

Causal relationship between polycystic ovary syndrome and coronary artery disease: A Mendelian randomisation study

Pomme I. H. G. Simons^{1,2,3}  | Merel E. B. Cornelissen⁴ | Olivier Valkenburg⁵ |
N. Charlotte Onland-Moret⁴ | Yvonne T. van der Schouw⁴ |
Coen D.A. Stehouwer^{2,3,6} | Stephen Burgess^{7,8} | Martijn C. G. J. Brouwers^{1,3}

¹Department of Internal Medicine, Division of Endocrinology and Metabolic Diseases, Maastricht University Medical Center, Maastricht, The Netherlands

²Laboratory for Metabolism and Vascular Medicine, Maastricht University, Maastricht, The Netherlands

³CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands

⁴Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

⁵Department of Reproductive Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

⁶Department of Internal Medicine, Division of General Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

⁷Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁸MRC Biostatistics Unit, University of Cambridge, Cambridge, UK

Correspondence

Martijn C. G. J. Brouwers, Department of Internal Medicine, Division of Endocrinology and Metabolic Diseases, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, The Netherlands.
Email: mcgj.brouwers@mumc.nl

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Abstract

Objective: Polycystic ovary syndrome (PCOS) has been associated with an increased risk of coronary artery disease (CAD). However, it remains uncertain whether this increased risk is the result of PCOS per se or, alternatively, is explained by obesity, a common feature of PCOS. The aim of this study was to assess the causal association between PCOS and CAD and the role of obesity herein.

Design and Methods: We conducted two-sample Mendelian randomisation analyses in large-scale, female-specific datasets to study the association between genetically predicted (1) risk of PCOS and risk of CAD, (2) body mass index (BMI) and risk of PCOS and (3) BMI and risk of CAD. Primary analyses were conducted with the inverse-variance weighted (IVW) method. Simple median, penalized weighted median and contamination mixture analyses were performed to assess the robustness of the outcomes.

Results: IVW analyses did not show a statistically significant association between PCOS and CAD (odds ratio [OR]: 0.99, 95% confidence interval [CI]: 0.89, 1.11). In contrast, genetically predicted BMI was statistically significantly associated with an increased odds of PCOS (OR: 3.21, 95% CI: 2.26, 4.56) and CAD (OR: 1.38, 95% CI: 1.14, 1.67). Similar results were obtained when secondary analyses were performed.

Conclusion: These sex-specific analyses show that the genetically predicted risk of PCOS is not associated with the risk of CAD. Instead, the genetically predicted risk of obesity (and its downstream metabolic effects) is the common denominator of both PCOS and CAD risk.

KEYWORDS

coronary artery disease, Mendelian randomisation, obesity, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women.¹ Epidemiological studies have shown that patients with PCOS are at increased risk of developing coronary artery disease (CAD).² There is, however, an ongoing discussion on whether this increased risk is explained by PCOS per se, or, alternatively, by other factors that are frequently observed in PCOS, such as obesity and its metabolic sequelae.³

The Mendelian randomisation (MR) approach may be helpful in resolving this conundrum. As individuals are randomized at conception to receive gene variants that either predispose to or protect from PCOS (or obesity), these gene variants can be used as instrumental variables to study the causal relationship between PCOS and CAD, and the role of obesity herein. A valid MR analysis is subject to three primary assumptions: (1) the genetic variants are associated with the exposure, (2) the genetic variants do not influence the outcome directly, other than through the exposure and (3) the genetic variants do not associate with any confounders.⁴

Although a recent MR study failed to demonstrate an association between genetically predicted risk of PCOS and risk of CAD, the validity of the outcomes is limited by the use of a gene-outcome data set that included women *and* men.⁵ The importance of a sex-specific data set is emphasized by the recognition of sexual dimorphism in gene-outcome associations.⁶

Therefore, in the present study, we conducted a two-sample MR analysis to assess the association between genetically predicted risk of PCOS and the risk of CAD, using female-specific data. Furthermore, we performed two-sample MR analyses to determine the association between genetically predicted body mass index (BMI) and risk of PCOS and CAD (Figure 1).

2 | MATERIALS AND METHODS

All analyses were conducted with female-specific, summary-level data, which were derived from large-scale cohorts as described below.

2.1 | Polycystic ovary syndrome

Gene-exposure data for the association between PCOS and CAD, and gene-outcome data for the association between BMI and PCOS, were retrieved from a meta-analysis of genome-wide association (GWA) studies of the PCOS trait, adjusted for age.⁷ This database includes 10,074 PCOS cases and 103,164 controls, of European ancestry. Cases were defined according to the National Institutes of Health (NIH), the Rotterdam criteria for the diagnosis of PCOS, or self-reported history of PCOS (Table 1). Single nucleotide polymorphisms (SNPs) were selected as instrumental variables if they demonstrated genome-wide significance ($p < 5 \times 10^{-8}$) for the

association with PCOS. SNPs were excluded if they were in linkage disequilibrium ($r^2 > .1$, the SNP with the largest absolute effect estimate was retained), had poor imputation quality ($R^2 < .3$ or INFO $< .4$), or were palindromic (with a minor allele frequency $> .42$). The mean F statistic (determined as the average F -statistic of all genetic variants, calculated as $\hat{\gamma}_j^2 / \sigma_{\epsilon_j}^2$, where $\hat{\gamma}_j$ and σ_{ϵ_j} represent the effect estimate and standard error of the gene-exposure regression, respectively⁸) was calculated as a measure of instrumental variable strength, where a mean F statistic > 10 is indicative of a strong set of instrumental variables.⁹

2.2 | Body mass index

Gene-exposure data for the association between BMI and PCOS, and between BMI and CAD were retrieved from a sex-stratified GWA study of BMI.¹⁰ This GWA study was performed in 73,137 women primarily of European descent ($\sim 99.5\%$; Table 1). The selection of female-specific, genome-wide significant SNPs was similar to the selection of the PCOS SNPs.

2.3 | Coronary artery disease

Summary-level, gene-outcome data for the association between BMI and CAD, and between PCOS and CAD were retrieved from the UK Biobank (application #7439).¹¹ This population-based cohort study includes 8403 female CAD cases and 190,435 female controls of European descent, aged between 40 and 69 years. CAD was defined according to ICD-9 codes (410.X-412.X, 414.X, 414.8, 414.9), ICD-10 or cause of death codes (I21.X-I24.X, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9), or self-reported history of CAD (Table 1).

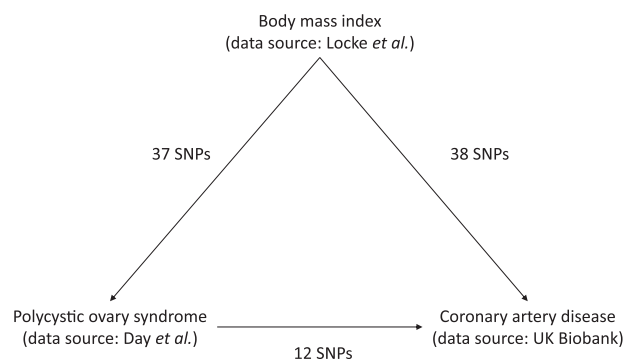


FIGURE 1 Overview of the Mendelian randomisation analyses. Three Mendelian randomisation analyses were conducted to assess the association between (1) genetically predicted risk of polycystic ovary syndrome (PCOS) and risk of coronary artery disease (CAD), (2) genetically predicted body mass index (BMI) and risk of CAD and (3) genetically predicted BMI and risk of PCOS. SNP, single nucleotide polymorphism

TABLE 1 Overview of databases used for gene-exposure and gene-outcome data

GWA study	Trait	N controls	N cases	Definition of cases	Ethnicity	Reference
Day et al.	PCOS	103,164	10,074	- National Institutes of Health criteria for PCOS (i.e., the presence of oligo- or amenorrhoea and clinical or biochemical hyperandrogenism) or - Rotterdam criteria for PCOS (i.e., the presence of two out of three characteristics: oligo- or amenorrhea, clinical or biochemical hyperandrogenism and/or polycystic ovarian morphology), or - Self-reported history of PCOS	European	⁷
Locke et al.	BMI	73,137 ^a		- Not applicable	Primarily European (~99.5%)	¹⁰
UK Biobank	CAD	190,435	8403	- ICD-9 codes: 410.X-412.X, 414.X, 414.8, 414.9, or - ICD-10 and cause of death codes: I21.X-I24.X, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9, or - Self-reported history of CAD	European	¹¹

Abbreviations: BMI, body mass index; CAD, coronary artery disease; GWA, genome-wide association; ICD, International Classification of Diseases; PCOS, polycystic ovary syndrome.

^aTotal number of included individuals.

2.4 | Statistical analyses

Inverse-variance weighted (IVW) MR analyses with a random-effects model were performed as the primary analysis for all three associations (Figure 1). Cochran's Q statistic was calculated to identify heterogeneity of the effect estimates. Egger's regression analyses were conducted to assess potential directional pleiotropy. A statistically significant intercept is indicative of directional pleiotropy, which is a violation of one of the instrumental variable assumptions.¹² We additionally conducted: (1) simple median (which provides a consistent effect estimate if at least 50% of the genetic variants are valid instruments¹³), penalized weighted median (which downweights the contribution of genetic variants with heterogeneous effect estimates, and is, therefore, less influenced by significant outliers¹³) and contamination mixture analyses (which assumes that the true effect estimate is represented by the largest number of genetic instruments, and, hence, only a minority of genetic variants need to be valid provided there is no larger group of invalid variants with similar estimates [i.e., the plurality assumption]^{14,15}), to assess the MR effect estimates under more stringent assumptions; (2) the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method, which excludes any variant that shows significant heterogeneity for the effect estimates, and, hence, is more robust for outliers¹⁶; and (3) Steiger-filtering analyses, which identifies any genetic variant that has a stronger association with the outcome than with the exposure, therefore accounting for potential reverse causality.¹⁷ The effect estimates for all analyses are presented as an increase in odds of the outcome per unit increase in log(odds) of PCOS, or per standard deviation increase in

BMI. All analyses were performed using R statistical software, version 4.0.1 (R Foundation for Statistical Computing) with the TwoSampleMR and MendelianRandomization packages.^{18,19}

3 | RESULTS

3.1 | PCOS and coronary artery disease

The GWA study of PCOS identified 19 SNPs that showed genome-wide significance.⁷ Seven SNPs were excluded as they were in linkage disequilibrium (rs1351592, rs10993397, rs11031006, rs1795379), were palindromic (rs1351592; rs2271194), or had poor imputation quality (rs151212108). This resulted in 12 independent SNPs that were used as genetic instruments for PCOS (Table S1), with a mean *F* statistic of 41.6. These SNPs were primarily associated with polycystic ovarian morphology and ovulatory dysfunction, but not with BMI (Table S2; data obtained from Day et al.⁷). Only one SNP (rs9696009) reached nominal statistical significance with BMI (*p* = .01), though it did not reach genome-wide significance.

IVW MR analysis with a random-effects model did not show a statistically significant association between genetically predicted risk of PCOS and risk of CAD (odds ratio [OR]: 0.99, 95% confidence interval [CI]: 0.89, 1.11; *Q*: 18.5; Figures 2 and S1). MR-Egger regression analysis showed a nonsignificant intercept (*p* = .89). Similar associations were observed when the simple median, penalized weighted median and contamination mixture methods were applied (Figure 2). Furthermore, the MR-PRESSO method did not identify any

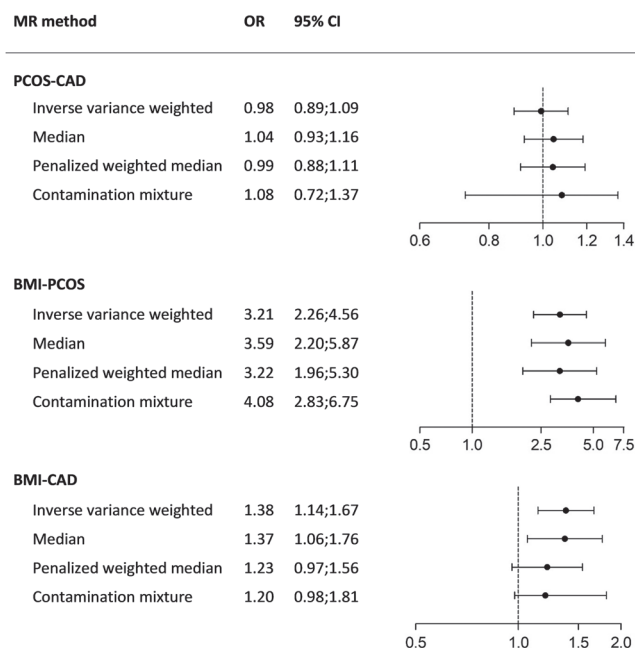


FIGURE 2 Effect estimates of the Mendelian randomisation analyses for the association between (1) PCOS and CAD, (2) BMI and PCOS and (3) BMI and CAD. Effect estimates are presented as increase in odds of the outcome per unit increase in log(odds) of PCOS, or per standard deviation increase in BMI. BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; MR, Mendelian randomisation; OR, odds ratio; PCOS, polycystic ovary syndrome

genetic variants that showed significant heterogeneity. Finally, the Steiger-filtering method did not identify any genetic variants that explained significantly more of the variance in the outcome than the exposure trait. Repeat analyses after exclusion of rs9696009 yielded similar results (data not shown).

In addition, we repeated the analyses using gene-exposure data for the individual diagnostic criteria of PCOS (i.e., NIH criteria, Rotterdam criteria or self-reported history of PCOS).⁷ The results remained similar for all three diagnostic criteria (IVW OR: 0.99, 95% CI: 0.93, 1.07; OR: 1.00, 95% CI: 0.90, 1.10; and OR: 1.03, 95% CI: 0.90, 1.17, respectively).

3.2 | BMI and PCOS

The female-specific GWA study identified 38 SNPs that were robustly associated with BMI.¹⁰ One SNP (rs1558902; *FTO*) was palindromic with a minor allele frequency of 0.43 in the gene-outcome data, and, therefore, excluded. The remaining 37 SNPs were used as genetic instruments for BMI used in the association between BMI and PCOS (Table S3), with a mean *F* statistic of 55.4.

IVW MR analysis with a random-effects model showed a significant association between genetically predicted BMI and risk of PCOS (OR: 3.21, 95% CI: 2.26, 4.56; *Q*: 38.4; Figures 2 and S2). The intercept of the MR-Egger regression analysis was not statistically

significant ($p = .97$). The simple median, penalized weighted median and contamination mixture methods showed comparable effect sizes and were all statistically significant (Figure 2). Furthermore, the MR-PRESSO method did not identify any genetic variant that showed significant heterogeneity. The Steiger-filtering method identified one genetic variant (rs2287019) that explained significantly more of the variance in the outcome than the exposure trait, which is suggestive of reverse causality. However, repeat analyses after exclusion of this variant showed similar results (data not shown).

In addition, as the excluded palindromic variant (rs1558902) maps to *FTO*, a very well-known and important obesity gene,²⁰ we repeated the analyses with a proxy, nonpalindromic variant (rs1121980) that is in high linkage disequilibrium with the excluded variant ($r^2 = 0.96$). The strength and statistical significance of the association remained similar after the inclusion of this proxy variant (IVW OR: 3.58, 95% CI: 2.57, 4.92; *Q*: 40.6).

3.3 | BMI and coronary artery disease

None of the 38 SNPs that showed genome-wide significance with BMI matched any of the exclusion criteria (Table S3), and were, therefore, used as genetic instruments for BMI, with a mean *F* statistic of 63.8.

IVW MR analysis with a random-effects model showed a significant association between genetically predicted BMI and risk of CAD (OR: 1.38, 95% CI: 1.14, 1.67; *Q*: 52.1; Figures 2 and S3). MR-Egger regression analysis showed a nonsignificant intercept ($p = .21$). The simple median, penalized weighted median and contamination mixture methods resulted in similar effect estimates, although not statistically significant in the latter two (Figure 2). The MR-PRESSO method did not identify any genetic variant that showed significant heterogeneity. Finally, the Steiger-filtering method did not identify any genetic variant that explained significantly more of the variance in the outcome than the exposure trait.

4 | DISCUSSION

The aim of this MR study was to examine the triangular association between BMI, PCOS and CAD (Figure 1), all by using female-specific data. We found that the genetically predicted risk of PCOS was not associated with an increased risk of CAD, suggesting that PCOS per se does not play a causal role in the pathogenesis of CAD. Instead, genetically predicted BMI was associated with an increased risk of both PCOS and CAD.

The results of our study corroborate with a recent MR study that also failed to show an association between genetically predicted risk of PCOS and risk of CAD.⁵ A serious limitation of that study, however, was the use of publicly available gene-outcome data from the UK Biobank and the Coronary ARtery Disease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics Consortium (CARDIoGRAMplusC4D) that

were not female-specific. In the present study, we were able to obtain female-specific gene outcome data from the UK Biobank, which allowed us to draw a more valid causal inference. Our findings appear to be in contrast with previous observational studies, which consistently reported that women with PCOS have an approximately twofold increased risk of developing CAD.^{2,21,22} This discrepancy may be explained by the presence of (residual) confounding in the observational studies. Indeed, one meta-analysis reported that adjustment for BMI reduced the strength of the association between PCOS and CAD,² suggesting that obesity, at least in part, accounts for both PCOS and CAD risk.

In support of this hypothesis, we found that genetically predicted BMI was associated with the risk of both PCOS and CAD. Although previous MR studies examining these associations were not conducted with sex-specific instrumental variables or sex-specific datasets, they reported similar findings.^{23–25} Further studies are warranted to unravel the downstream effects of obesity that mediate these relationships. Intrahepatic lipid accumulation—which is a frequently observed phenomenon in obesity²⁶—may be one of the denominators of both PCOS and CAD risk. Intrahepatic lipid accumulation, more specifically de novo lipogenesis, has been associated with a decrease in serum sex hormone-binding globulin levels,^{27,28} which has been causally associated with PCOS risk.²⁹ Furthermore, we have previously shown that genetically predicted intrahepatic lipid accumulation is also associated with CAD risk, which appears to be mediated by serum lipid levels.^{30,31} Intrahepatic lipid accumulation, reduced serum sex hormone-binding globulin levels and dyslipidemia are commonly observed in patients with PCOS, in particular those who are obese.^{32,33}

Although both gene–BMI and gene–CAD data were derived from the general population, the findings in this study support a more personalized approach towards women with PCOS. Since BMI appears the common denominator of both PCOS and CAD, our results suggest that particularly obese patients with PCOS should be offered counselling about future risk of CAD upon which preventive measures can be undertaken. Although scientific evidence on the (cost) effectiveness of such a strategy is currently lacking (and will require decades of follow-up), we believe that the clinical presentation of this metabolic disorder relatively early in life offers opportunities to prevent cardiometabolic complications in the sixth decade and onwards.

This study has several strengths and limitations. First, as already mentioned, by using large-scale, female-specific datasets, we were able to draw valid conclusions on the relationships between PCOS and CAD, and the role of BMI herein. Second, an advantage of the current study design is that, where in traditional epidemiological research a long follow-up is required to obtain sufficient CAD cases in a cohort of PCOS patients, a two-sample MR allows for gene-outcome data to be retrieved from a cohort of older individuals with significantly more CAD cases. Of note, the participants from all currently used cohorts were primarily of European descent (Table 1). One limitation is the relatively small number of PCOS SNPs that have been identified and, hence, could be used as instrumental variables.

This could have restricted statistical power, and it is, therefore, advisable to repeat the current analyses once additional PCOS SNPs have been identified. Furthermore, these SNPs have primarily been associated with two of the three PCOS features, that is, polycystic ovarian morphology and ovulatory dysfunction, but to a lesser extent with hyperandrogenism,⁷ and, consequently, may represent only a subset of the PCOS phenotype. Although sensitivity analyses with the different diagnostic criteria of PCOS likewise did not identify a statistically significant association between genetically predicted PCOS and CAD, it would be relevant to further study the effects of PCOS subphenotypes on CAD if GWA studies for the different features of PCOS become available in the future.

In conclusion, in this female-specific MR study, we did not observe an association between genetically predicted PCOS and risk of CAD, suggesting that PCOS per se is not causal in the pathogenesis of CAD. Rather, obesity appears to be the common denominator of both PCOS and CAD.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Summary-level data of the polycystic ovary syndrome and body mass index genome-wide association studies used in this study are available from the original publications.^{7,10} Summary data for coronary artery disease are available from the UK Biobank upon request.

ORCID

Pomme I. H. G. Simons  <https://orcid.org/0000-0003-4929-8330>

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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