No Causal Association between Anti-Mullerian hormone (AMH)levels and Polycystic Ovary Syndrome (PCOS)-A Mendelian Randomization analysis

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PCOS is a common endocrine disorder that affects women of reproductive age and is characterized by hyperandrogenism, menstrual irregularities, and polycystic ovaries(1). Recent studies have shown Anti-Mullerian hormone (AMH)levels are elevated in women with PCOS and have the potential to be used as a marker for polycystic ovarian morphology in women with PCOS(1). However, it is unclear whether the raised AMH levels in PCOS are a cause or a consequence of the disorder.

We performed a Mendelian Randomization analysis (MR) using publicly available data to investigate the causal relationship between AMH levels and PCOS. The genetic variants used as instrumental variables were obtained from the NHGRI catalogue of GWAS studies(2, 3), and the summary statistics for the GWAS were obtained from a study by Felix Day et al(4). We used the MendelianRandomization (5) package in R to perform the analysis. The MendelianRandomization package in R implements various MR methods using summary-level data from the GWAS analysis. The NGHRI catalogue for GWAS studies consisted of 14 SNPs associated with AMH levels (P<10-5) in 13 mapped genes. Of these 14 SNPs, nine (*TNN, OR56B4-OR52X1P, SEPHS1P2, AMH, RRM2-RN7SL66P, TEX41, CDCA7-JPT1P1, MCM8, TTC28*) were available in the publicly available GWAS for PCOS and were used in the MR analysis. In a candidate gene association analysis, none of the SNPs associated with AMH levels was associated with PCOS in this GWAS study.

The MR analysis revealed no significant causal effect of AMH levels on PCOS. The estimate of the causal effect using the inverse variance weighted (IVW) method was -0.067, with a 95% confidence interval ranging from -0.905 to 0.771 (P-value=0.87). These results suggest that there is no evidence to suggest that AMH levels cause PCOS. The results from other MR methods, including simple median, weighted median, penalized weighted median, MR-Egger, robust MR-Egger, penalized MR-Egger, and robust IVW, were consistent with the findings from the IVW method (Table 1).

The findings of our study agree with a recent study(3), which used four SNPs in *AMH, TEX41, MCM8* and *CDCA7* loci to perform the MR analysis and showed no causal association of AMH with PCOS. We have extended this analysis to include five additional GWAS loci (P-value<10^{-5}) associated with AMH levels and show no causal association between AMH levels and PCOS. The limitation of this analysis is that the available genetic markers explain only a small proportion of variability in circulating AMH levels (~15%), and hence the genetic instrument from these might not have sufficient power to detect causal association in MR analysis. Nevertheless, these analyses suggest that larger GWAS studies for AMH levels and MR analysis are needed to explore the causal association between AMH and PCOS.

Table 1:Mendelian Randomization analysis for AMH levels and PCOS

Method	Estimate	Std Error	95% CI		P-value
Simple median	-0.009	0.806	-1.588	1.57	0.991
Weighted median	0.072	0.991	-1.871	2.015	0.942
Penalized weighted median	0.072	0.991	-1.871	2.015	0.942
IVW	-0.067	0.428	-0.905	0.771	0.875
Penalized IVW	-0.067	0.428	-0.905	0.771	0.875
Robust IVW	0.133	1.833	-3.459	3.726	0.942
Penalized robust IVW	0.133	1.833	-3.459	3.726	0.942
MR-Egger	0.368	0.789	-1.178	1.915	0.641
(intercept)	-0.069	0.105	-0.274	0.136	0.511
Penalized MR-Egger	0.368	0.789	-1.178	1.915	0.641
(intercept)	-0.069	0.105	-0.274	0.136	0.511
Robust MR-Egger	0.174	0.524	-0.854	1.201	0.741
(intercept)	-0.069	0.067	-0.2	0.061	0.297
Penalized robust MR-Egger	0.174	0.524	-0.854	1.201	0.741
(intercept)	-0.069	0.067	-0.2	0.061	0.297

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