Supplementary Material

Supplementary Table 1. Evidence for the relationship between the 16 candidate mediators and estrogen-related gynecologic diseases from previous literature.

Supplementary Table 2. Univariable Mendelian Randomization Analyses of SES on estrogen-related gynecologic diseases.

Supplementary Table 3. Multivariable Mendelian Randomization Analyses of education on ovarian cancer.

Supplementary Table 4. Univariable Mendelian Randomization Analyses of education attainment on various sub-phenotypes of endometriosis.

Supplementary Table 5. Two-step Mendelian Randomization Analyses.

Supplementary Figure 1. MVMR estimates the causal associations of education with endometriosis.

Supplementary Figure 2. MVMR estimates the causal associations of education with two sub-phenotypes of endometriosis.

Supplementary Figure 3. MR leave-one-out sensitivity analysis for educational attainment on endometriosis of the uterus.

Supplementary Figure 4. Two-step MR identifying causal mediators in the association of educational attainment with endometriosis of uterus.

Supplementary Table 1. Evidence for the relationship between the 16 candidate mediators and estrogen-related gynecologic diseases from previous literature.

Candidate mediators	Evidence from previous literature
Lifestyle (n=10)	
Diet (Carbohydrate, Fat, Protein)	Previous studies point to an association between diet and the development of endometriosis, which is unclear. It can be hypothesized that dietary factors influence the formation of sex hormones and exert pro- or antioxidant effects and proinflammatory effects. These factors play an essential role in the pathogenesis of endometriosis. A diet rich in red meat and a high intake of Palmitic acid or trans-unsaturated fats have been shown to increase the risk of endometriosis [1].
Coffee	A meta-analysis that included ten studies (five cohort and five case-control studies) showed that when stratified according to the level of consumption, high caffeine intake (>300 mg/day) was associated with increased risk of endometriosis (RR 1.30, 95%CI 1.04–1.63, I2 = 56%) [2].
Sleep	
Sleep duration	Data based on 45,748 participants aged 40-69 years from the Japan Public Health Center-based Prospective Study cohort revealed that among women who usually slept >7 h per day, an HR of 0.4 (95% CI 0.2-0.9) emerged compared to those who slept <6 h [3].
Sleeplessness/Insomnia	Data based on 289,162 patients (144,581 and 144,581 in the sleep disorder and nonsleep disorder groups) of Taiwan's National Health Insurance (NHI) Research Database (NHIRD) revealed that the adjusted hazard ratio (aHR; 95% confidence interval [CI]) of cancer risk in the sleep disorder group compared with the nonsleep disorder group was 1.07 (1.04-1.12; P = 0.0001). The adjusted IRR (95% CIs) for ovarian cancer in patients with sleep disorders was 1.30 (1.10-1.52), which suggested that sleep disorder was a significant risk factor for ovarian cancer [4].
Physical activity	
MVPA	A study based on Nurses' Health Study II cohort revealed that strenuous activity during ages 12–13 was associated with endometriosis, which observed a 16% increase in the risk for endometriosis comparing the greatest amount of activity (≥80 MET-h/wk) with the least (<20 MET-h/wk) during ages 12–13 (RR=1.16, 95% CI=0.98–1.37, p-value test for trend=0.02) [5].
Sedentary	A meta-analysis that included seven studies (three prospective cohort studies and four case-control studies, 2060 ovarian cancer cases in total) indicated a statistically significant increase in the risk of ovarian cancer in relation to prolonged sitting time (RR = 1.29, 95% CI= 1.07–1.57), comparing highest versus lowest levels of sedentary behavior [6].
Behavior	
Smoking	Data based on 75,918 French women aged 40–65 from the E3N cohort revealed that there were positive linear associations between endometriosis risk and level of indoor exposure to passive smoking during childhood (OR = 1.34 [95% confidence interval =1.09–1.64] with several hours exposure a day) [7].

Alcohol	Alcohol intake could increase the level of estrogen in blood circulation and induce a variety of cells to produce proinflammatory cytokines, which may be related to the pathogenesis of endometriosis. A meta-analysis that included fifteen studies provided evidence for an association between alcohol consumption and endometriosis risk. Considering the results of the analyses of infrequent, moderate/regular, and heavy alcohol intake vs no alcohol intake, the summary RR estimates were, respectively, 1.14 (95% CI, 0.86-1.52), 1.23 (95% CI, 1.08-1.40), and 1.19 (95% CI, 0.99-1.43) [8].
Psychology (n=3)	
Major depression	A genetic association study performed between September 13, 2021, and June 24, 2022, in 202,276 unrelated female participants (8,276 women with endometriosis and 194,000 controls) indicated the genetic liability to depression was associated with increased odds of endometriosis (OR, 1.09; 95% CI, 1.08-1.11), with the application of 1-sample mendelian randomization [9].
Schizophrenia	A two-sample Mendelian randomization analysis determined a causal relationship between genetic predisposition to schizophrenia and cancer, with schizophrenia increasing ovarian cancer (OR = 1.0770; CI, 1.0352-1.1203; p = 0.0002) [10].
BIP	A real-world observational study that included 72 drug-naïve bipolar disorder (BD) patients, 98 healthy controls (HCs), and 72 BD patients with long-term medication indicated that drug-naïve BD patients presented higher rates of PCOS than the HCs (OR: 3.02, 95 % CI: 1.09 –8.36), and valproate is correlated with increased occurrence and development of PCOS [11].
Biology (n=3)	
Graves' disease	A retrospective cohort study consisting of 5,399 patients with Graves disease (GD) and 10,798 patients without GD obtained from the National Health Insurance Research Database (NHIRD) indicated that the cumulative incidence curve of polycystic ovary syndrome (PCOS) in patients with GD was significantly higher than that in patients without GD (p = 0.02). The adjusted hazard ratio for PCOS in patients with GD compared with patients without GD was 1.47 (95%CI = 1.09–1.98) [12].
Hashimoto thyroiditis	The immune system seems to be involved in the pathogenesis of endometriosis. A retrospective case-control study consisting of 148 women with endometriosis and 150 controls aged between 18 and 45 indicated a significant correlation between endometriosis and autoimmune thyroiditis (p<.0001) [13].
Type 1 diabetes	A meta-analysis that included 48 articles showed a tendency towards a higher risk of ovarian cancer in those with type 1 diabetes mellitus (SIR 1.49, 95% CI 0.98 to 2.28); however, this was not statistically significant [14].

REFERENCES

1. Zhang Y, Ma N-Y. Environmental Risk Factors for Endometriosis: An Umbrella Review of a Meta-Analysis of 354 Observational Studies With Over 5 Million Populations. Front Med. 2021;8:680833.

2. Kechagias KS, Katsikas Triantafyllidis K, Kyriakidou M, Giannos P, Kalliala I, Veroniki AA, et al. The Relation between Caffeine Consumption and Endometriosis: An Updated Systematic Review and Meta-Analysis. Nutrients. 2021;13:3457.

3. Weiderpass E, Sandin S, Inoue M, Shimazu T, Iwasaki M, Sasazuki S, et al. Risk factors for epithelial ovarian cancer in Japan - results from the Japan Public Health Center-based Prospective Study cohort. Int J Oncol. 2012;40:21–30.

4. Wu Zheng S-M, Chen J-W, Huang Y-M, Chen W-M, Wu S-Y. Effect of sleep disorders on the risks of cancers and site-specific cancers. Sleep Med. 2022;100:254–61.

5. Vitonis AF, Maruti SS, Hankinson SE, Hornstein MD, Missmer SA. Adolescent physical activity and endometriosis risk. J Endometr. 2009;1:157–63.

6. Biller VS, Leitzmann MF, Sedlmeier AM, Berger FF, Ortmann O, Jochem C. Sedentary behaviour in relation to ovarian cancer risk: a systematic review and meta-analysis. Eur J Epidemiol. 2021;36:769–80.

7. Kvaskoff M, Bijon A, Clavel-Chapelon F, Mesrine S, Boutron-Ruault M-C. Childhood and adolescent exposures and the risk of endometriosis. Epidemiol Camb Mass. 2013;24:261–9.

8. Parazzini F, Cipriani S, Bravi F, Pelucchi C, Chiaffarino F, Ricci E, et al. A metaanalysis on alcohol consumption and risk of endometriosis. Am J Obstet Gynecol. 2013;209:106.e1-10.

9. Koller D, Pathak GA, Wendt FR, Tylee DS, Levey DF, Overstreet C, et al. Epidemiologic and Genetic Associations of Endometriosis With Depression, Anxiety, and Eating Disorders. JAMA Netw Open. 2023;6:e2251214.

10. Zhou K, Zhu L, Chen N, Huang G, Feng G, Wu Q, et al. Causal associations between schizophrenia and cancers risk: a Mendelian randomization study. Front Oncol. 2023;13:1258015.

11. Liu J, Teng Z, Xie H, Yuan H, Liu M, Chen J, et al. Prevalence and characteristics of polycystic ovarian syndrome in patients with bipolar disorder. J Affect Disord. 2023;340:387–95.

12. Chen H-H, Chen C-C, Hsieh M-C, Ho C-W, Hsu S-P, Yip H-T, et al. Graves' disease could increase polycystic ovary syndrome and comorbidities in Taiwan. Curr Med Res Opin. 2020;36:1063–7.

13. Porpora MG, Scaramuzzino S, Sangiuliano C, Piacenti I, Bonanni V, Piccioni MG, et al. High prevalence of autoimmune diseases in women with endometriosis: a case-control study. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2020;36:356–9.

14. Wouters R, Vankerckhoven A, Verreet W, Ceusters J, Coosemans A. Do autoimmune diseases influence the onset and progression of ovarian cancer? A systematic review and meta-analysis. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2022;32:1583–91.

Supplementary Table 2. Univariable Mendelian Randomization Analyses of SES on estrogen-related gynecologic diseases.

exposure	outcome	Number of SNPs	Inverse variance weighted		Weighted median		MR Egger	
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Educational attainment (years of education)	Endometriosis	198	0.94 (0.91, 0.98)	0.001	0.94 (0.89, 0.99)	0.014	0.84 (0.72, 0.99)	0.044
	Endometrial cancer	202	1.02 (0.97, 1.08)	0.417	1.02 (0.94, 1.10)	0.686	0.95 (0.75, 1.21)	0.703
	Ovarian cancer	202	1.08 (1.01, 1.15)	0.027	1.06 (0.96, 1.16)	0.244	0.99 (0.74, 1.32)	0.927
	Uterine fibroids	202	1.01 (0.99, 1.03)	0.395	1.01 (0.98, 1.04)	0.500	1.00 (0.91, 1.10)	0.938
	polycystic ovary syndrome	180	1.03 (0.97, 1.08)	0.374	1.04 (0.96, 1.12)	0.385	0.99 (0.77, 1.28)	0.931
Average totol hosehold income before tax	Endometriosis	41	0.97 (0.66, 1.43)	0.877	0.83 (0.51, 1.35)	0.447	0.25 (0.03, 1.79)	0.175
	Endometrial cancer	23	1.58 (0.79, 3.18)	0.197	1.65 (0.62, 4.42)	0.318	2.18 (0.09, 53.98)	0.638
	Ovarian cancer	42	1.58 (0.87, 2.84)	0.130	1.72 (0.79, 3.77)	0.174	1.47 (0.14, 15.63)	0.750
	Uterine fibroids	22	0.90 (0.70, 1.16)	0.420	0.95 (0.67, 1.36)	0.782	1.21 (0.53, 2.74)	0.661
	polycystic ovary syndrome	23	0.86 (0.41, 1.78)	0.685	1.73 (0.69, 4.33)	0.244	13.01 (0.50, 339.04)	0.138
Occupational attainment	Endometriosis	24	0.95 (0.77, 1.17)	0.622	0.80 (0.63, 1.01)	0.061	0.49 (0.14, 1.77)	0.289
	Endometrial cancer	16	1.31 (0.89, 1.93)	0.177	1.33 (0.85, 2.07)	0.215	0.57 (0.04, 8.43)	0.688
	Ovarian cancer	23	0.92 (0.69, 1.23)	0.582	1.07 (0.71, 1.61)	0.735	1.22 (0.19, 7.86)	0.839
	Uterine fibroids	15	0.97 (0.87, 1.09)	0.636	0.96 (0.82, 1.12)	0.601	0.44 (0.21, 0.93)	0.052
	polycystic ovary syndrome	13	1.03 (0.71, 1.50)	0.889	0.98 (0.61, 1.55)	0.919	0.81 (0.07, 8.92)	0.865

SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Supplementary Table 3. Multivariable Mendelian Randomization Analyses of education on ovarian cancer.

Analysis	Method	Number of SNPs	OR (95% CI)	P-value
Education, unadjusted	Education	202	1.08 (1.01, 1.15)	0.027
Education, adjusted for WHR	Education	109	1.08 (1.00, 1.16)	0.124
	WHR	259	0.98 (0.79, 1.21)	0.821
Education, adjusted for AM	Education	166	1.05 (0.98, 1.13)	0.016
	AM	82	1.29 (1.07, 1.57)	0.201
Education, adjusted for WHR and AM	Education	98	1.05 (0.97, 1.14)	0.332
	WHR	220	0.94 (0.75, 1.18)	0.591
	AM	58	1.23 (1.01, 1.50)	0.126

WHR, waist-hip ratio; AM, age at menopause; SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Supplementary Table 4. Univariable Mendelian Randomization Analyses of education attainment on various sub-phenotypes of endometriosis.

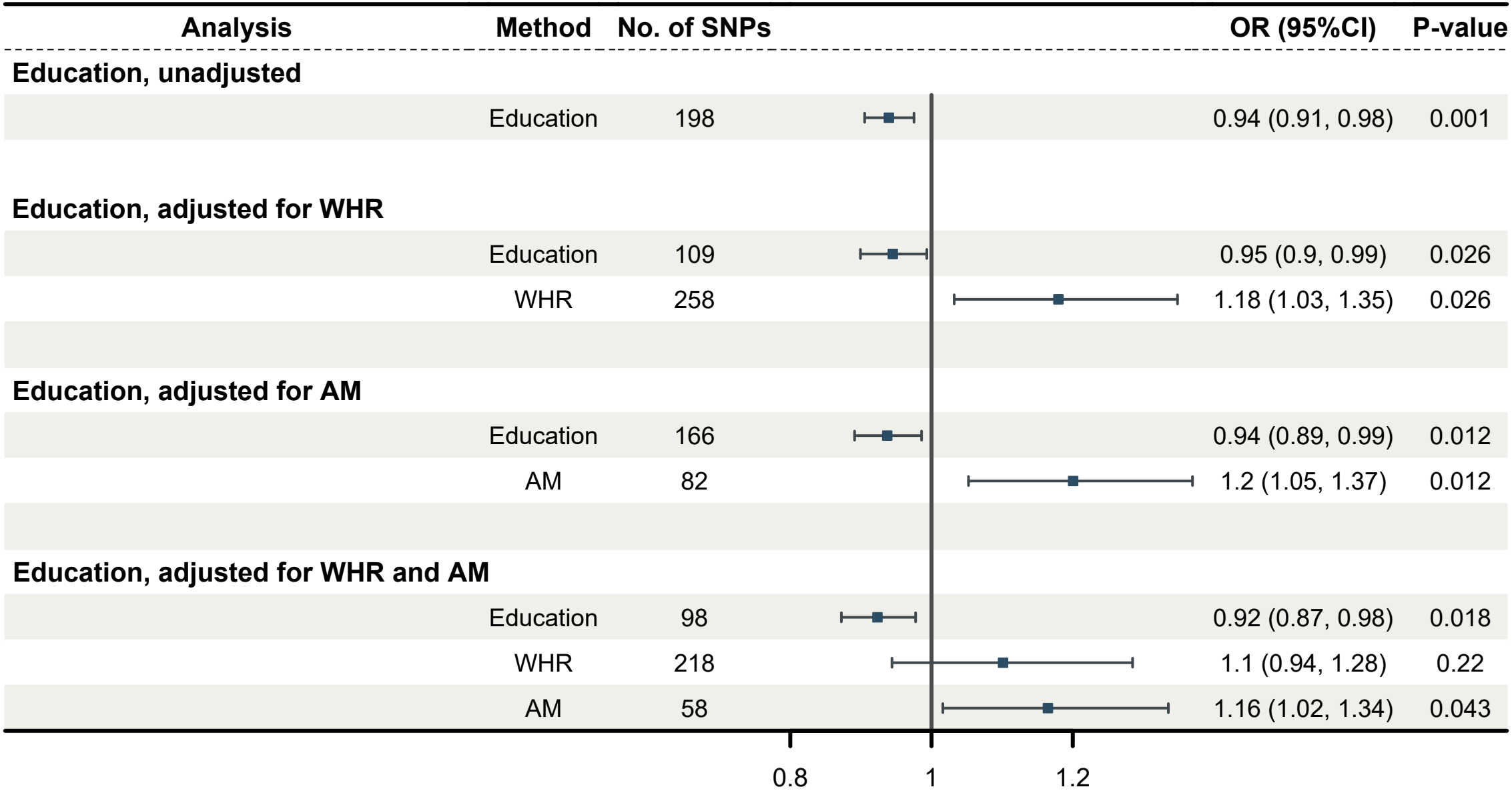
exposure	outcome	Number of SNPs	Inverse variance weighted		Weighted median		MR Egger	
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Educational attainment (years of education)	Endometriosis of uterus	197	0.91 (0.86, 0.98)	0.007	0.90 (0.81, 0.99)	0.028	0.84 (0.63, 1.11)	0.225
	Endometriosis of ovary	199	0.98 (0.93, 1.04)	0.531	0.96 (0.89, 1.04)	0.365	0.90 (0.71, 1.15)	0.397
	Endometriosis of fallopian tube	196	0.86 (0.65, 1.14)	0.299	0.89 (0.59, 1.34)	0.578	1.48 (0.43, 5.07)	0.537
	Endometriosis of pelvic peritoneum	197	0.94 (0.88, 0.99)	0.028	0.96 (0.88, 1.05)	0.375	0.88 (0.68, 1.14)	0.348
	Endometriosis of intestine	198	0.94 (0.75, 1.18)	0.590	0.90 (0.64, 1.26)	0.526	1.04 (0.38, 2.84)	0.939
	Endometriosis of rectovaginal septum and vagina	195	0.98 (0.90, 1.06)	0.612	0.98 (0.86, 1.10)	0.689	0.83 (0.57, 1.21)	0.332

SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Supplementary Table 5. Two-step Mendelian Randomization Analyses.

exposure	outcome	Number of SNPs	Inverse variance weighted		Weighted median		MR Egger	
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Educational attainment (years of education)	depression	203	0.97 (0.95, 0.98)	3.21E-05	0.97 (0.96, 0.98)	4.63E-05	0.94 (0.88, 1.00)	0.052
depression	Endometriosis of uterus	44	1.43 (1.01, 2.02)	0.043	1.43 (0.88, 2.32)	0.149	0.84 (0.11, 6.57)	0.872

SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.


Analysis
Method
No. of SNPs
OR (95%CI)
P-value
Education, unadjusted
Education
198
0.94 (0.91, 0.98)
0.001
Education, adjusted for WHR
Education
109
0.95 (0.9, 0.99)
0.026
WHR
258
1.18 (1.03, 1.35)
0.026
Education, adjusted for AM
Education
166
0.94 (0.89, 0.99)
0.012
AM
82
1.2 (1.05, 1.37)
0.012
Education, adjusted for WHR and AM
Education
98
0.92 (0.87, 0.98)
0.018
WHR
218
1.1 (0.94, 1.28)
0.22
AM
58
1.16 (1.02, 1.34)
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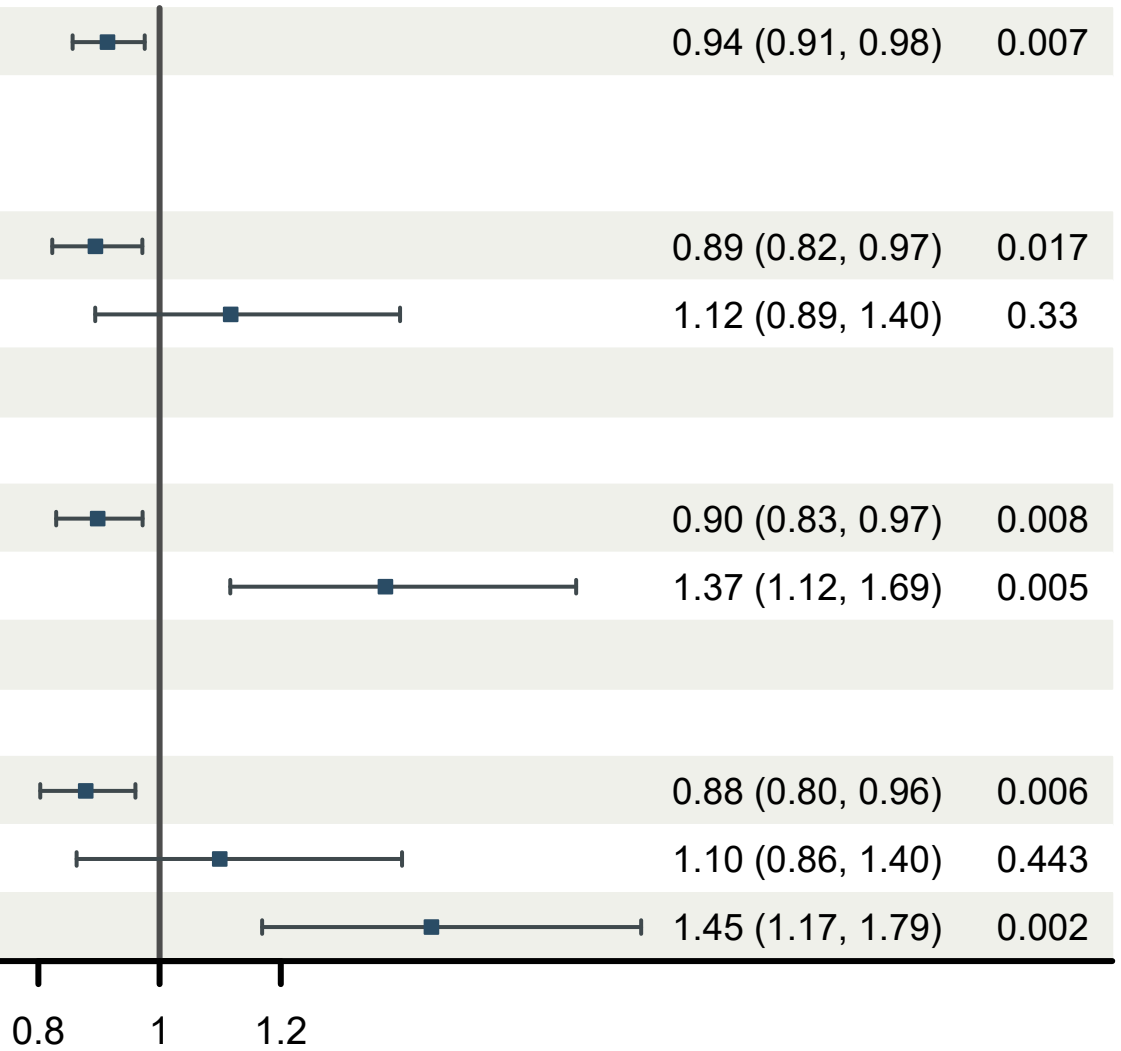
A

Analysis	Method	No. of SNPs	OR (95%CI)	P-value
Education, unadjusted				
	Education	197	0.94 (0.91, 0.98)	0.007
Education, adjusted for WHR				
	Education	109	0.89 (0.82, 0.97)	0.017
	WHR	259	1.12 (0.89, 1.40)	0.33
Education, adjusted for AM				
	Education	166	0.90 (0.83, 0.97)	0.008
	AM	82	1.37 (1.12, 1.69)	0.005
Education, adjusted for WHR and AM				
	Education	98	0.88 (0.80, 0.96)	0.006
	WHR	218	1.10 (0.86, 1.40)	0.443
	AM	58	1.45 (1.17, 1.79)	0.002



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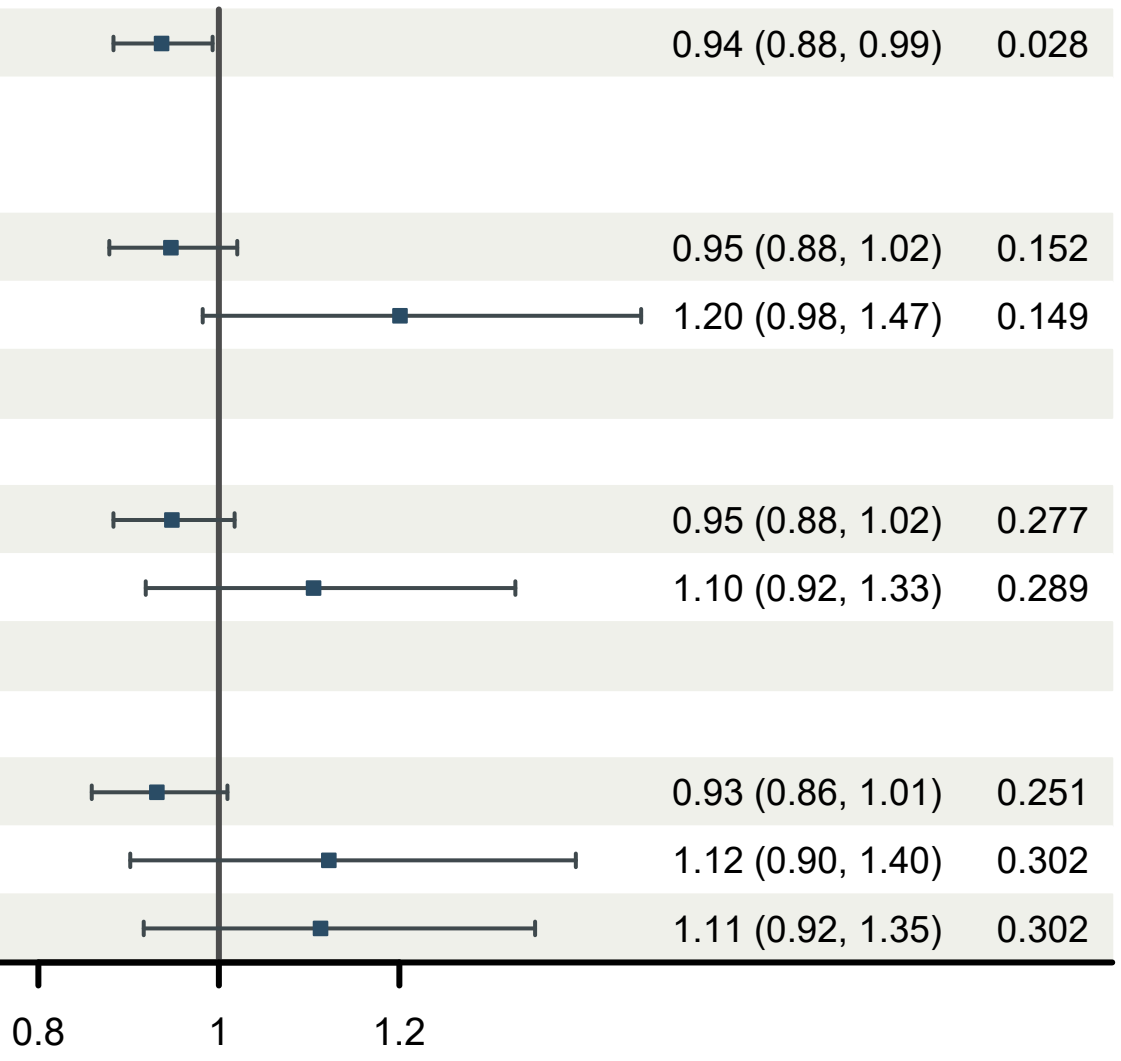
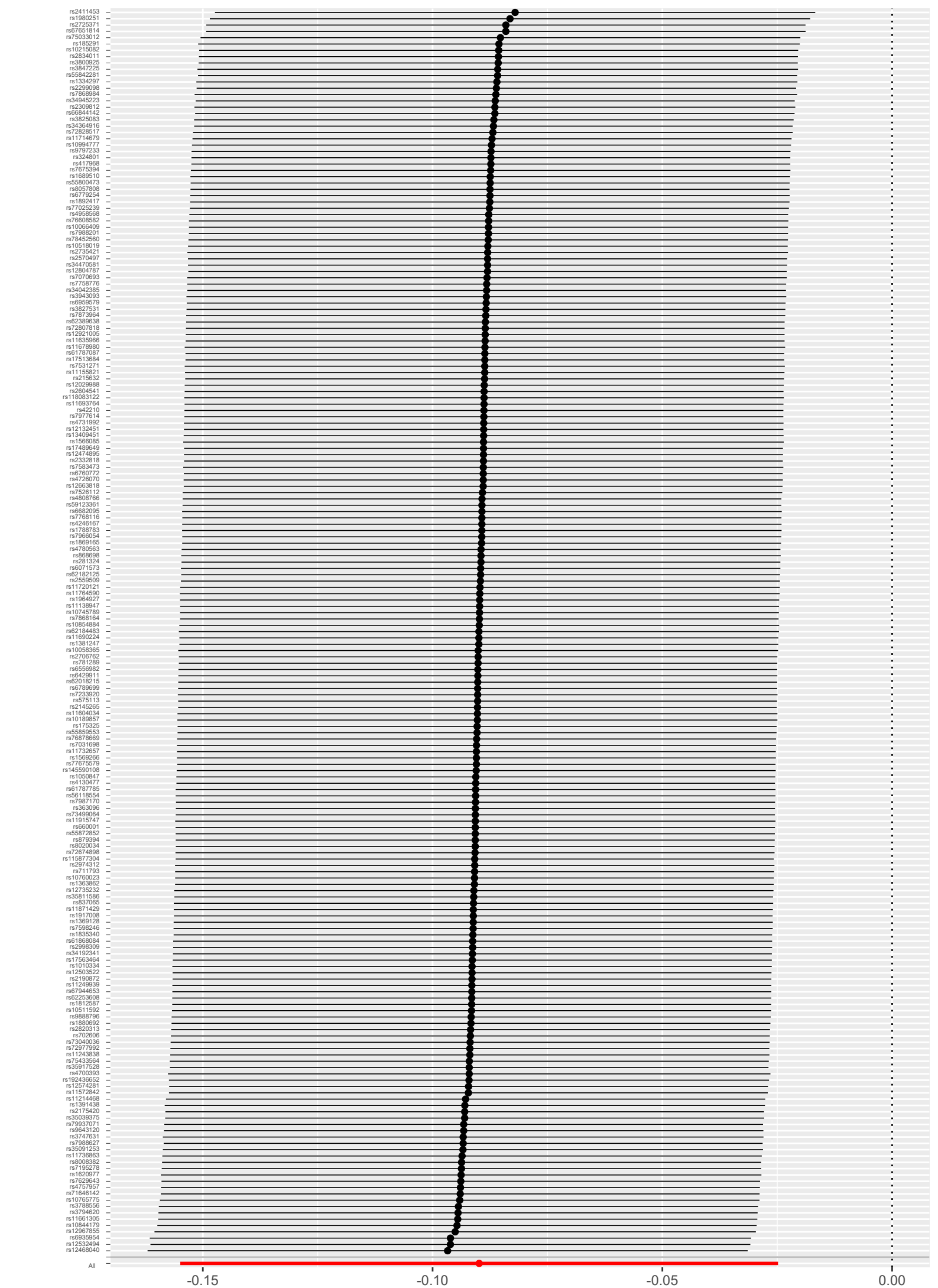
Analysis	Method	No. of SNPs	OR (95%CI)	P-value
Education, unadjusted				
	Education	197	0.94 (0.88, 0.99)	0.028
Education, adjusted for WHR				
	Education	109	0.95 (0.88, 1.02)	0.152
	WHR	259	1.20 (0.98, 1.47)	0.149
Education, adjusted for AM				
	Education	166	0.95 (0.88, 1.02)	0.277
	AM	82	1.10 (0.92, 1.33)	0.289
Education, adjusted for WHR and AM				
	Education	98	0.93 (0.86, 1.01)	0.251
	WHR	218	1.12 (0.90, 1.40)	0.302
	AM	58	1.11 (0.92, 1.35)	0.302

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MR leave-one-out sensitivity analysis for
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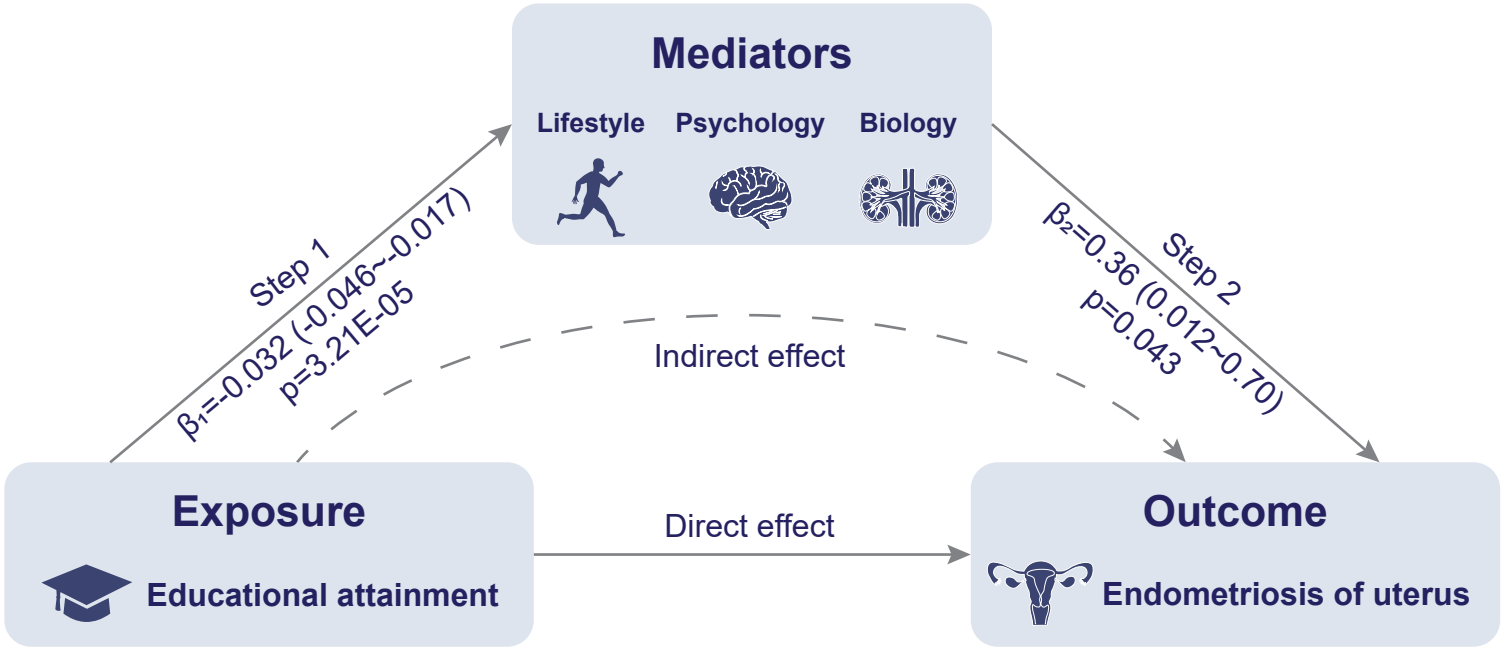

Mediator	Total effect	Mediated effect	Mediated proportion
	β (95%CI)	β (95%CI)	% (95%CI)
MDD	-0.090 (-0.15~-0.025)	-0.011 (-0.023~-0.0019)	12.22 (2.11~25.56)

Figure legend

Supplementary Figure 1. MVMR estimates the causal associations of education with endometriosis.

In MVMR (adjust for waist-hip ratio and age at menopause), genetically predicted longer years of education remained causally associated with a low risk of endometriosis.

Supplementary Figure 2. MVMR estimates the causal associations of education with two sub-phenotypes of endometriosis.

(A) MVMR analysis provided evidence for a consistent, causal, protective effect of education on endometriosis of the uterus. (B) The association with endometriosis of the pelvic peritoneum was no longer statistically significant.

Supplementary Figure 3. MR leave-one-out sensitivity analysis for educational attainment on endometriosis of the uterus.

Supplementary Figure 4. Two-step MR identifying causal mediators in the association of educational attainment with endometriosis of uterus.