately 100 000 study participants, accelerometer-based PA data (Axivity AX3 wrist-worn accelerometer) were gathered.[9] We used genetic variants proxying two accelerometer-based PA measures: average accelerations (mean acceleration in milligravities) and the fraction of accelerations >425 milligravities,[12] the latter corresponding to an equivalent of vigorous PA (≥6 metabolic equivalent tasks (METs)). Accelerometer-based SB was defined as a MET ≤1.50.[15]

Selection of instrumental variables for PA

Most UK Biobank participants were genotyped with the Affymetrix UK Biobank Axiom Array (Santa Clara, California, USA), while about 10% were genotyped with the Affymetrix UK BiLEVE Axiom Array.[16]

We initially selected eight SNPs associated with average accelerations and eight SNPs associated with vigorous PA at a genome-wide significance level ($p<5\times10^{-8}$) in 91 084 UK Biobank participants.[12] In addition, we selected six SNPs associated with SB at $p<5\times10^{-8}$.[15] We looked up each instrument SNP and its proxies ($r^2>0.8$) in the PhenoScanncer genome-wide association study (GWAS) database (http://phenoscanner.medschl.cam.ac.uk)[17] to assess any previous associations ($p<1\times10^{-8}$) with the outcomes or potential confounders. Smoking was considered a relevant confounder.[18 19] We identified one of the SNPs for average accelerations (rs28749810) nominally associated with type 2 diabetes and the metabolic syndrome, respectively. After removing this SNP, seven, eight, and six SNPs were used as instrumental variables for average accelerations, vigorous PA, and SB in the primary analysis.

GWAS summary data for outcomes

Summary data for the associations of genetic variants with type 2 diabetes were obtained from a GWAS meta-analysis of 32 studies including 898 130 individuals of European ancestry from the Diabetes Genetics Replication And Meta-analysis (DIAGRAM Consortium; 74 124 type 2 diabetes cases and 824 006 controls).[20] For HbA1c, summary data from a publication by Wheeler *et al*[21] based on 123 665 diabetes-free participants' data from the Meta-Analyses of Glucose and Insulin-related Traits Consortium (MAGIC) were used. Summary data for fasting glucose (sample size n=58 074), HOMA-B (n=36 466), and HOMA-IR (n=37 037) were drawn from publications by Manning *et al*[22] and Dupuis *et al*[23] based on data of diabetes-free individuals of European ancestry from the MAGIC. The GWAS for the outcomes did not include data from the UK Biobank. Online supplemental tables 2–4 provide associations of genome-wide significant harmonized SNPs for accelerometer-based PA and SB with type 2 diabetes and glycemic traits.

Data availability

The present study is based on summary-level data that have been made publicly available. In all original studies, ethical approval had been obtained. The summary statistics for the PA and SB GWAS is available at https://klimentidis.lab.arizona.edu/content/data and at https://doi.org/10.5287/bodleian:yJp6zZmdj. The summary data

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for the type 2 diabetes GWAS are available at http://diagram-consortium.org/downloads.html, while for the HbA1c, fasting glucose, HOMA-B and HOMA-IR GWASs, summary data are available at www.magicinvestigators.org/downloads.

Statistical power

The a priori statistical power for the binary trait was calculated according to Burgess[24] and for continuous traits according to Deng.[25]

The eight SNPs for average accelerations explained 0.25%, and the eight SNPs for vigorous activity explained 0.25% of the phenotypic variance. The analyses were sufficiently powered to identify associations between the different exposure variables and outcomes (online supplemental table 6).

Statistical analyses

The principal analysis was conducted using a multiplicative random effects inverse-variance weighted (IVW) method, which allows for each SNP to have different mean effects.[26] The results for the outcome type 2 diabetes are presented as ORs and 95% CIs per 1 SD increment in average accelerations and vigorous PA or SB. One SD of objectively measured PA in the UK Biobank study has been reported to be approximately 8 milligravities (or 0.08 m/s^2) of acceleration in a mean 5 s window of analyzed accelerometer data.[15] A 1-SD increment in average accelerations (8.14 milligravities or 0.08 m/s^2) approximates to about 3 MET-hour/day,[27] with one MET equal to the metabolic cost of sitting quietly.[28]The results for the continuous outcomes are presented as β-estimates and 95% CIs per SD of objectively measured PA or SB.

One key assumption for IVW to produce a valid estimate is that there is no other way SNPs could affect the outcome than through the exposure. Violations of this assumption through horizontal pleiotropy can introduce bias, whereby the instruments exert an effect on the outcome independent of the exposure. To examine possible violations of this assumption, we checked each candidate SNP and its proxies ($r^2>0.8$) in PhenoScanner (online supplemental table 5) for previously reported associations ($p<5\times10^{-8}$) with confounders. The presence of pleiotropy was further investigated using between-instrument heterogeneity of the IVW estimates based on a modified Cochran's Q statistic (online supplemental table 7). If the pleiotropy is 'balanced' (ie, pleiotropic effects are independent in the magnitude of the SNP–exposure associations, and its mean is zero), the effect can be reliably estimated by the multiplicative random effects IVW method. However, if the mean pleiotropic effect is non-zero, as shown by the presence of a deviation from a zero intercept of an MR Egger regression, robust MR methods are indicated. Thus, IVW results were compared with other MR methods to address the violations of specific instrumental variable assumptions: weighted median MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and MR Mixture. The weighted median approach selects the median MR estimate as the causal estimate.[29] To detect and correct for any outliers reflecting likely pleiotropic biases for all reported results, the MR-PRESSO method was applied.[30] For sedentary behavior, there were less than five variants in combination with fasting glucose, HOMA-B and HOMA-IR. The MR-PRESSO method is based on the assumption that at least 50% of the variants are valid instruments relying on the Instrument Strength Independent of Direct Effect (InSIDE) condition. Thus, with less than five SNPs, the MR-PRESSO results were not very meaningful, and therefore, we omitted this analysis. The MRMix approach is a robust MR analysis tool that has the ability to trade off bias and efficiency for estimation of causal effects in the presence of invalid instruments.[31]

We performed leave-one-out analyses and exclusion of potentially pleiotropic SNPs to rule out possible pleiotropic effects (see online supplemental tables 8–10). The study was not preregistered. Analyses were performed using the TwoSampleMR (V.0.4.25)[32] and MRPRESSO (V.1.0) packages in R (V.3.6.1). Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology statement.[33]

ETHICS APPROVAL

In the present study, publicly available summary statistics were used, and therefore, no ethical approval was required.

RESULTS

Accelerometer-based PA and type 2 diabetes and glycemic traits

Average accelerations were unrelated to type 2 diabetes (IVW OR per 1 SD: 1.00; 95% CI 0.94 to 1.07), HbA1c (IVW β-estimate per 1 SD: 0.001; 95% CI −0.007 to 0.01), fasting glucose (IVW β-estimate per 1 SD: −0.001; 95% CI −0.017 to 0.015), HOMA-B (IVW β-estimate per 1 SD: −0.002; 95% CI −0.021 to 0.017), and HOMA-IR (IVW β-estimate per 1 SD: −0.001; 95% CI −0.019 to 0.016 (table 1)) across all MR methods.

We also found no evidence that vigorous PA was associated with type 2 diabetes (IVW OR per 1 SD: 0.83; 95% CI 0.56 to 1.23). Also, there was no association between vigorous PA and the investigated glycemic traits HbA1c, fasting glucose, HOMA-B, and HOMA-IR (table 2).

Accelerometer-based SB and type 2 diabetes and glycemic traits

We found that genetically predicted SB was unrelated to type 2 diabetes (IVW OR per 1 SD: 0.86; 95% CI 0.69 to 1.08) and all the other investigated outcomes (table 3). This result was confirmed across all MR methods.

We conducted a series of sensitivity analyses to assess the robustness of the results. The F statistics for the genetic instruments were 30 or higher, consistent with an absence of weak instrument bias (online supplemental table 1).

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Table 1 Mendelian randomization (MR) estimates between accelerometer-based average accelerations and type 2 diabetes and glycemic traits

Method	No. of SNPs	OR/beta	95% CI	P value	Outcome
Inverse variance weighted (multiplicative random effects)	7	1.00	(0.94 to 1.07)	0.948	Type 2 diabetes
Weighted median	7	1.01	(0.97 to 1.06)	0.562	Type 2 diabetes
MR-PRESSO: outlier corrected	4	1.03	(1.01 to 1.06)	0.103	Type 2 diabetes
MRMix	7	1.52	(1.14 to 2.03)	0.004	Type 2 diabetes
Inverse variance weighted (multiplicative random effects)	5	0.001	(-0.007 to 0.01)	0.767	HbA1c
Weighted median	5	0.000	(–0.01 to 0.01)	0.968	HbA1c
MR-PRESSO: raw	5	0.001	(–0.007 to 0.01)	0.782	HbA1c
MRMix	5	0.035	(–0.917 to 0.987)	0.943	HbA1c
Inverse variance weighted (multiplicative random effects)	5	–0.001	(–0.017 to 0.015)	0.914	Fasting glucose
Weighted median	5	0.002	(–0.019 to 0.023)	0.861	Fasting glucose
MR-PRESSO: raw	5	–0.001	(–0.012 to 0.01)	0.886	Fasting glucose
MRMix	5	–0.010	(–0.204 to 0.184)	0.919	Fasting glucose
Inverse variance weighted (multiplicative random effects)	5	–0.002	(–0.021 to 0.017)	0.811	HOMA-B
Weighted median	5	–0.010	(–0.03 to 0.009)	0.294	HOMA-B
MR-PRESSO: raw	5	–0.002	(–0.021 to 0.017)	0.822	HOMA-B
MRMix	5	–0.360	(–0.698 to –0.022)	0.037	HOMA-B
Inverse variance weighted (multiplicative random effects)	5	–0.001	(–0.019 to 0.016)	0.871	HOMA-IR
Weighted median	5	–0.003	(–0.026 to 0.02)	0.786	HOMA-IR
MR-PRESSO: raw	5	–0.001	(–0.018 to 0.015)	0.875	HOMA-IR
MRMix	5	–0.010	(–0.269 to 0.249)	0.940	HOMA-IR

HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance ; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; SNPs, single nucleotide polymorphisms.

The intercept test from MR-Egger regression suggested no presence of pleiotropy (online supplemental table 11). The estimates from the weighted median approach were consistent with the estimates from the IVW models, and the MR-PRESSO test identified no pleiotropic SNPs. Furthermore, the results from the leave-one-out analysis did not reveal any influential SNPs driving the associations (online supplemental table 8–10).

DISCUSSION

In this MR study, genetic predisposition to accelerometer-based average PA, vigorous PA and SB were not associated with the risk of type 2 diabetes. Furthermore, the present results did not provide clear evidence for a relationship between the different PA measures or SB and insulin resistance, beta-cell function, HbA1c as well as fasting glucose.

Our findings are not consistent with most previous observational studies and meta-analyses showing a protective association of PA with type 2 diabetes risk.[2 34] A recent systematic review and dose-response meta-analysis[2] reported a 39% risk reduction (95% CI 0.51 to 0.74) when comparing high with low self-reported vigorous PA, with moderate heterogeneity across the included eight prospective observational studies in that subanalysis (I^2=73%) and varying levels of adjustment for confounding factors. The discrepancies to our results might be attributable to residual confounding due to unmeasured or imprecisely measured confounders in observational studies. Furthermore, our MR analysis reflect long-term/lifelong PA in contrast to studies using short-term self-reported PA habits or PA interventions as exposure. Usually, higher PA is linked to other healthy lifestyle factors (healthier diet, lower prevalence of obesity and smoking).[35] The ability to disentangle the impact of highly correlated healthy lifestyle habits from each other and from other positive effects associated with PA and subsequently with a lower risk of diabetes (eg, lower blood pressure and weight, improved lipid profile, and mental well-being) may be limited when using conventional multivariable regression methods.[36] Furthermore, the association between PA and type 2

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Table 2 Mendelian randomization (MR) estimates between accelerometer-based vigorous PA (fraction of accelerations>425 milli-gravities) and type 2 diabetes and glycemic traits

Method	No. of SNPs	OR/beta	95% CI	P value	Outcome
Inverse variance weighted (multiplicative random effects)	8	0.83	(0.56 to 1.232)	0.357	Type 2 diabetes
Weighted median	8	0.80	(0.58 to 1.11)	0.177	Type 2 diabetes
MR-PRESSO: outlier corrected	6	0.86	(0.60 to 1.21)	0.421	Type 2 diabetes
MRMix	8	1.45	(0.86 to 2.44)	0.165	Type 2 diabetes
Inverse variance weighted (multiplicative random effects)	6	−0.018	(−0.085 to 0.05)	0.606	HbA1c
Weighted median	6	0.016	(−0.07 to 0.102)	0.717	HbA1c
MR-PRESSO: raw	6	−0.018	(−0.079 to 0.043)	0.595	HbA1c
MRMix	6	−0.035	(−0.169 to 0.099)	0.609	HbA1C
Inverse variance weighted (multiplicative random effects)	6	0.065	(−0.11 to 0.24)	0.469	Fasting glucose
Weighted median	6	0.059	(−0.148 to 0.266)	0.578	Fasting glucose
MR-PRESSO: raw	6	0.065	(−0.11 to 0.24)	0.502	Fasting glucose
MRMix	6	−0.010	(−0.574 to 0.554)	0.972	Fasting glucose
Inverse variance weighted (multiplicative random effects)	6	0.069	(−0.071 to 0.209)	0.336	HOMA-B
Weighted median	6	0.013	(−0.17 to 0.197)	0.886	HOMA-B
MR-PRESSO: raw	6	0.069	(−0.071 to 0.209)	0.380	HOMA-B
MRMix	6	0.110	(−0.902 to 1.122)	0.831	HOMA-B
Inverse variance weighted (multiplicative random effects)	6	0.102	(−0.111 to 0.316)	0.349	HOMA-IR
Weighted median	6	−0.041	(−0.258 to 0.176)	0.708	HOMA-IR
MR-PRESSO: raw	6	0.102	(−0.111 to 0.316)	0.392	HOMA-IR
MRMix	6	−0.030	(−0.455 to 0.395)	0.890	HOMA-IR

HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance ; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; PA, physical activity; SNPs, single nucleotide polymorphisms.

diabetes in observational studies might be due to reverse causation. Individuals screened for high risk of type 2 diabetes or with a diagnosis of pre-diabetes possibly change their lifestyle to delay or prevent a manifestation of the disease.[37 38] A change in lifestyle might include increasing levels of PA in addition to diet changes, weight loss, and quitting smoking.[37 38]

In an exposure-wide umbrella review of meta-analyses (including observational studies) regarding risk factors for type 2 diabetes, the association between sedentary time and risk of type 2 diabetes was supported by convincing evidence.[39] Another systematic review and meta-analysis on the association between self-reported SB and different health outcomes found an increased risk for incident type 2 diabetes with higher levels of total sitting as well as TV viewing time, independent of PA.[40] This finding was not replicated in the present study. However, in that meta-analysis, there was substantial heterogeneity in exposure measurement and unmeasured confounding was likely,[40] and thus it is difficult to ascertain causality. It is conceivable that in SB studies, confounding by socioeconomic status is more likely than in PA studies because TV time is strongly negatively associated with education level.[41]

A number of randomized controlled trials (RCTs) have examined the effect of exercise interventions on glycemic traits. However, the majority of these RCTs used an intervention that combined exercise and diet components, which make it difficult to attribute the effect to PA[42]; only one RCT focused exclusively on PA intervention.[43] Recently, a Cochrane Intervention Review of 12 RCTs with a total of 5238 persons on the issue whether PA, diet or both can prevent or delay type 2 diabetes and its associated complications was published.[42] Most of the trials included persons at increased risk of type 2 diabetes and the duration of the intervention varied between 2 and 6 years. Only one trial compared diet with PA in one of its trial arms.[44] There was no clear evidence that diet alone or PA alone compared with standard treatment influences the risk for type 2 diabetes,[42] and the overall quality of evidence was very low. Our study confirms this finding by showing that objectively measured PA of

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Table 3 Mendelian randomization (MR) estimates between accelerometer-based sedentary behavior (MET ≤1.5) and type 2 diabetes and glycemic traits

Method	No. of SNPs	OR/beta	95% CI	P value	Outcome
Inverse variance weighted (multiplicative random effects)	5	0.86	(0.69 to 1.08)	0.190	Type 2 diabetes
Weighted median	5	0.80	(0.60 to 1.08)	0.141	Type 2 diabetes
MR-PRESSO: raw	6	0.86	(0.69 to 1.08)	0.260	Type 2 diabetes
MRMix	6	1.00	(0.58 to 1.73)	1.000	Type 2 diabetes
Inverse variance weighted (multiplicative random effects)	4	0.010	(–0.078 to 0.099)	0.818	HbA1c
Weighted median	4	0.030	(–0.069 to 0.129)	0.553	HbA1c
MR-PRESSO: raw	5	0.010	(–0.078 to 0.099)	0.833	HbA1c
MRMix	5	0.025	(–0.130 to 0.180)	0.751	HbA1c
Inverse variance weighted (multiplicative random effects)	3	0.014	(–0.142 to 0.171)	0.856	Fasting glucose
Weighted median	3	0.045	(–0.144 to 0.234)	0.643	Fasting glucose
MRMix	4	0.025	(–0.185 to 0.235)	0.816	Fasting glucose
Inverse variance weighted (multiplicative random effects)	3	0.001	(–0.264 to 0.267)	0.991	HOMA-B
Weighted median	3	0.126	(–0.068 to 0.319)	0.203	HOMA-B
MRMix	4	0.230	(–0.122 to 0.582)	0.200	HOMA-B
Inverse variance weighted (multiplicative random effects)	3	0.023	(–0.363 to 0.409)	0.907	HOMA-IR
Weighted median	3	0.113	(–0.154 to 0.38)	0.407	HOMA-IR
MRMix	4	0.320	(–0.078 to 0.718)	0.115	HOMA-IR

HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance ; MET, metabolic equivalent task; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; SNPs, single nucleotide polymorphisms.

different intensities alone does not significantly reduce the risk of type 2 diabetes.

We also found no associations between objectively measured PA levels or SB and various glycemic traits. RCTs on this topic have yielded inconsistent results. In a systematic review and meta-analysis of randomized trials including 7487 participants aged 18–90 years (78.1% free of diabetes) based on 160 RCTs, moderate to long duration exercise training (2 weeks–2 years)[45] had a protective effect on insulin resistance (HOMA-IR) and HbA1c but not on fasting glucose levels.[45] Other systematic reviews and meta-analyses also suggested a protective effect of PA on insulin resistance. However, the quality of the included studies in those meta-analyses was mostly poor (high risk of bias),[46] and the quality of evidence was low or very low for all outcomes.[47]

In addition, a systematic review and meta-analysis reported inverse relations of HbA1c and insulin to resistance exercise training intensity,[47] and other meta-analyses found a reduction in fasting glucose levels after resistance exercise interventions in non-diabetic persons[47] or a reduction of fasting glucose and HbA1c in physically active persons with type 2 diabetes or metabolic syndrome only.[46] Another systematic review and meta-analysis supported a decrease in HbA1c levels in favor of the physically active group (effect size 0.32; 95% CI 0.01 to 0.62) noting substantial heterogeneity (I^2=63.2%; p=0.008).[48]

Our MR analysis found no effect of average PA, vigorous PA and SB on glycemic traits. This seems plausible because it is unlikely that PA will have a significant effect on these glycemic traits in the normal range in non-diabetic individuals. Most previous RCTs investigating the effects of PA on fasting glucose and HbA1c levels were conducted in high-risk groups, such as individuals with pre-diabetes or obesity or people with manifest type 2 diabetes. Hence, from observational studies and RCTs on this issue, it is not clear so far whether associations between PA and type 2 diabetes are causal or biased due to self-report measurement error, residual confounding, reverse causality, or ascertainment bias in RCTs.

The findings of our two-sample MR study regarding the outcome type 2 diabetes are in line with results reported by Doherty *et al*.[15] In that study, the MR analysis on the causal association between moderate accelerometer measured PA and diabetes in UK Biobank participants who were not in the accelerometer discovery dataset

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resulted in an OR for diabetes of 0.86 (p=0.079), indicating no causal effect.

Strengths and limitations

Contrary to observational studies and RCTs for PA, the major advantage of our study is the use of MR, which has the ability to reflect lifelong exposure to a causal factor that might differ from self-reported PA habits or PA interventions for shorter time periods later in life. A further advantage of our study is the two-sample MR study design, diminishing unobserved confounding and reverse causality. The very large sample size (almost 900 000 individuals in the type 2 diabetes outcome study, almost 500 000 individuals for PA) provided the power to detect effect sizes previously reported in observational studies and to perform multiple sensitivity analyses for testing the validity of the MR assumptions, thus minimizing the possibility of biased results. Our study also has limitations. Because only data from European populations was used, our findings may differ in other ethnicities. The outcome type 2 diabetes may be affected by a degree of misclassification because case ascertainment in the studies included in the DIAGRAM Consortium was not carried out according to certain specifications and thus a broad spectrum of type 2 diabetes cases (those with or without complications, different disease durations and so on) was included. The appeal of accelerometers to objectively monitor PA is their ability to quantify ambulatory activity during walking, jogging and so on. However, accelerometers are not without limitations. The disadvantages of accelerometers are their difficulties to measure posture and sedentary, light activites and non-ambulatory activites (cycling and weightlifting), and for estimating energy expenditure.[49] Furthermore, awareness that PA is being monitored might influence habitual behavior.[50]

CONCLUSIONS

In summary, the present two-sample MR study found no evidence of a causal association between genetically determined objectively measured PA and SB with the risk of type 2 diabetes and glycemic traits. There is no question that PA has a positive impact on health, but it seems that the complex interplay of the numerous metabolic effects and multiple biological mechanisms mediating the beneficial role of PA on disease development[51] are not fully understood so far. Further studies are necessary to deepen our understanding of the biological pathways of PA.

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Contributors CM, SEB, and HB designed the work and interpreted the data; HB conducted the analysis; CM drafted the work; all authors critically revised the work and approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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