

ORIGINAL ARTICLE

Appraising the causal role of physical activity and sedentary behavior in female reproductive health: A Mendelian randomization study

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ABSTRACT

Background: Physical inactivity and sedentary behavior have been associated with adverse female reproductive outcomes, but whether these associations are causal remains uncertain. **Methods:** We used genome-wide association study summary data to evaluate four self-reported activity-related traits—leisure screen time (LST), moderate-to-vigorous physical activity (MVPA), sedentary behavior at work (SDW), and sedentary commuting behavior (SDC)—in relation to 25 female reproductive conditions. Linkage disequilibrium score regression was used to assess genetic correlations. Univariable and multivariable Mendelian randomization (MR) analyses were performed, with MR-Egger, weighted median, weighted mode, MR-RAPS, and Causal Analysis Using Summary Effect Estimates (CAUSE) used for sensitivity analyses. **Results:** Longer LST was causally associated with higher odds of adenomyosis, endometriosis, excessive, frequent, and irregular menstruation, ectopic pregnancy, and abortion. MVPA was causally associated with lower odds of adenomyosis, endometriosis, and excessive, frequent, and irregular menstruation. Multivariable MR further supported independent associations of LST with abortion and postpartum depression. SDW showed limited associations, whereas no significant causal association was identified for SDC. **Conclusions:** Genetic evidence supports causal associations of physical activity and sedentary behavior with several female reproductive outcomes. Reducing leisure screen time and increasing moderate-to-vigorous physical activity may represent modifiable strategies to support female reproductive health.

Keywords: physical activity, sedentary behavior, female reproductive health, Mendelian randomization, causality

INTRODUCTION

Physical inactivity contributes substantially to the global disease burden and has been estimated to account for more than 5 million deaths annually.^[1,2] However, worldwide, there is a growing trend of insufficient physical activity occurring during leisure hours (27.5%), particularly in high-income Western countries (42.3%).^[3,4] Moreover, research has shown that sedentary time increases among women of reproductive age over time,^[5] thereby potentially posing a health risk.^[6]

To date, physical activity and sedentary behavior have only been associated with a subset of female reproductive conditions. For example, a correlation between sedentary behavior and postpartum depression has been reported.^[7] However, evidence regarding most female reproductive conditions is limited and inconsistent. Previously, two systematic reviews were unable to conclusively demonstrate an association between physical activity and endometriosis,^[8,9] whereas individual studies have reported associations with higher levels of physical activity.^[10,11] The effects of prolonged sitting behavior on

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Received: 2 July 2026; Revised: 4 August 2026; Accepted: 5 September 2026

<https://doi.org/10.54844/prm.2026.1355>

gestational diabetes^[12-14] and gestational hypertension^[15,16] are also inconsistent. These discrepancies may reflect biases, including small sample size, reverse causation, and the confounding impact of lifestyle and environmental factors. Moreover, a negative genetic correlation between physical activity and sedentary behavior may result in an exaggeration of individual effects on female reproductive conditions.^[17]

Mendelian randomization (MR) is a causal inference approach that employs genetic variations associated with exposure as instrumental variables (IVs). This approach shifts the focus of causal association studies from phenotypic to genotypic investigations.^[18] With a random allocation of genetic variations occurring at conception, MR can significantly mitigate the influence of residual confounding factors and reverse causality issues.^[19] In the present study, MR and linkage disequilibrium score regression (LDSC) were employed to examine potential genetic correlations and causal associations between four self-reported physical activity and sedentary behavior traits and 25 female reproductive conditions.

METHODS

Study design

To investigate potential causal associations between the exposure traits and reproductive outcomes, single-nucleotide polymorphisms (SNPs) associated with the exposures were screened for use as instrumental variables. Univariable MR, multivariable MR (MVMR), and sensitivity analyses were performed. In addition, full genome-wide association study (GWAS) summary statistics were used for LDSC and Causal Analysis Using Summary Effect Estimates (CAUSE). These complementary approaches were used to evaluate genetic correlations and causal associations between physical activity, sedentary behavior, and female reproductive health (Figure 1).

GWAS of exposure and IVs selection

Exposure data pertaining to four self-reported physical activity and sedentary behaviors, specifically leisure screen time (LST), moderate-to-vigorous physical activity (MVPA), sedentary behavior at work (SDW), and sedentary commuting behavior (SDC), were obtained from a recent meta-analysis GWAS.^[17] All four traits were based on self-reported assessments as defined in the source GWAS. Briefly, the relevant cohort included 703,901 individuals from 51 studies representing European (94.0%), African (2.1%), East Asian (0.8%), and South Asian (1.3%) lineages. In addition, individuals of Hispanic descent (1.9%) were included. To minimize the influence of including such a diverse set of populations on our results, only data from participants of European ancestry were analyzed. Consequently, the

LST data were based on 526,725 individuals, while the MVPA data were based on 608,595 individuals. Additionally, the SDW and SDC datasets were based on 372,609 and 159,606 individuals, respectively.

Independent ($r^2 = 0.001$, clumping window size = 10 MB) and genome-wide significant ($P < 5 \times 10^{-8}$) genetic instruments for LST, MVPA and SDW were extracted from each GWAS. Rare SNPs with a minor allele frequency (MAF) < 0.01 were excluded. SNPs associated with confounding factors ($P < 5 \times 10^{-8}$) identified by Phenoscanner, and those that highly correlated with the outcomes ($P < 5 \times 10^{-8}$), were also excluded.

GWAS of outcomes

Outcome data were obtained from FinnGen, a comprehensive database exclusively comprising individuals of Finnish descent. This database is regularly updated and encompasses a substantial number of participants. The phenotypes in this database are defined based on the International Classification of Diseases codes, specifically Revisions 8, 9, and 10, where available. There were 25 female reproductive conditions examined.

LDSC

Genome-wide genetic correlations of self-reported physical activity and sedentary behaviors on each of 25 female reproductive conditions were determined using LDSC, which utilized GWAS summary data.^[20] To determine the necessary linkage disequilibrium (LD) score of the SNPs, we estimated the LD structure for the European populations based on the European 1000 Genomes database and Hap-Map3 SNPs (<https://github.com/bulik/Ldsc>).

MR analysis

Two-sample MR analyses were conducted to examine the causal associations of four self-reported physical activity and sedentary behaviors with female reproductive conditions. Multiple methods were employed in the MR analysis to ensure accuracy and stability of the results. First, an inverse-variance weighted (IVW) analysis based on a random-effects model was utilized as the primary analysis. Weighted median, MR-Egger, and MR-robust adjusted profile score (MR-RAPS) were also employed for sensitivity analysis. A causal association was considered significant only when the IVW analysis was statistically significant and the direction of effect was consistent across all four MR methods. CAUSE, a Bayesian posterior probabilities-based MR method, was further applied in our analysis to enhance statistical power. Instead of relying solely on significant loci, full genome-wide results were submitted for CAUSE.^[21] Finally, we conducted Cochran's IVW Q test and MR-Egger regression to assess heterogeneity and pleiotropy, respectively.

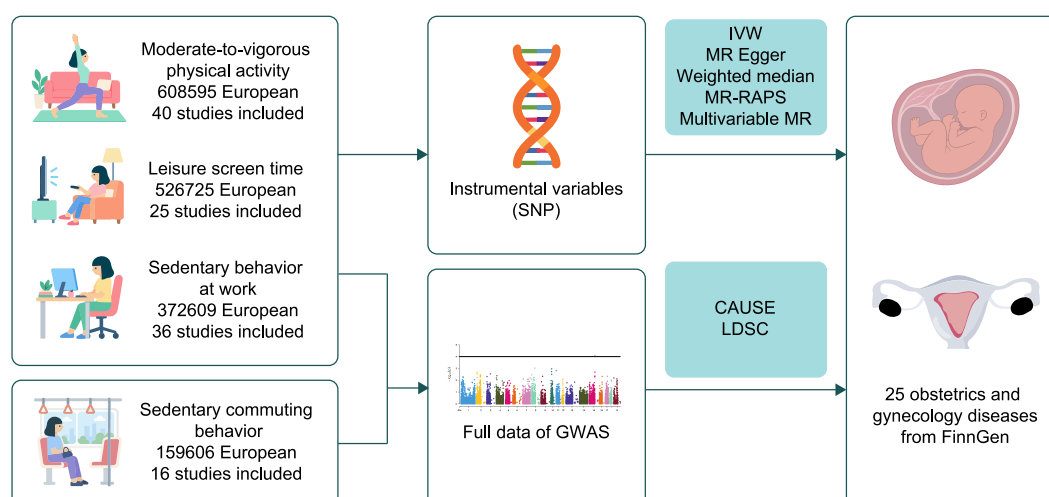


Figure 1. Flowchart of study design. SNP, single-nucleotide polymorphism; GWAS, genome-wide association study; MR, Mendelian randomization; IVW, inverse-variance weighted; MR-RAPS, MR-robust adjusted profile scoring; CAUSE, Causal Analysis Using Summary Effect Estimates; LDSC, linkage disequilibrium score.

MVMR was employed to address the potential for individual contributions of physical activity and sedentary behavior to be overstated regarding female reproductive conditions, given the negative correlation between them. Briefly, MVMR utilizes genetic variants associated with multiple exposures to estimate the specific effect of each exposure on a specific outcome.^[22,23] Consequently, we considered all IVs associated with LST, MVPA and SDW to comprehensively evaluate their individual impacts on female reproductive health.

F statistic was calculated to represent the strength of the instrumental variables and equals: $\beta_{\text{exposure}}^2 / SE_{\text{exposure}}^2$. SNPs with an F statistic value ≤ 10 are considered weak instrumental variables.^[24,25] All female reproductive conditions are binary. Consequently, odds ratio (OR) and 95% confidence interval values were used to assess the strength of the causal association between exposure and outcome.

Statistically significant associations were defined using a Bonferroni-corrected threshold of $P < 0.002$ (0.05/25 outcomes), whereas associations with $0.002 < P < 0.050$ were considered suggestive. Two-tailed P values were used for all analyses. Statistical analyses were conducted using the “TwoSampleMR”, “MendelianRandomization”, and “CAUSE” packages in R version 4.2.1.

RESULTS

Genetic correlation of physical activity and sedentary behavior on female reproductive health

The LDSC analysis revealed genetic correlations of three self-reported physical activity and sedentary behaviors

on various female reproductive outcomes: LST, MVPA and SDW (Figure 2, Supplementary Table 1). In contrast, few female reproductive conditions were found to genetically correlate with SDC. Specifically, gestational diabetes ($r_g = -0.40$ – 0.33 , $P < 0.001$ for all) exhibited genetic links to all four categories of physical activity and sedentary behavior, and was also the sole female reproductive condition that significantly correlated with SDC. Moreover, abortion ($r_g = -0.44$ – 0.26 , $P < 0.001$ for all), excessive, frequent, and irregular menstruation ($r_g = -0.25$ – 0.23 , $P < 0.001$ for all), inflammatory disease of uterus ($r_g = -0.50$ – 0.32 , $P < 0.002$ for all), and postpartum depression ($r_g = -0.34$ – 0.25 , $P < 0.001$ for all), all concurrently displayed genetic correlations with LST, MVPA and SDW.

Causal associations of LST with female reproductive health

IVs for LST included 115 SNPs that were selected from a pool of 20,320,958 SNPs. The F statistic of these SNPs ranged from 29.3 to 97.2 (Supplementary Table 2).

Prolonged LST showed significant causal associations with adenomyosis (OR = 1.57, $P < 0.001$), endometriosis (OR = 1.29, $P < 0.001$), excessive, frequent and irregular menstruation (OR = 1.23, $P < 0.001$), ectopic pregnancy (OR = 1.51, $P < 0.001$), and abortion (OR = 1.27, $P < 0.001$) (Figure 3). These associations were supported by MR-RAPS ($P < 0.001$ for all). Weighted median analysis also supported associations of LST with endometriosis (OR = 1.32, $P = 0.002$), excessive, frequent, and irregular menstruation (OR = 1.25, $P = 0.001$), and abortion (OR = 1.26, $P < 0.001$) (Supplementary Table 3). MR additionally sugges-

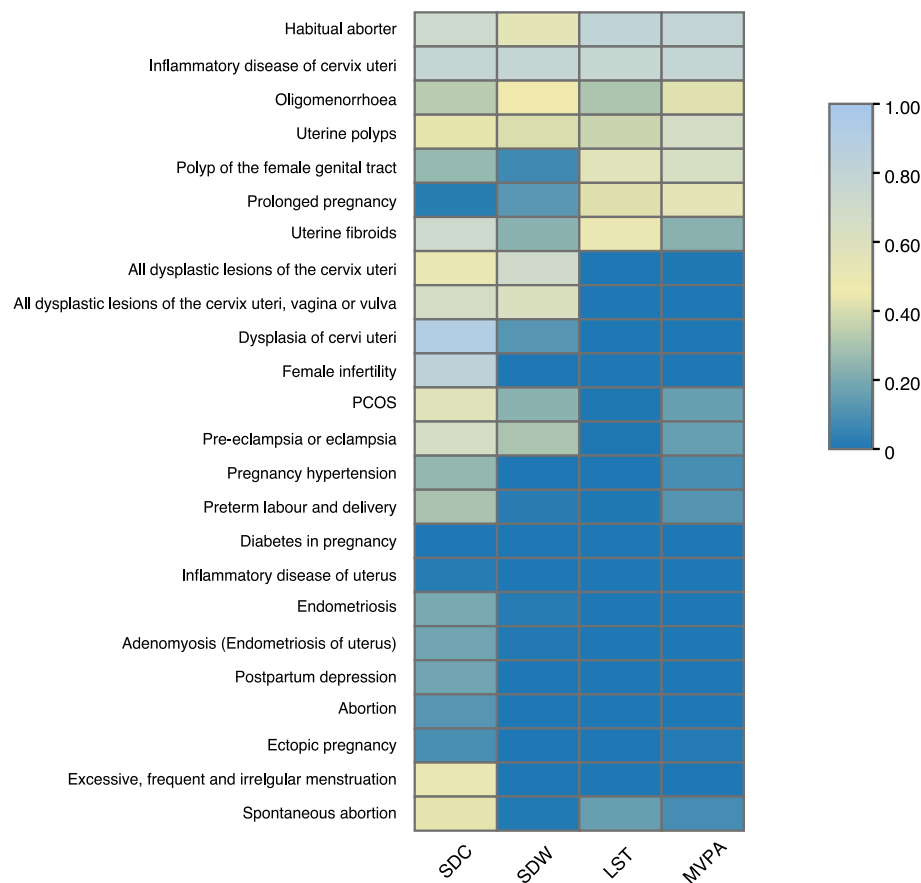


Figure 2. Genetic correlations of physical activity and sedentary behavior with female reproductive health. Colors represent *P* values from the LDSC genetic-correlation tests; darker blue indicates smaller *P* values. SDC, sedentary commuting behavior; SDW, sedentary behavior at work; LST, leisure screen time; MVPA, moderate-to-vigorous physical activity.

ted potential associations of prolonged LST with postpartum depression (OR = 1.36, *P* < 0.001), three dysplastic lesion indicators (OR = 1.31–1.34, *P* = 0.002–0.001), spontaneous abortion (OR = 1.17, *P* = 0.014), and inflammatory disease of the uterus (OR = 1.39, *P* = 0.004). These suggestive findings were not consistently supported across all four MR methods after multiple-testing correction. Although heterogeneity was detected by Cochran's *Q* test, the primary IVW analysis used a random-effects model.

The CAUSE analysis provided additional support for several associations. Excessive, frequent, and irregular menstruation (OR = 1.13, *P* = 0.014), abortion (OR = 1.14, *P* = 0.040), ectopic pregnancy (OR = 1.25, *P* = 0.026), and postpartum depression (OR = 1.14, *P* = 0.040) were found to correlate with LST (Supplementary Table 4).

Causal associations of MVPA with female reproductive health
After conducting a search of 12,000,000 SNPs, 16 SNPs were selected as IVs for MVPA based on their qualifica-

tion. The *F* statistic of these SNPs ranged from 30.1 to 81.4 (Supplementary Table 5).

MVPA showed significant causal associations with lower odds of adenomyosis (OR = 0.36, *P* < 0.001), endometriosis (OR = 0.47, *P* < 0.001), and excessive, frequent, and irregular menstruation (OR = 0.55, *P* < 0.001) (Figure 4). MR-RAPS also supported these three associations (*P* < 0.001 for all). The association of MVPA with excessive, frequent, and irregular menstruation (OR = 0.56, *P* = 0.001) was additionally supported by weighted median analysis. MR additionally suggested potential associations of MVPA with preterm birth (OR = 0.58, *P* = 0.012) and female infertility (OR = 0.62, *P* = 0.038). The reported associations were robust in the heterogeneity and pleiotropy sensitivity analyses (Supplementary Table 6).

The CAUSE analysis indicated associations of MVPA with excessive, frequent, and irregular menstruation (OR = 0.83, *P* = 0.011), abortion (OR = 0.89, *P* = 0.047), and inflammatory disease of the uterus (OR =

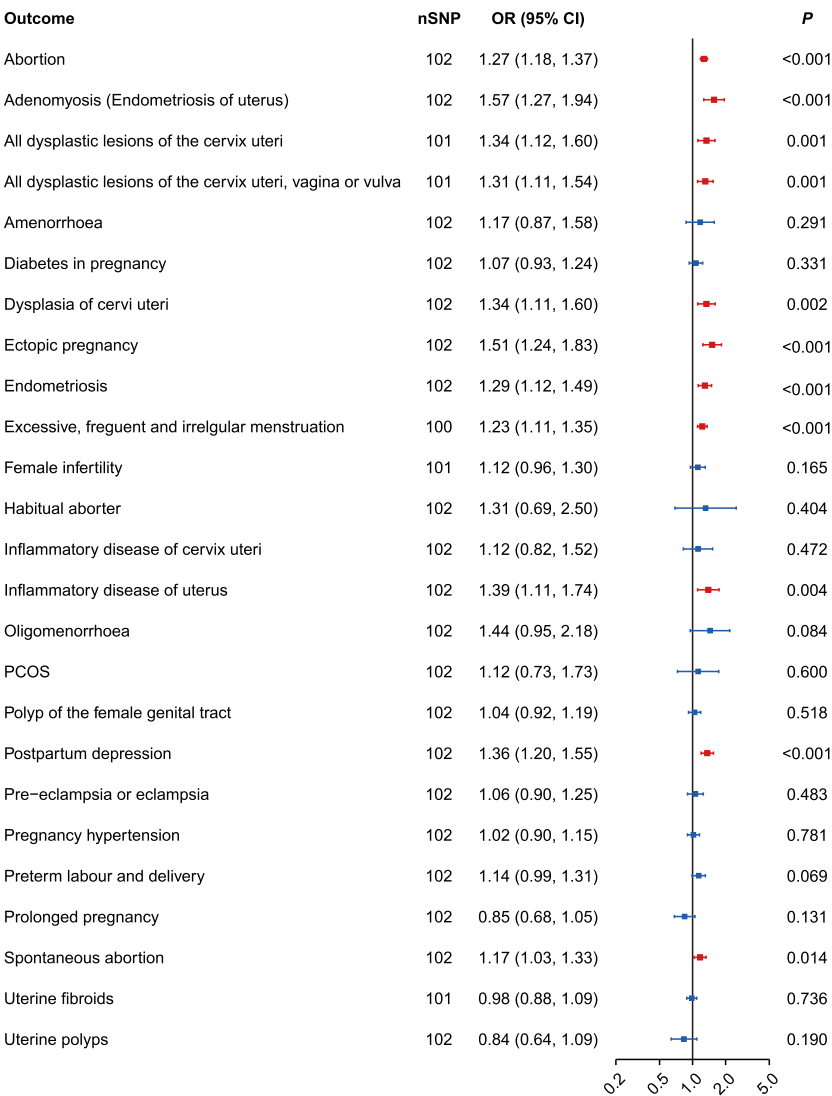


Figure 3. Forest plot of inverse-variance weighted Mendelian randomization estimates for leisure screen time and female reproductive health. Points indicate odds ratios (ORs), and horizontal bars indicate 95% confidence intervals (CIs). nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

0.63, $P = 0.026$)(Supplementary Table 4).

Causal associations of SDW and SDC with female reproductive health

A search of 12,000,000 SNPs resulted in the identification of nine SNPs that satisfied the criteria to serve as IVs for SDW. The range of F statistic for these SNPs varied from 29.9 to 88.4 (Supplementary Table 7).

MR results showed a causal association of SDW with lower odds of endometriosis ($OR = 0.58$, $P = 0.001$) (Figure 5), which was also supported by MR-RAPS ($OR = 0.57$, $P = 0.002$) (Supplementary Table 8). MR also suggested associations with excessive, frequent, and irregular menstruation ($OR = 0.63$, $P < 0.001$) and abortion ($OR = 0.80$, $P = 0.023$). CAUSE additionally identified an association between SDW and gestational dia-

betes ($OR = 0.80$, $P = 0.048$). Heterogeneity was assessed using Cochran's Q test, and directional pleiotropy was evaluated using the MR-Egger intercept (Supplementary Table 8).

SDC did not yield genome-wide significant SNPs in the GWAS dataset. Consequently, only the Bayesian CAUSE method was used to investigate potential causal associations. No significant causal associations were identified between SDC and the included female reproductive conditions (Supplementary Table 4).

MVMR

A negative genetic correlation between physical activity and sedentary behavior can lead to an exaggeration of their respective impacts on each female reproductive condition. To counter this concern, MVMR was employed.

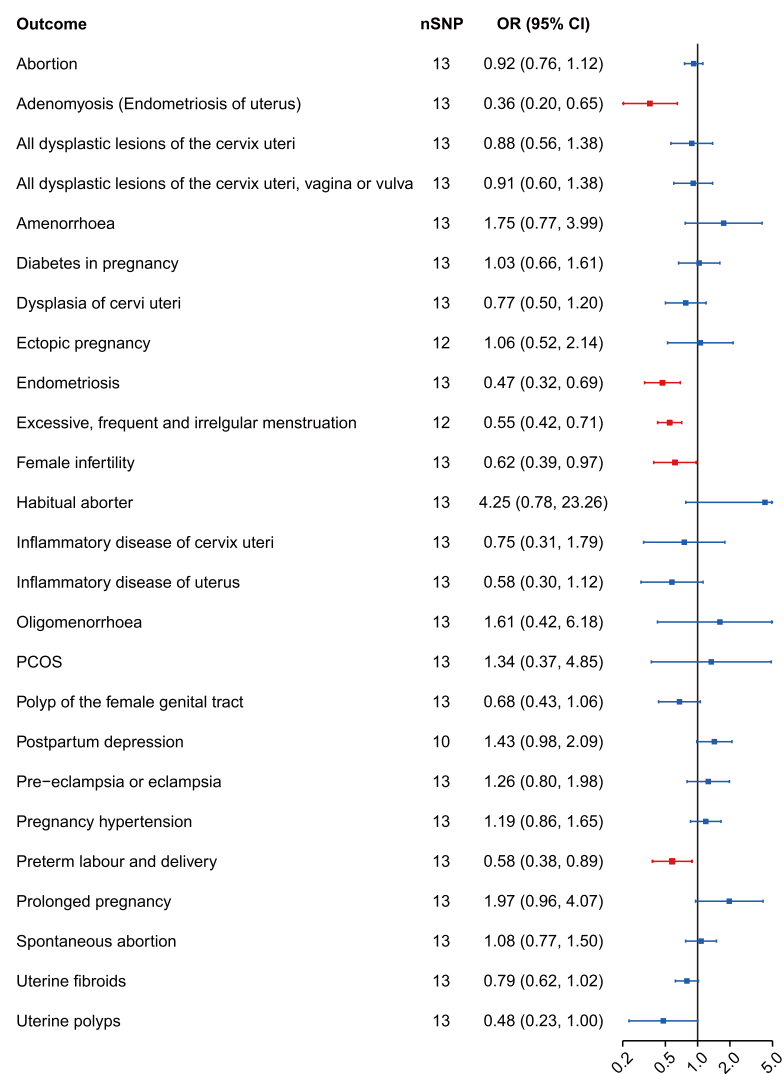


Figure 4. Forest plot of inverse-variance weighted Mendelian randomization estimates for moderate-to-vigorous physical activity and female reproductive health. Points indicate odds ratios (ORs), and horizontal bars indicate 95% confidence intervals (CIs). nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

In MVMR, LST was independently associated with abortion (OR = 1.12, $P = 0.002$) (Figure 6) and postpartum depression (OR = 1.26, $P = 0.001$). MVPA was independently associated with adenomyosis (OR = 0.46, $P = 0.002$), endometriosis (OR = 0.62, $P = 0.002$), excessive, frequent, and irregular menstruation (OR = 0.66, $P < 0.001$), and prolonged pregnancy (OR = 2.43, $P = 0.001$).

DISCUSSION

To systematically assess the influence of physical activity and sedentary behavior on female reproductive health, we analyzed comprehensive GWAS data using LDSC and MR. The findings support the potential relevance of reducing sedentary behavior and increasing physical activity for female reproductive health.

Consistent with previous research, the present findings indicate a positive correlation between sedentary behavior and postpartum depression. In a prospective cohort study conducted in France, an elevated risk of postpartum depression was found to be linked to sedentary behavior in the final trimester of pregnancy.^[7] Similarly, a study conducted among non-pregnant women has consistently demonstrated a higher risk of depression among women who engaged in prolonged sitting (*e.g.*, in front of a computer, watching television) or overall sedentary behaviors.^[26] Sedentary behavior influences depression through multiple biological mechanisms which involve changes in plasma beta-endorphin levels, core body temperature, the central serotonergic system, neurotransmitter availability, and cerebral blood flow in regions associated with emotional regulation.^[27] A case-control study also identified prolonged sedentary behavior during

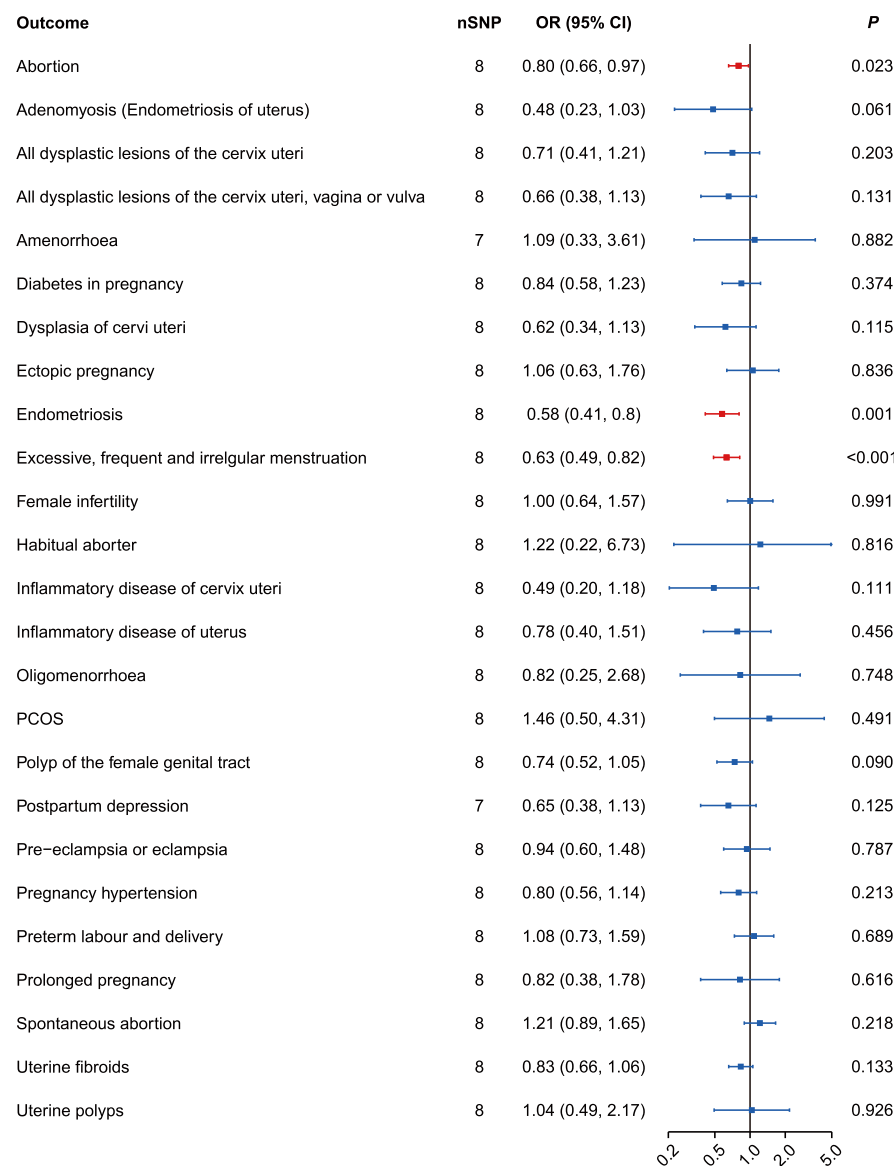


Figure 5. Forest plot of inverse-variance weighted Mendelian randomization estimates for sedentary behavior at work and female reproductive health. Points indicate odds ratios (ORs), and horizontal bars indicate 95% confidence intervals (CIs). nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

pregnancy as a risk factor for abortion.^[28] It has been demonstrated that prolonged sedentary behavior influences a range of symptoms and indicators throughout pregnancy. For example, elevated sedentary time during pregnancy has been linked to unfavorable self-rated health,^[29] long-term absences from work due to sickness,^[30] and heightened overall mental distress symptoms encompassing depression and anxiety.^[31] Furthermore, sedentary behavior was found to positively correlate with C-reactive protein and low density lipoprotein cholesterol levels,^[32,33] fasting glucose levels, abnormal glucose tolerance,^[12] as well as arterial and venous cord blood partial pressure of carbon dioxide and acidic arterial and venous pH during pregnancy.^[34,35] These factors

may potentially contribute to abortions that occur due to prolonged sedentary behavior.

It is intriguing that the impact of sedentary behavior on female reproductive conditions was found to be limited to LST in the present study, and no discernible effect was observed in relation to SDW or SDC. This phenomenon could potentially be attributed to expectant mothers consciously limiting their occupational and commuting engagements in the mid and later phases of pregnancy. Prior investigations have indicated that among children and adolescents, excessive LST was linked to adverse dietary patterns^[36,37] and diminished sleep duration.^[38,39] Nonetheless, observation of this

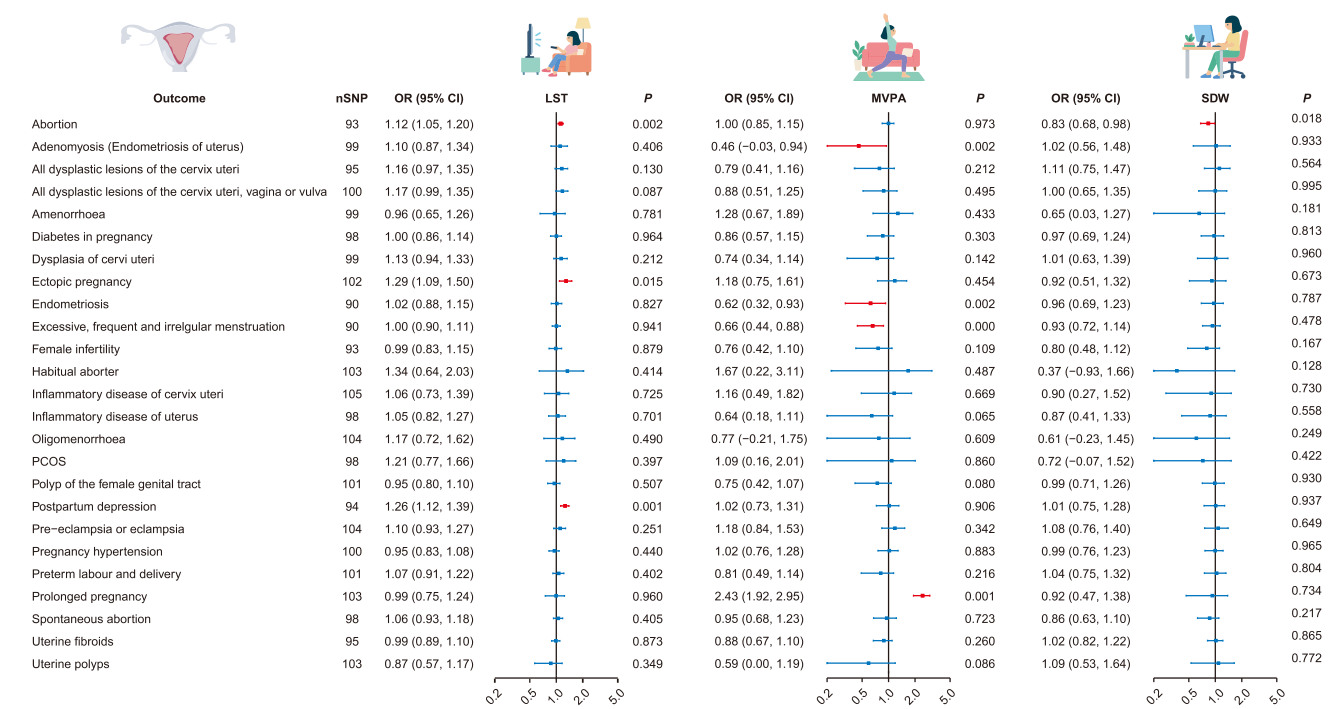


Figure 6. Forest plot of multivariable Mendelian randomization estimates for physical activity, sedentary behavior, and female reproductive health. Points indicate odds ratios, and horizontal bars indicate 95% confidence intervals. LST, leisure screen time; MVPA, moderate-to-vigorous physical activity; SDW, sedentary behavior at work; nSNP, number of single-nucleotide polymorphisms.

association within a pregnant demographic, and its potential to clarify the varied impact of prolonged sedentary behavior in diverse settings on abortion, warrant further validation.

The relationship between physical activity and endometriosis remains a topic of ongoing debate. In two systematic reviews, a link between physical activity and endometriosis was not established.^[8,10] In contrast, there are individual studies which have demonstrated this correlation.^[40] However, in the latter, frequent and intense engagement in high-intensity physical activity over an extended period was a factor. In a recent randomized controlled trial, therapeutic exercise regimens were found to enhance patient quality of life, alleviate pain, and reduce pelvic injuries in women with endometriosis who do not respond to conventional treatment.^[41] The present findings support a potential protective association of MVPA with endometriosis, but clinical intervention studies are required before physical activity can be considered a therapeutic strategy.

Regarding menstruation, the impact of physical activity remains inconclusive. Two studies have demonstrated that physical activity does not influence menstrual regularity.^[42,43] However, a large-scale cohort study reported that highly active women exhibited a 10% lower likelihood of experiencing heavy menstrual bleeding compared to those who reported no physical activity.^[43] It is possible

that discrepancies in reporting physical activity levels and categorizing different levels of physical activity intensity may underlie these divergent findings.

The present study has several strengths. First, recent and comprehensive GWAS data on physical activity and sedentary behavior were analyzed, enabling a broad evaluation of causal associations with female reproductive conditions. Second, the CAUSE method uses full genome-wide summary data, thereby enhancing statistical power, addressing sample overlap and enabling assessment of horizontal pleiotropy. Third, LDSC and MR analyses provided complementary perspectives on the associations between exposures and outcomes. Several limitations should also be acknowledged. First, the physical activity and sedentary behavior traits were based on self-reported information and may therefore be subject to measurement bias. Second, the analyses were restricted to European-ancestry datasets, which may limit generalizability to other populations. Third, female reproductive outcomes were obtained from FinnGen to address sample overlap; replication in additional cohorts would strengthen the robustness and generalizability of the findings.

CONCLUSIONS

In summary, our genetic analyses support causal associations of physical activity and sedentary behavior with

several female reproductive conditions. Further studies are warranted to clarify the underlying mechanisms and to evaluate whether reducing sedentary behavior and increasing physical activity can improve female reproductive health in clinical settings.

DECLARATIONS

Supplementary information

Supplementary materials are only available at the official site of the journal (<https://www.hksmp.com/journals/prm>).

Acknowledgments

We are very grateful to all the researchers and participants from NHGRI-EBI GWAS Catalog and FinnGen.

Author contributions

Li YZ contributed solely to this Article.

Source of funding

None.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Use of large language models, AI and machine learning tools

None declared.

Data availability statement

Summary statistics for the genome-wide association study of four self-reported physical activity and sedentary behaviors are available through the NHGRI-EBI GWAS Catalog (<https://www.ebi.ac.uk/gwas/download/s/summary-statistics>, GCP ID: GCP000358). Additionally, the GWAS summary statistics for female reproductive diseases can be obtained from FinnGen (<https://r7.finnngen.fi/>).

Conflict of interest

The authors declare no competing interests.

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