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ORIGINAL RESEARCH

Causal Relationships Among Lifestyle, Lipidome, and Polycystic Ovary Syndrome: A Mendelian Randomization Study

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Background: Lifestyle interventions often influence lipid levels in patients with polycystic ovary syndrome (PCOS), thereby modulating disease progression. However, whether lipid levels play a mediating role remains unclear.

Objective: To investigate causal associations between lifestyle, lipidome, and PCOS, as well as mediating role of lipidome.

Methods: This study employed a bidirectional two-sample Mendelian randomization (MR) analysis, with lifestyle and lipidome as exposures and PCOS as outcome. A two-step MR approach was used to assess mediating role of lipidome. Inverse-variance weighted (IVW) method was primarily applied, and sensitivity analyses were conducted to test robustness of results.

Results: Overall physical activity time (OR = 0.590, 95% CI: 0.394–0.882, $P = 0.010$) was significantly negatively associated with PCOS risk, while leisure screen time (OR = 1.377, 95% CI: 1.050–1.804, $P = 0.021$) was significantly positively associated with PCOS risk. 25 lipid levels were significantly associated with PCOS risk, with 3 showing negative correlations and 22 showing positive correlations ($P < 0.05$). Mediation analysis revealed that TAG (50:1) (triacylglycerol with 50 carbon atoms and 1 double bond) levels mediated causal relationship between increased overall physical activity time and lowered PCOS risk. The median effect accounted for 23.8% of the total effect (B = −0.126, 95% CI: −0.238 to −0.014, $P = 0.027$).

Conclusion: This study revealed causal associations between overall physical activity time, leisure screen time, and PCOS, and identified mediating role of TAG (50:1) levels. These findings provide scientific insights for lifestyle management in PCOS patients.

Keywords: lifestyle, lipidome, polycystic ovary syndrome, mendelian randomization

Introduction

With a prevalence of 5–18%, polycystic ovarian syndrome (PCOS) is an endocrine condition that impacts women's reproductive, metabolic, and mental health.[1] Clinical features of PCOS include hyperandrogenemia (clinical or biochemical), irregular ovulation cycles, and polycystic ovarian morphology.[2,3] Obesity is a significant risk factor for PCOS, with up to 65% of affected women being overweight or obese.[4] Dyslipidemia plays a critical role, as obesity often leads to elevated triacylglycerol (TAG), increased low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C).[5] Notably, TAG molecules can induce insulin resistance through serine phosphorylation of insulin receptor substrate-1 (IRS-1) and promote the release of inflammatory factors, directly participating in the pathological progression of PCOS.[6,7] These abnormal lipid profiles not only exacerbate the progression of PCOS but also increase the risk of cardiovascular complications.[8,9] Therefore, improving obesity and lipid metabolism is a key objective in the management of PCOS.

Lifestyle interventions (diet, exercise, behavioral, or combined) are recommended as first-line management for PCOS patients in international evidence-based guidelines.[2] Their benefits have been demonstrated in multiple studies. A Cochrane review including 15 randomized controlled trials and 498 participants reported that lifestyle interventions significantly reduced body weight and BMI and improved secondary reproductive outcomes, such as the free androgen

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index, compared to minimal intervention or usual care.[10] Moderate weight loss through lifestyle interventions improves ovulation and menstrual regularity in PCOS, thereby promoting reproductive health.[11] More importantly, lifestyle interventions can specifically modulate lipid metabolism, reducing total cholesterol and LDL-C levels.[12,13] This evidence supports a potential causal cascade: lifestyle interventions influence lipidome remodeling (specifically altering TAG levels), thereby alleviating PCOS pathology. However, whether lipid metabolites act as mediators in this pathway has not been verified using causal inference methods.

Therefore, this study employed Mendelian Randomization (MR) to quantify the causal effects of lifestyle factors on PCOS risk and to investigate lipid metabolites significantly associated with PCOS. Furthermore, the mediating role of the lipidome in the lifestyle-PCOS pathway was evaluated. The findings may provide a theoretical basis for precise lifestyle interventions in PCOS management.

Methods

Study Design

A two-sample MR approach was employed to estimate causal relationships between 14 lifestyle factors and 179 lipid levels as exposures, with PCOS as outcome. Mediating role of lipid levels was explored (Figure 1). To reduce heterogeneity, genome-wide association study (GWAS) data were collected from people with European ancestry.

This study utilized only fully de-identified, publicly available summary data from previously published GWAS (data accessed before February 2025). Therefore, no additional ethical approval or patient consent was required. The study protocol was reviewed and granted an exemption by the Ethics Committee of Xi'an Gaoxin Hospital. This exemption is fully compliant with Article 32 of China's *Ethical Review Measures for Life Sciences and Medical Research Involving Humans* (issued on February 18, 2023), which states that research using publicly sourced data may be exempt from ethical review.

GWAS Data Acquisition

This study included 13 lifestyle-related factors. Alcohol intake frequency and coffee intake involved 462,346 and 428,860 participants of European ancestry, respectively (https://gwas.mrcieu.ac.uk/). Smoking initiation included 607,291 individuals of European descent.[14] Insomnia data comprised 453,379 participants,[15] while sleep duration involved 446,118 individuals.[16] Chronotype (sleep rhythm) was assessed in 449,734 participants.[17] Data on total physical activity, moderate-intensity activity, walking time, and sedentary behavior duration were each derived from 91,105 participants. Leisure screen time, moderate-to-vigorous physical activity, and sedentary behavior at work involved 526,725, 608,595, and 72,609 participants, respectively.[18]

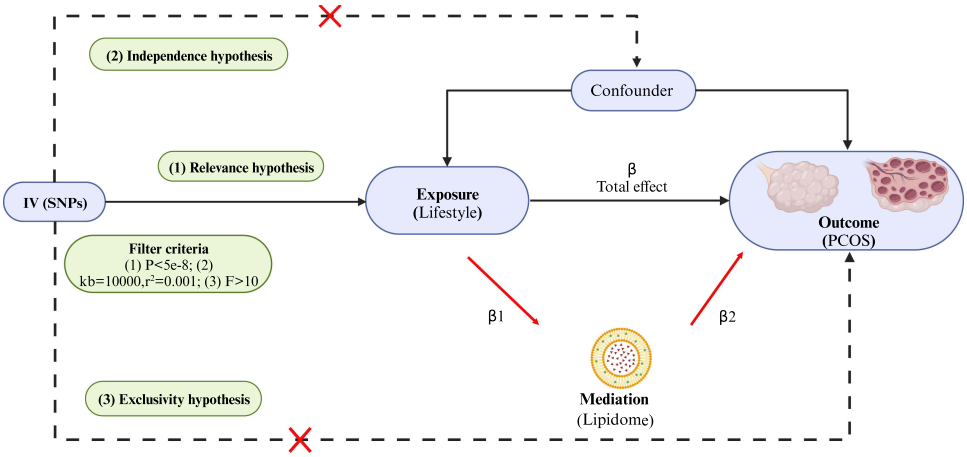

Figure 1 Flow chart of the Mendelian Randomization study design.
Notes: Created in BioRender. ming, H. (2025) https://BioRender.com/a5j9wem.
Abbreviations: PCOS, polycystic ovary syndrome; IV, Instrumental Variable(s); SNP, Single Nucleotide Polymorphisms.

Lipid levels (n = 179) were obtained from 7,174 participants,[19] including phosphatidylcholine (PC), cholesteryl ester (CE), phosphatidylinositol (PI), diacylglycerol (DAG), triacylglycerol (TAG), and phosphatidylcholine ether (PCO). For detailed information on all lipid molecules, please refer to Table S1.

The GWAS data for the outcome (PCOS) were obtained from the latest release (R12) of the FinnGen database (https://www.finngen.fi/en),[20] comprising 269,994 participants.

Detailed information on all GWAS datasets included in this study is provided in Table 1.

Instrumental Variable (IV) Selection

IVs must satisfy three key assumptions: the IV must be directly associated with the exposure; it must be independent of any confounding factors; and it must not be directly associated with the outcome. The selection criteria for IVs were as follows: (1) Single nucleotide polymorphisms (SNPs) were used as IVs. A genome-wide significance threshold of $P<5e-08$ was applied. For 179 lipid traits, walking time, sedentary behavior, moderate-intensity physical activity, total physical activity time, and when PCOS was used as the exposure, a threshold of $P<5e-06$ was adopted. (2) PLINK's clumping algorithm was employed to remove SNPs in linkage disequilibrium, ensuring the independence of the genetic instruments ($r2=0.001$, window size = 10,000 kb). (3) The harmonise_data() function in the R package "TwoSampleMR" was used to align and harmonize the effect alleles and strands between exposure and outcome summary statistics. Palindromic SNPs and incompatible SNPs were excluded during this process. (4) The F-statistic was calculated to exclude weak IVs ($F>10$). (5) The MR-PRESSO method was applied to perform a global test and remove outliers, thereby correcting for potential horizontal pleiotropy.

MR Analysis

For bidirectional two-sample MR analysis, five techniques were used: weighted median estimator, MR-Egger regression, random-effects inverse-variance weighted (IVW), weighted mode, and simple mode. The results from the IVW method with random effects were considered the primary reference, as this model accommodates a certain degree of heterogeneity among IVs and is more robust than fixed-effect models in the presence of potential pleiotropy.[21–23] Results from other methods were used as supplementary evidence to validate the stability of the main findings.

A two-step MR approach was employed for mediation analysis[24,25] to explore whether lipid traits mediate the causal pathway from lifestyle factors to PCOS. First, we identified lifestyle and lipid-related traits that showed significant causal associations with PCOS and were free of horizontal pleiotropy. Second, using the same analytical criteria, we evaluated the causal effects of these lifestyle factors on the lipid traits genetically associated with PCOS. The total effect (β)

Table 1 Detailed Information of the Genome-Wide Association Studies in Our Analysis

Traits	ID	Population	Sample	Case	Control	PMID	Year
Alcohol intake frequency	ukb-b-5779	European	462,346	NA	NA	NA	2018
Coffee intake	ukb-b-5237	European	428,860	NA	NA	NA	2018
Smoking initiation	ieu-b-4877	European	607,291	NA	NA	30643251	2019
Insomnia	GCST007387	European	453,379	345,022	108,357	30,804,566	2019
Sleep duration	GCST007561	European	446,118	NA	NA	30846698	2019
Chronotype	GCST007576	European	449,734	NA	NA	30696823	2019
Walking duration	GCST007110	European	91,105	NA	NA	30531941	2018
Moderate intensity activity duration	GCST006915	European	91,105	NA	NA	30531941	2018
Overall physical activity time	GCST006912	European	91,105	NA	NA	30531941	2018
Sedentary behavior duration	GCST006913	European	91,105	NA	NA	30531941	2018
Leisure screen time	GCST90104339	European	526,725	NA	NA	36071172	2022
Moderate-to-vigorous intensity physical activity	GCST90104341	European	608,595	NA	NA	36071172	2022
Sedentary behavior at work	GCST90104345	European	72,609	NA	NA	36071172	2022
179 Lipids	GCST90277238-416	European	7,174	NA	NA	37907536	2023
PCOS	NA	European	269,994	2,214	267,780	36,653,562	2024

represents the overall causal association from lifestyle factor to PCOS. Potential mediators with logically consistent effect directions were retained. The mediation analysis consisted of two steps: the association between the lifestyle factor and the lipid trait (β_1), and the causal effect of the lipid trait on PCOS (β_2). The mediation effect was calculated as the product of β_1 and β_2. The proportion mediated was estimated by dividing the mediation effect by the total effect. The delta method was used to estimate the 95% confidence interval for the mediation effect.

Sensitivity analyses in this study primarily included assessments of heterogeneity, horizontal pleiotropy, and leave-one-out validation.[26] The MR-PRESSO outlier test was applied to detect and remove outliers among the IVs before MR analysis. Heterogeneity among SNPs was evaluated using Cochran's Q test; a P-value < 0.05 indicated the presence of heterogeneity, in which case the random-effects IVW model was adopted. To evaluate deviations from the standard IV assumptions, MR-Egger regression and the MR-PRESSO global test were used to assess horizontal pleiotropy. MR-Egger performs weighted linear regression without constraining the intercept; a statistically significant MR-Egger intercept ($P < 0.05$) suggests the presence of horizontal pleiotropy, and results under such conditions were excluded to ensure robustness. Additionally, a leave-one-out sensitivity analysis was conducted by iteratively removing each SNP to confirm that the MR results were not driven excessively by any single variant.[27]

The statistical power for each analysis was independently calculated using an online tool (https://sb452.shinyapps.io/power/). Power estimation was based on the following parameters: the proportion of variance in the exposure explained by the instruments (R^2), sample size of the outcome, expected causal effect size, and a significance level of $\alpha = 0.05$, thereby ensuring the validity of the MR results.[28]

Sensitivity Analysis

The following methods were employed for sensitivity analysis:[26] Cochran's Q test to examine SNP heterogeneity; MR-Egger regression to evaluate directional pleiotropy; MR-PRESSO global test to assess horizontal pleiotropy; Leave-one-out analysis to determine influence of particular SNPs on causations; Steiger analysis to confirm directionality of causal associations.[27]

Statistical Analysis

MR analyses were done on R software (version 4.4.1) utilizing R packages "TwoSampleMR" (version 0.6.8) and "MR-PRESSO" (version 1.0). P-value < 0.05 indicated statistically significant.

Results

Genetic Associations Between Lifestyle and PCOS

Genetic associations between lifestyle factors and PCOS were explored (IVs are listed in Table S2). Overall physical activity time (OR = 0.590, 95% CI: 0.394–0.882, $P = 0.010$) and chronotype (OR = 0.668, 95% CI: 0.506–0.882, $P = 0.004$) had a significant negative association with PCOS risk. Leisure screen time (OR = 1.377, 95% CI: 1.050–1.804, $P = 0.021$) and alcohol intake frequency (OR = 1.456, 95% CI: 1.073–1.976, P = 0.016) were significantly positively linked with PCOS risk (Figure 2). These findings were consistent across four additional MR methods (Table S3).

MR results passed sensitivity analyses (Table S4 and Figure S1). Reverse MR analysis revealed that PCOS was negatively linked with chronotype (OR = 0.989, 95% CI: 0.980–0.998, $P = 0.018$) and alcohol intake frequency (OR = 0.987, 95% CI: 0.979–0.995, $P = 0.002$) (Table S5). The statistical power analysis indicated that the IVs for all lifestyle factors, with the exception of leisure screen time, exhibited adequate statistical power (Power > 0.6) (Table S6).

Genetic Associations Between Lipidome and PCOS

Genetic associations between lipidome and PCOS were analyzed (IVs are listed in Table S7). IVW results indicated that 25 lipid levels were significantly associated with PCOS risk, with 3 showing negative correlations and 22 showing positive correlations (Figure 3). PC(15:0_18:1), CE(27:1/16:1), and CE(27:1/20:2) levels all had a significant negative association with PCOS risk. PC(18:0_22:5, 18:0_18:1, 17:0_18:2), PI(18:1_18:1, 18:0_18:1, 18:0_18:2, 16:0_18:2), DAG(18:1_18:1, 18:1_18:2, 16:1_18:1), TAG(50:4, 51:4, 50:3, 50:2, 49:1, 54:6, 48:3, 48:2, 48:1, 50:1), and PCO

Exposure	Outcome	N(snp)	Pval	OR(95% CI)
Overall physical activity time	PCOS	47	0.010	0.590 (0.394 to 0.882)
Sleep duration	PCOS	61	0.183	0.661 (0.359 to 1.216)
Chronotype	PCOS	142	0.004	0.668 (0.506 to 0.882)
Moderate−to−vigorous intensity physical activity	PCOS	10	0.561	0.782 (0.341 to 1.794)
Walking duration	PCOS	23	0.416	0.784 (0.437 to 1.408)
Moderate intensity activity duration	PCOS	27	0.728	0.904 (0.510 to 1.600)
Sedentary behavior at work	PCOS	9	0.888	0.956 (0.514 to 1.779)
Sedentary behaviour duration	PCOS	37	0.782	1.058 (0.710 to 1.577)
Smoking initiation	PCOS	85	0.683	1.065 (0.786 to 1.445)
Leisure screen time	PCOS	107	0.021	1.377 (1.050 to 1.804)
Alcohol intake frequency	PCOS	92	0.016	1.456 (1.073 to 1.976)
Insomnia	PCOS	37	0.457	1.594 (0.466 to 5.454)
Coffee intake	PCOS	36	0.136	1.801 (0.831 to 3.905)

Figure 2 Results of IVW Mendelian randomization of lifestyle and PCOS.
Abbreviation: PCOS, polycystic ovary syndrome.

Exposure	Outcome	N(snp)	Pval	OR(95% CI)
PC (15:0_18:1) levels	PCOS	8	0.013	0.734 (0.576 to 0.936)
CE (27:1/16:1) levels	PCOS	15	0.005	0.767 (0.637 to 0.924)
CE (27:1/20:2) levels	PCOS	19	0.028	0.862 (0.755 to 0.984)
PC (18:0_22:5) levels	PCOS	18	0.042	1.163 (1.006 to 1.346)
PI (18:1_18:1) levels	PCOS	16	0.032	1.173 (1.014 to 1.358)
PI (18:0_18:1) levels	PCOS	16	0.016	1.174 (1.030 to 1.339)
DAG (18:1_18:1) levels	PCOS	19	0.028	1.176 (1.018 to 1.359)
PI (18:0_18:2) levels	PCOS	23	0.005	1.184 (1.053 to 1.330)
DAG (18:1_18:2) levels	PCOS	24	0.009	1.195 (1.045 to 1.366)
TAG (50:4) levels	PCOS	19	0.008	1.223 (1.054 to 1.419)
TAG (51:4) levels	PCOS	15	0.010	1.230 (1.050 to 1.441)
PC (O−17:0_17:1) levels	PCOS	15	0.024	1.233 (1.028 to 1.478)
PC (18:0_18:1) levels	PCOS	18	0.010	1.252 (1.055 to 1.486)
DAG (16:1_18:1) levels	PCOS	13	0.010	1.271 (1.059 to 1.525)
PI (16:0_18:2) levels	PCOS	19	0.002	1.272 (1.094 to 1.479)
TAG (50:3) levels	PCOS	16	0.003	1.276 (1.088 to 1.496)
TAG (50:2) levels	PCOS	9	0.027	1.277 (1.028 to 1.587)
TAG (49:1) levels	PCOS	11	0.023	1.299 (1.037 to 1.628)
TAG (54:6) levels	PCOS	9	0.013	1.308 (1.059 to 1.614)
PC (17:0_18:2) levels	PCOS	14	0.002	1.350 (1.118 to 1.630)
TAG (48:3) levels	PCOS	17	<0.001	1.359 (1.134 to 1.630)
TAG (48:2) levels	PCOS	14	<0.001	1.365 (1.137 to 1.640)
PC (O−16:0_16:0) levels	PCOS	7	0.015	1.413 (1.070 to 1.866)
TAG (48:1) levels	PCOS	11	<0.001	1.467 (1.183 to 1.820)
TAG (50:1) levels	PCOS	11	<0.001	1.572 (1.282 to 1.926)

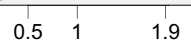

Figure 3 Results of IVW Mendelian randomization of lipidome and PCOS.
Abbreviations: CI, Confidence Interval; DAG, Diacylglycerol; CE, Cholesteryl Ester; OR, Odds Ratio; PC, Phosphatidylcholine; PC(O-), Phosphatidylcholine Ether; PI, Phosphatidylinositol; PCOS, Polycystic Ovary Syndrome; TAG, Triacylglycerol; N(snp), Number of instrumental SNPs used in the analysis.

(17:0_17:1, 16:0_16:0) levels were substantially positively linked with PCOS risk. Other approaches produced similar results (Table S8).

Sensitivity analysis confirmed robustness of these causal relations (Table S9 and Figure S2). Reverse MR analysis showed no reverse causal associations except for CE(27:1/16:1) levels (OR = 0.951, 95% CI: 0.914–0.990, $P = 0.014$) (Table S10).

Mediation Analysis Results

After excluding results with reverse causal associations, we evaluated causal relationships between two lifestyle factors (overall physical activity time and leisure screen time) and 24 lipid-related traits. Overall physical activity time was

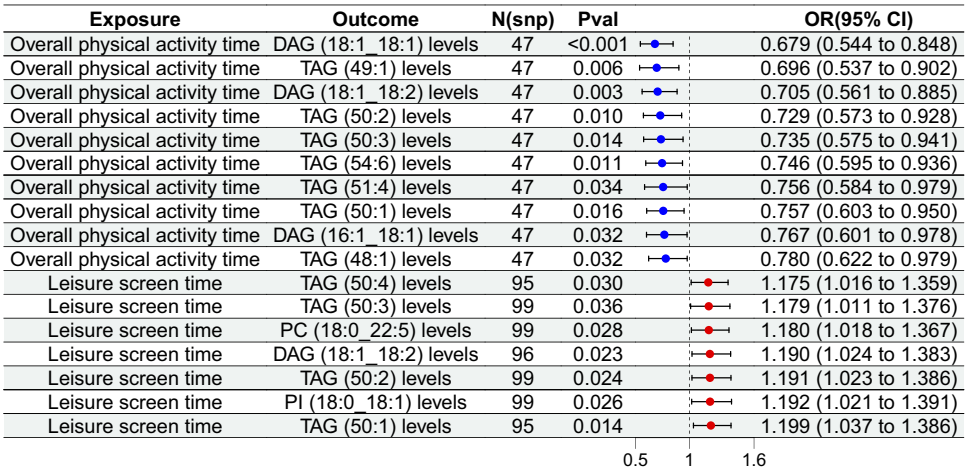

Figure 4 Results of IVW Mendelian randomization of lifestyle and associated lipids.
Abbreviations: CI, Confidence Interval; DAG, Diacylglycerol; OR, Odds Ratio; PC, Phosphatidylcholine; PI, Phosphatidylinositol; SNP, Single Nucleotide Polymorphism; TAG, Triacylglycerol; N(snp), Number of instrumental SNPs used in the analysis.

strongly negatively linked with ten lipid characteristics, including DAG(18:1_18:1, 18:1_18:2, 16:1_18:1) and TAG. Leisure screen time was significantly positively linked with seven lipid characteristics, including TAG(50:4, 50:3, 50:2, 50:1), PC(18:0_22:5), DAG(18:1_18:2), and PI(18:0_18:1) (Figure 4). Sensitivity studies verified robustness of these findings (Table S11), and no reverse relationships were found (Table S12).

Mediation analysis revealed that TAG (50:1) levels significantly mediated causal relationship between increased overall physical activity time and lowered PCOS risk, accounting for 23.8% of total effect (B = −0.126, 95% CI: −0.238 to −0.014, P = 0.027) (Table 2).

Table 2 Mediation Analysis Result

Exposure	Mediator	Outcome	Beta	Beta1	Beta2	Mediated Effect (95% CI)	Mediated Proportion	Pval
Leisure screen time	DAG (18:1_18:2) levels	PCOS	0.320	0.174	0.178	0.031 (−0.004,0.066)	9.67% (−1.39%, 20.7%)	0.086
Leisure screen time	PC (18:0_22:5) levels	PCOS	0.320	0.165	0.151	0.025 (−0.008,0.058)	7.84% (−2.46%, 18.1%)	0.136
Leisure screen time	PI (18:0_18:1) levels	PCOS	0.320	0.175	0.161	0.028 (−0.006,0.063)	8.82% (−1.92%, 19.6%)	0.107
Leisure screen time	TAG (50:1) levels	PCOS	0.320	0.182	0.452	0.082 (−0.014,0.178)	25.7% (−4.25%, 55.6%)	0.093
Leisure screen time	TAG (50:2) levels	PCOS	0.320	0.175	0.245	0.043 (−0.017,0.102)	13.4% (−5.18%, 31.9%)	0.158
Leisure screen time	TAG (50:3) levels	PCOS	0.320	0.165	0.244	0.040 (−0.006,0.087)	12.6% (−1.93%, 27.1%)	0.089
Leisure screen time	TAG (50:4) levels	PCOS	0.320	0.161	0.201	0.032 (−0.006,0.070)	10.1% (−1.74%, 22%)	0.094
Overall physical activity time	DAG (16:1_18:1) levels	PCOS	−0.528	−0.265	0.24	−0.064 (−0.142,0.014)	12% (26.8%, −2.71%)	0.110
Overall physical activity time	DAG (18:1_18:1) levels	PCOS	−0.528	−0.386	0.162	−0.063 (−0.152,0.026)	11.9% (28.7%, −4.96%)	0.167
Overall physical activity time	DAG (18:1_18:2) levels	PCOS	−0.528	−0.350	0.178	−0.062 (−0.146,0.021)	11.8% (27.6%, −4.02%)	0.144
Overall physical activity time	TAG (48:1) levels	PCOS	−0.528	−0.248	0.383	−0.095 (−0.195,0.005)	18% (37%, −0.914%)	0.062
Overall physical activity time	TAG (49:1) levels	PCOS	−0.528	−0.362	0.262	−0.095 (−0.206,0.016)	18% (38.9%, −3.03%)	0.094
Overall physical activity time	TAG (50:1) levels	PCOS	−0.528	−0.278	0.452	−0.126 (−0.238,-0.014)	23.8% (45%, 2.7%)	0.027
Overall physical activity time	TAG (50:2) levels	PCOS	−0.528	−0.316	0.245	−0.077 (−0.170,0.016)	14.6% (32.2%, −2.94%)	0.103
Overall physical activity time	TAG (50:3) levels	PCOS	−0.528	−0.307	0.244	−0.075 (−0.160,0.010)	14.2% (30.3%, −1.93%)	0.085
Overall physical activity time	TAG (51:4) levels	PCOS	−0.528	−0.280	0.207	−0.058 (−0.138,0.022)	11% (26%, −4.07%)	0.153
Overall physical activity time	TAG (54:6) levels	PCOS	−0.528	−0.293	0.268	−0.079 (−0.166,0.009)	14.9% (31.4%, −1.62%)	0.077

Abbreviations: PCOS, polycystic ovary syndrome; CI, Confidence Interval; DAG, Diacylglycerol; PC, Phosphatidylcholine; PI, Phosphatidylinositol; TAG, Triacylglycerol.

Discussion

Our MR analysis revealed that overall physical activity time was significantly negatively associated with PCOS risk, while leisure screen time was significantly positively associated with PCOS risk. TAG (50:1) levels played a significant mediating role in causal relationship between increased overall physical activity time and lowered PCOS risk.

Numerous previous studies support the protective effect of physical activity against PCOS. Meta-analyses have demonstrated that exercise improves lipid profiles, reduces waist circumference, systolic blood pressure, and fasting insulin levels, and enhances cardiometabolic parameters in women with PCOS.[29] Randomized controlled trials have shown that physical activity interventions lead to weight loss, decreased oxidized LDL-C,[30] improved sexual function, and reduced anxiety and depressive symptoms in women with PCOS compared to control groups.[31] The underlying protective mechanisms primarily involve improvements in insulin resistance (IR), hyperandrogenism, and chronic inflammation.[32] IR is a key driver of PCOS pathophysiology, affecting most patients and significantly disrupting ovarian function and lipid metabolism.[33,34] Regular aerobic exercise (eg, 1 hour per session, 3 times per week, at 60% VO_2max) significantly enhances insulin sensitivity in PCOS patients,[35] strengthens insulin signaling in skeletal muscle, and promotes changes in insulin gene expression and metabolic signaling that resemble those observed in healthy women.[36] Additionally, exercise contributes to weight loss and improved body composition, effectively reducing testosterone levels and the free androgen index,[37–40] while also mitigating chronic inflammation.[41–43]

This study is the first to use MR to suggest that lipid metabolism may mediate the protective effect of physical activity on PCOS. Mediation analysis indicated that a reduction in TAG (50:1) levels accounts for approximately 23.8% of the total effect. TAG, a critical energy storage molecule synthesized primarily in the liver and stored in adipose tissue as lipid droplets, plays an essential role in maintaining insulin sensitivity when metabolically balanced. Excessive accumulation of TAG disrupts insulin signaling, promotes lipotoxicity, and induces low-grade inflammation.[44,45] Previous studies have reported elevated TAG levels in women with PCOS,[46] which may exacerbate IR by inducing serine phosphorylation of insulin receptor substrate-1[47] and correlate with increased leukocyte and neutrophil counts, further aggravating chronic inflammation.[48] Lowering TAG levels not only helps improve IR and inflammatory responses but may also support the restoration of ovulatory function in PCOS patients.[49] From a genetic perspective, this study highlights the regulation of TAG metabolism as a potential key mechanism through which exercise interventions ameliorate PCOS, offering new targets for precise prevention and treatment.

In recent years, with the widespread use of electronic devices, the potential health impact of leisure screen time has garnered increasing attention. Our findings identify leisure screen time as a risk factor for PCOS, potentially mediated through the promotion of obesity. Prolonged screen time is associated with an increased risk of obesity,[50] which can lead to adipocyte dysfunction, elevated release of free fatty acids, and subsequent inhibition of glucose uptake in peripheral tissues, thereby inducing IR.[51] Concurrently, obesity triggers low-grade inflammation through the activation of pro-inflammatory pathways (eg, the JNK signaling pathway), increasing the production of pro-inflammatory cytokines, endothelial adhesion molecules, and chemotactic mediators. These factors stimulate monocyte infiltration into adipose tissue and their differentiation into classically activated macrophages, inducing a local or systemic pro-inflammatory state,[52] collectively promoting IR and PCOS development. Furthermore, excessive leisure screen time may indirectly contribute to PCOS onset by increasing the risk of depression,[53] which is itself a known risk factor for the disorder.[54]

This study suggests that increasing physical activity and reducing screen time may lower the risk of PCOS by regulating lipid metabolism. These findings support the implementation of early lifestyle interventions in high-risk populations, such as adolescent girls or individuals with a family history of PCOS, integrating body composition management and blood lipid monitoring into preventive strategies. This provides new insights for the primary prevention of PCOS. However, the study has certain drawbacks. First, the study population was predominantly composed of people of European ancestry, which limited the findings' generalizability to other ethnic groups. Due to significant differences in genetic backgrounds, environmental factors, and lifestyles among ethnic groups, caution is needed when extrapolating these results to other populations. Second, although our analysis demonstrated causal relationships between overall physical activity time, leisure screen time, and PCOS, PCOS onset is closely related to age. However, the lack of demographic information in GWAS data precluded subgroup analyses to explore the specific role of age. Third, given the

exploratory nature of this study, we conducted statistical tests on a wide range of exposures and mediators. While this generated abundant hypothesis-building data, the lack of multiple testing correction may have increased the risk of false-positive results. Subsequent studies are needed to validate these preliminary findings in independent samples. Finally, although the mediation analysis suggested the mediating role of lipids such as TAG (50:1), the specific molecular mechanisms remain unclear and require further clarification through cellular or animal experiments, or more refined omics data.

Conclusion

This study employed MR combined with mediation analysis to reveal a causal relationship between overall physical activity time, leisure screen time, and the risk of PCOS, and for the first time identified the specific lipid molecule TAG (50:1) as a key mediator in this association. These findings not only enhance the understanding of the metabolic mechanisms through which lifestyle influences PCOS but also provide potential targets for the precise prevention of the disorder. Monitoring and regulating TAG (50:1) levels may become a novel intervention strategy for high-risk populations, such as adolescents or overweight women. As the results of this study are primarily based on genetic data from European populations, future research is needed to validate the generalizability of the lipid mediation effect and elucidate its specific molecular mechanisms across diverse ethnic groups and experimental settings to facilitate its translation into clinical practice.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Ethics Approval and Consent to Participate

Ethical approval and consent were not required as this study was based on publicly available data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known conflicts of interest in this work.

References

1. Joham AE, Norman RJ, Stener-Victorin E, et al. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol*. 2022;10(9):668–680. doi:10.1016/S2213-8587(22)00163-2
2. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum Reprod*. 2018;33(9):1602–1618. doi:10.1093/humrep/dey256
3. Chappell NR, Gibbons WE, Blesson CS. Pathology of hyperandrogenemia in the oocyte of polycystic ovary syndrome. *Steroids*. 2022;180:108989. doi:10.1016/j.steroids.2022.108989
4. Radwan A, Al-Juhani AA, Alshehri AA, et al. The association of polycystic ovarian syndrome among reproductive-aged women with consumption of junk food in Jeddah, Saudi Arabia. *Cureus*. 2023;15(11):e48299. doi:10.7759/cureus.48299
5. Vekic J, Stefanovic A, Zeljkovic A. Obesity and dyslipidemia: a review of current evidence. *Curr Obes Rep*. 2023;12(3):207–222. doi:10.1007/s13679-023-00518-z
6. Vilarino-Garcia T, Guadix P, Dorado-Silva M, Sanchez-Martin P, Perez-Perez A, Sanchez-Margalet V. Decreased expression of sam68 is associated with insulin resistance in granulosa cells from PCOS patients. *Cells*. 2022;11:18. doi:10.3390/cells11182821
7. Woo JR, Bae SH, Wales TE, et al. The serine phosphorylations in the IRS-1 PIR domain abrogate IRS-1 and IR interaction. *Proc Natl Acad Sci U S A*. 2024;121(17):e2401716121. doi:10.1073/pnas.2401716121

8. Liu Q, Xie YJ, Qu LH, Zhang MX, Mo ZC. Dyslipidemia involvement in the development of polycystic ovary syndrome. *Taiwan J Obstet Gynecol*. 2019;58(4):447–453. doi:10.1016/j.tjog.2019.05.003
9. Su P, Chen C, Sun Y. Physiopathology of polycystic ovary syndrome in endocrinology, metabolism and inflammation. *J Ovarian Res*. 2025;18 (1):34. doi:10.1186/s13048-025-01621-6
10. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2019;3(3):. doi:10.1002/14651858.CD007506.pub4
11. Oberg E, Gidlof S, Jakson I, Mitsell M, Tollet Egnell P, Hirschberg AL. Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. *Clin Endocrinol*. 2019;90(3):468–478. doi:10.1111/cen.13919
12. Zhang Y, Zhang Z, Martinez-Tellez B, et al. Moderate-intensity exercise training uniquely modulates circulating lipid species beyond classical lipid levels in humans. *EBioMedicine*. 2025;118:105849. doi:10.1016/j.ebiom.2025.105849
13. Mosteoru S, Gaita L, Gaita D. Sport as medicine for dyslipidemia (and other risk factors). *Curr Atheroscler Rep*. 2023;25(9):613–617. doi:10.1007/s11883-023-01133-y
14. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51(2):237–244. doi:10.1038/s41588-018-0307-5
15. Lane JM, Jones SE, Dashti HS, et al. Biological and clinical insights from genetics of insomnia symptoms. *Nat Genet*. 2019;51(3):387–393. doi:10.1038/s41588-019-0361-7
16. Dashti HS, Jones SE, Wood AR, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun*. 2019;10(1):1100. doi:10.1038/s41467-019-08917-4
17. Jones SE, Lane JM, Wood AR, et al. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. *Nat Commun*. 2019;10(1):343. doi:10.1038/s41467-018-08259-7
18. Wang Z, Emmerich A, Pillon NJ, et al. Genome-wide association analyses of physical activity and sedentary behavior provide insights into underlying mechanisms and roles in disease prevention. *Nat Genet*. 2022;54(9):1332–1344. doi:10.1038/s41588-022-01165-1
19. Ottensmann L, Tabassum R, Ruotsalainen SE, et al. Genome-wide association analysis of plasma lipidome identifies 495 genetic associations. *Nat Commun*. 2023;14(1):6934. doi:10.1038/s41467-023-42532-8
20. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613 (7944):508–518. doi:10.1038/s41586-022-05473-8
21. Liu Y, Rao J, Hu W, et al. Genetic causality between type 1 diabetes and arrhythmia identified by a two-sample mendelian randomization study. *Diabet Res Clin Pract*. 2024;213:111725. doi:10.1016/j.diabres.2024.111725
22. Jiang H, Zhang K, Zhang X. Mendelian randomization analysis of the association between childhood overweight or obesity and gestational diabetes mellitus. *Diabetes Obes Metab*. 2024;26(12):6016–6022. doi:10.1111/dom.15975
23. Qin Q, Zhao L, Ren A, et al. Systemic lupus erythematosus is causally associated with hypothyroidism, but not hyperthyroidism: a Mendelian randomization study. *Front Immunol*. 2023;14:1125415. doi:10.3389/fimmu.2023.1125415
24. Lu Z, Yang Y, Zhao G, et al. The association of redox regulatory drug target genes with psychiatric disorders: a mendelian randomization study. *Antioxidants*. 2024;13(4). doi:10.3390/antiox13040398
25. Liang Y, Yin S, Chen X, Li C, Chen Q. The causal relationship between autoimmune diseases and rhinosinusitis, and the mediating role of inflammatory proteins: a Mendelian randomization study. *Exp Biol Med*. 2024;249:10196. doi:10.3389/ebm.2024.10196
26. Jiang Y, Li Y, Huang Y. Circulating cytokines levels and the risk of polycystic ovary syndrome: a mendelian randomization analysis. *Medicine*. 2025;104(9):e41359. doi:10.1097/MD.0000000000041359
27. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet*. 2017;13(11):e1007081. doi:10.1371/journal.pgen.1007081
28. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497–1501. doi:10.1093/ije/dyt179
29. Benham JL, Yamamoto JM, Friedenreich CM, Rabi DM, Sigal RJ. Role of exercise training in polycystic ovary syndrome: a systematic review and meta-analysis. *Clin Obes*. 2018;8(4):275–284. doi:10.1111/cob.12258
30. Woodward A, Broom D, Dalton C, Metwally M, Klonizakis M. Supervised aerobic exercise training and increased lifestyle physical activity to reduce cardiovascular disease risk for women with polycystic ovary syndrome: a randomized controlled feasibility trial. *J Phys Act Health*. 2022;19 (6):436–445. doi:10.1123/jpah.2022-0103
31. Lopes IP, Ribeiro VB, Reis RM, et al. Comparison of the effect of intermittent and continuous aerobic physical training on sexual function of women with polycystic ovary syndrome: randomized controlled trial. *J Sex Med*. 2018;15(11):1609–1619. doi:10.1016/j.jsxm.2018.09.002
32. Armanini D, Boscaro M, Bordin L, Sabbadin C. Controversies in the pathogenesis, diagnosis and treatment of PCOS: focus on insulin resistance, inflammation, and hyperandrogenism. *Int J Mol Sci*. 2022;23(8). doi:10.3390/ijms23084110
33. Barber TM, Dimitriadis GK, Andreou A, Franks S. Polycystic ovary syndrome: insight into pathogenesis and a common association with insulin resistance. *Clin Med*. 2016;16(3):262–266. doi:10.7861/clinmedicine.16-3-262
34. Stepto NK, Cassar S, Joham AE, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. *Hum Reprod*. 2013;28(3):777–784. doi:10.1093/humrep/des463
35. Aye MM, Butler AE, Kilpatrick ES, et al. Dynamic change in insulin resistance induced by free fatty acids is unchanged though insulin sensitivity improves following endurance exercise in PCOS. *Front Endocrinol*. 2018;9:592. doi:10.3389/fendo.2018.00592
36. Dantas WS, Murai IH, Perandini LA, et al. Acute exercise elicits differential expression of insulin resistance genes in the skeletal muscle of patients with polycystic ovary syndrome. *Clin Endocrinol*. 2017;86(5):688–697. doi:10.1111/cen.13307
37. Mohamed AH, Albasheer O, Ghoniem MA, et al. Impact of lifestyle interventions on reproductive and psychological outcomes in women with polycystic ovary syndrome: a systematic review. *Medicine*. 2025;104(3):e41178. doi:10.1097/MD.0000000000041178
38. Yuan C, Liu X, Mao Y, Diao F, Cui Y, Liu J. Polycystic ovary syndrome patients with high BMI tend to have functional disorders of androgen excess: a prospective study. *J Biomed Res*. 2016;30(3):197–202. doi:10.7555/JBR.30.20140111
39. Motaharinezhad F, Emadi A, Hosnian M, Kheirkhahan A, Jayedi A, Ehsani F. The effects of different exercises on weight loss and hormonal changes in women with polycystic ovarian syndrome: a network meta-analysis study. *BMC Womens Health*. 2024;24(1):512. doi:10.1186/s12905-024-03297-4

40. Kogure GS, Silva RC, Miranda-Furtado CL, et al. Hyperandrogenism enhances muscle strength after progressive resistance training, independent of body composition, in women with polycystic ovary syndrome. *J Strength Cond Res*. 2018;32(9):2642–2651. doi:10.1519/JSC.0000000000002714
41. Khalafi M, Symonds ME. The impact of high-intensity interval training on inflammatory markers in metabolic disorders: a meta-analysis. *Scand J Med Sci Sports*. 2020;30(11):2020–2036. doi:10.1111/sms.13754
42. Rudnicka E, Kunicki M, Suchta K, Machura P, Grymowicz M, Smolarczyk R. Inflammatory markers in women with polycystic ovary syndrome. *Biomed Res Int*. 2020;2020:4092470. doi:10.1155/2020/4092470
43. Dantas WS, Neves WD, Gil S, et al. Exercise-induced anti-inflammatory effects in overweight/obese women with polycystic ovary syndrome. *Cytokine*. 2019;120:66–70. doi:10.1016/j.cyto.2019.04.006
44. Calejman CM, Doxsey WG, Fazakerley DJ, Guertin DA. Integrating adipocyte insulin signaling and metabolism in the multi-omics era. *Trends Biochem Sci*. 2022;47(6):531–546. doi:10.1016/j.tibs.2022.02.009
45. Nagarajan SR, Cross E, Sanna F, Hodson L. Dysregulation of hepatic metabolism with obesity: factors influencing glucose and lipid metabolism. *Proc Nutr Soc*. 2022;81(1):1–11. doi:10.1017/S0029665121003761
46. Wild RA. Dyslipidemia in PCOS. *Steroids*. 2012;77(4):295–299. doi:10.1016/j.steroids.2011.12.002
47. Kim DS, Jeong SK, Kim HR, Kim DS, Chae SW, Chae HJ. Effects of triglyceride on ER stress and insulin resistance. *Biochem Biophys Res Commun*. 2007;363(1):140–145. doi:10.1016/j.bbrc.2007.08.151
48. Zhou Y, Wang X, Guo S, et al. Correlation between chronic low-grade inflammation and glucose and lipid metabolism indicators in polycystic ovary syndrome. *Gynecol Endocrinol*. 2024;40(1):2302402. doi:10.1080/09513590.2024.2302402
49. Chen Z, Jing S, Sun Y. Correlation between serum thyroid stimulating hormone level and glycolipid metabolism in patients with polycystic ovary syndrome. *Medicine*. 2023;102(52):e36791. doi:10.1097/MD.0000000000036791
50. Wakasa H, Kimura T, Hirata T, Tamakoshi A. Relationship of work-related and leisure-based screen time with obesity: a cross-sectional study on adults including older adults. *Endocrine*. 2025;87(1):170–177. doi:10.1007/s12020-024-04014-9
51. Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol*. 2021;95(4):531–541. doi:10.1111/cen.14421
52. Rudnicka E, Suchta K, Grymowicz M, et al. Chronic low grade inflammation in pathogenesis of PCOS. *Int J Mol Sci*. 2021;22(7). doi:10.3390/ijms22073789
53. Kunugi H. Depression and lifestyle: focusing on nutrition, exercise, and their possible relevance to molecular mechanisms. *Psychiatry Clin Neurosci*. 2023;77(8):420–433. doi:10.1111/pcn.13551
54. Ling S, Dai Y, Weng R, et al. Epidemiologic and genetic associations of female reproductive disorders with depression or dysthymia: a mendelian randomization study. *Sci Rep*. 2024;14(1):5984. doi:10.1038/s41598-024-55993-8