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Analysis

Unraveling the causal association between lifestyle and metabolic factors with endometrial cancer: evidence from a Mendelian randomization study

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Abstract

Background Endometrial carcinoma (EC) remain a malignancy with incompletely understood risk factors. To address this knowledge gap, we employed mendelian randomization study to investigate potential protective and risk elements associated with endometrial cancer.

Methods We conducted a two-sample Mendelian randomization (MR) study using genetic association data for overall EC and its subtypes from a large-scale genome-wide association study (GWAS). This GWAS encompassed 12,906 EC patients and 108,979 healthy controls. The EC cases were further categorized into 8758 endometrioid and 1230 non-endometrioid subtypes. To serve as instrumental variables, we identified independent genetic variants strongly associated with 5 lifestyle factors and 14 metabolic factors from relevant GWASs. Subsequently, we conducted univariable Mendelian randomization (MR) analyses.

Results Our study revealed the relationship among EC with lifetime smoking index (OR: 1.43; 95% CI 1.05–1.96), frequency of alcohol consumption (OR:1.23; 95% CI 1.04–1.45), body mass index (BMI) (OR:1.82; 95% CI 1.64–2.01), type 2 diabetes mellitus (T2DM) (OR:1.06; 95% CI 1.00–1.12), and fasting insulin (OR:1.97; 95% CI 1.30–2.98). Conversely, inverse associations with EC were observed for education level (OR:0.72, 95% CI 0.62–0.83), moderate-level physical exercise (OR 0.35, 95% CI 0.15–0.84), and low-density lipoproteins (LDL) (OR 0.91, 95% CI 0.84–0.99).

Conclusions Our findings underscore a causal association between genetically predicted lifetime smoking index, alcohol intake frequency, BMI, T2DM, and fasting insulin with EC risk. Furthermore, our study highlights the potential protective effects of a high education level, moderate-intensity physical exercise, and LDL reduction against EC risk. This MR analysis provided valuable insights into underlying EC risk mechanisms and paved new ways for EC prevention strategies.

Keywords Lifestyle factors · Metabolic factor · Mendelian randomization · Endometrial Carcinoma

Xu Zhang and Caiyu Pu have contributed equally to this work.

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1 Introduction

Endometrial cancer (EC) ranks as the sixth most prevalent cancer among women, with 417,367 newly diagnosed cases worldwide in 2020 [1]. Its incidence demonstrates a steady rise, with projections indicating a 40–50% increase in the coming decade [2]. EC is broadly classified into two main subtypes, including endometrioid (Type I) and non-endometrioid (Type II), each with distinct risk factors, molecular profiles, and clinical outcomes [3]. Understanding the etiology of these subtypes is crucial for developing targeted prevention and treatment strategies.

Previous observational studies have delineated potential risk factors associated with EC, including lifestyle factors such as smoking [4, 5], alcohol consumption [6, 7], coffee intake [8, 9], educational attainment [10, 11], and physical activity levels [12, 13]. Additionally, metabolic factors such as blood pressure [14], blood glucose level [15], blood lipid profiles [16] and anthropometric indices [17] have been implicated. However, the inherent limitations of observational studies, including confounding variables, impede definitive causal inference. Moreover, most studies have not differentiated between EC subtypes, potentially obscuring subtype-specific risk factors.

The complex biological mechanisms underlying these associations, particularly in the context of EC subtypes. Understanding subtype-specific risk factors is essential for developing tailored prevention strategies, improving risk assessment, gaining insights into disease mechanisms, and informing personalized treatment approaches. These advancements could significantly improve patient outcomes and contribute to more effective management of endometrial cancer.

In recent years, Mendelian randomization (MR) analyses have offered a promising approach to overcome some limitations of observational studies by using genetic variants as proxies for modifiable risk factors. Existing MR studies have investigated individual risk factors for EC in [18–24], but they often focus on these factors in isolation and rarely address subtype-specific risks. In this study, we aim to expand upon existing analyses by comprehensively estimating the causal effects of 5 lifestyle and 14 potentially modifiable risk factors on EC risk through the MR approach. Importantly, we will differentiate between endometrioid and non-endometrioid EC subtypes, addressing a significant gap in current research. This approach seeks to provide a more nuanced understanding of EC etiology, potentially uncovering subtype-specific risk factors that could inform targeted prevention strategies and improve patient outcomes.

2 Materials and methods

2.1 Study design

A two-sample Mendelian randomization (MR) analysis was employed to investigate the causal relationships between genetic variants and endometrial cancer risk in this study. The study protocol has not been registered elsewhere. The Mendelian randomization (MR) approach relies on the fulfillment of three fundamental assumptions (Fig. 1): (1) the chosen instrumental variables exhibit associations with the targeted lifestyle and metabolic factors; (2) the genetic variants remain unaffected by any unmeasured confounders influencing the exposure-outcome relationship; and (3) the genetic variants exclusively influence EC risk through the mediation of lifestyle and metabolic factors, without involvement in alternative pathways. For this investigation, we utilized publicly available summary-level statistics, which have previously obtained ethics approval from the original genome-wide association studies (GWASs). Consequently, no additional ethical clearance was necessary for the present MR analysis.

2.2 Instrumental variables identification and data source

Single-nucleotide polymorphisms (SNPs) correlated with lifestyle and metabolic elements were obtained at the genome-wide significance level ($p \leq 5 \times 10^{-8}$) from relevant genome-wide association studies (GWASs). The genetic correlation between these SNPs was assessed by calculating linkage disequilibrium, utilizing data from the European cohort of the 1000 Genomes Project as a reference population [24]. SNPs exhibiting substantial correlation which defined by a linkage disequilibrium threshold of $r^2 \geq 0.01$ were filtered out. From each correlated cluster, we retained only the variant demonstrating the highest statistical significance with lowest p-value in our genome-wide association analysis. We investigated the relationships between 5 lifestyle factors (tobacco consumption, alcohol drinking, coffee intake, education level, and physical activity) and 14 metabolic factors with the risk of EC, including

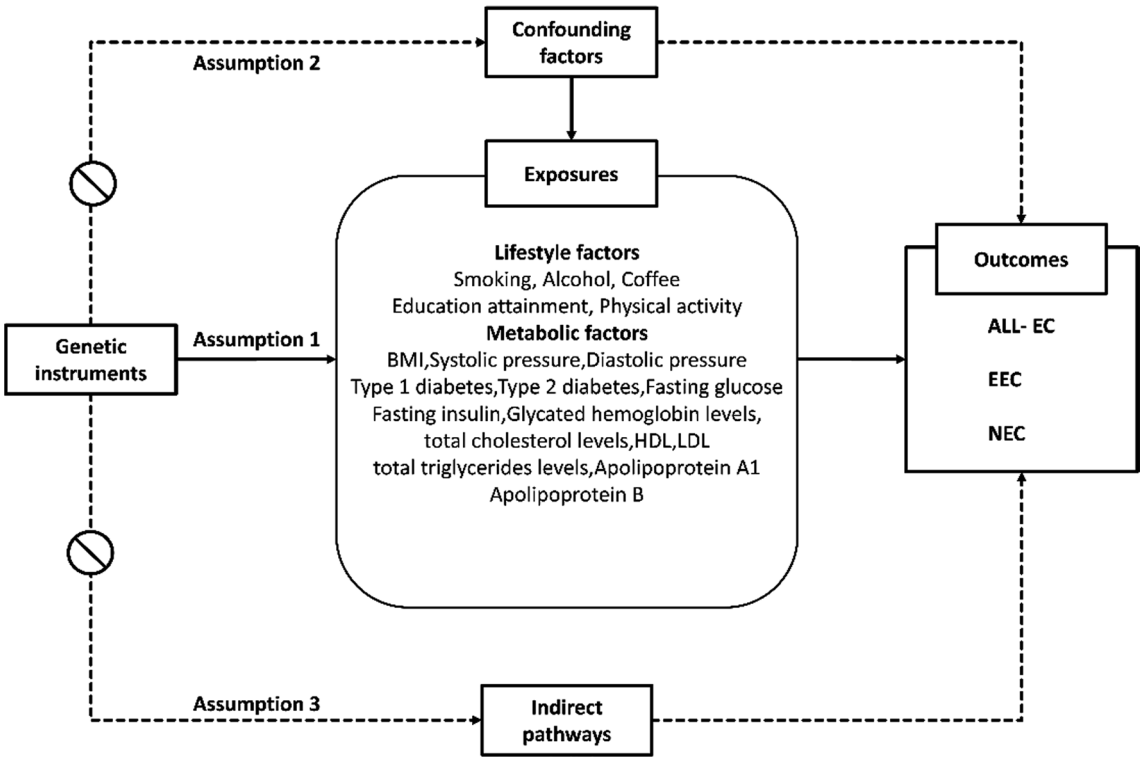

Fig. 1 Fundamental assumptions of the Mendelian Randomization (MR) approach

its subtypes such as endometrioid and non-endometrioid EC. Detailed information regarding the GWASs of the studied exposures is provided in supplemetal Table 1.

We extracted aggregated genetic association statistics for both overall EC susceptibility and subtype-specific risk from a large-scale genomic analysis. This comprehensive study incorporated data from 12,906 individuals diagnosed with EC, comprising 8758 cases of endometrioid subtype and 1230 cases of non-endometrioid variants. The analysis was further strengthened by the inclusion of up to 108,979 unaffected individuals, all of whom were of European descent. Comprehensive details regarding the GWASs conducted for the studied outcomes are delineated in supplemental Table S1.

2.3 Mendelian randomization analysis

The estimation of the causal effect of each lifestyle and metabolic factor on outcomes was primarily conducted using inverse-variance weighting under a multiplicative random-effect model, which synthesizes a combined causal estimate from each single-nucleotide polymorphism (SNP). The assumptions and advantages of the employed methodologies are succinctly presented in Tables 1, 2.

We calculated the weighted median, penalized weighted median, MR pleiotropy residual sum and outlier approaches by sensitivity analyses, were performed (Table 3). Additionally, we applied the Egger regression intercept test to examine potential directional pleiotropy. An intercept not significantly different from zero ($p > 0.05$) in the MR-Egger analysis was interpreted as evidence against substantial pleiotropic bias. Additionally, we implemented the Cochran Q test to assess potential instrument heterogeneity to evaluate the presence of multifunctional genetic effects. Single SNP analysis utilizing the wald ratio approach and leave-one-out sensitivity test were conducted to ascertain whether associations between genetic variants and EC were influenced by individual SNPs. The F-statistic was computed to assess the association advantages of genetic variants for each exposure. "TwoSampleMR" package in R 4.0.3 was used in the analyses (Tables 1–3).

Table 1 Lifestyle factors F statistic and R2

Lifestyle factors	Outcomes	Mean F (min,max)	R^2
Age of smoking initiation	ALL-EC	39.17 (30.7–52.7)	0.001
Age of smoking initiation	EC	32.35 (30.7–52.7)	0.001
Age of smoking initiation	NEC	39.17 (30.7–52.7)	0.001
Smoking initiation	ALL-EC	42.16 (29.8–145)	0.006
Smoking initiation	EC	42.16 (29.8–145)	0.006
Smoking initiation	NEC	67.63 (27–514.87)	0.053
Cigarettes per day	ALL-EC	103.34 (30.9–961)	0.009
Cigarettes per day	EC	103.34 (30.9–961)	0.009
Cigarettes per day	NEC	106.73 (30.9–961)	0.009
Lifetime smoking index	ALL-EC	44.41 (29.9–172.8)	0.011
Lifetime smoking index	EC	44.41 (29.9–172.8)	0.011
Lifetime smoking index	NEC	44.52 (29.9–172.8)	0.011
Alcohol intake frequency	ALL-EC	53.44 (29.74–811.85)	0.011
Alcohol intake frequency	EC	53.44 (29.74–811.85)	0.011
Alcohol intake frequency	NEC	34.79 (29.74–269.71)	0.005
Alcoholic drinks per week	ALL-EC	78.64 (29.8–926.99)	0.005
Alcoholic drinks per week	EC	78.64 (29.8–926.99)	0.005
Alcoholic drinks per week	NEC	52.73 (29.8–206)	0.003
Coffee intake	ALL-EC	74.71 (30.1–646.73)	0.007
Coffee intake	EC	39.72 (30.1–646.73)	0.003
Coffee intake	NEC	74.71 (30.1–646.73)	0.007
Years of schooling	ALL-EC	48.98 (29.69–240.25)	0.020
Years of schooling	EC	48.98 (29.69–240.25)	0.020
Years of schooling	NEC	49.03 (29.69–240.25)	0.020
Moderate to vigorous physical activity	ALL-EC	34.39 (29.98–51.82)	0.002
Moderate to vigorous physical activity	EC	34.39 (29.98–51.82)	0.002
Moderate to vigorous physical activity	NEC	34.39 (29.98–51.82)	0.002
Vigorous physical activity	ALL-EC	40.81 (32.13–55.26)	0.001
Vigorous physical activity	EC	40.81 (32.13–55.26)	0.001
Vigorous physical activity	NEC	40.81 (32.13–55.26)	0.001

3 Results

3.1 Lifestyle factors and endometrial cancer

In the primary inverse-variance weighting (IVW) analysis, several lifestyles were examined in relation to ALL-EC risk. The results revealed that a higher lifetime smoking index was significantly associated with an increased risk of ALL-EC (OR: 1.43, 95% CI 1.05–1.96), suggesting a cumulative effect of smoking on cancer development (Fig. 2 and Supplemental Table S2). When examining alcohol intake, frequency of alcohol consumption was associated with a modest but significant increase in ALL-EC risk (OR: 1.23, 95% CI 1.04–1.45), although overall alcohol intake itself was not significantly linked. Additionally, coffee consumption did not significantly impact ALL-EC risk (OR: 1.39, 95% CI 0.91–2.12). Interestingly, higher education levels of education associated with a significantly decreased risk of ALL-EC (OR: 0.72, 95% CI 0.62–0.83). However, both moderate-intensity and intense physical activity did not show significant effects on ALL-EC.

In secondary analyses, we examined the associations between the same factors with risks of specific histological subtypes of ALL-EC, including EC and NEC. For EC, the associations were largely consistent with those observed for ALL-EC. A genetic predisposition to a lifetime smoking index (OR: 1.54; 95% CI 1.08–2.20) and alcohol intake frequency (OR: 1.24; 95% CI 1.02–1.50) was associated with increased risks of endometrioid EC. However, age at smoking initiation, smoking status, cigarette amounts per day and overall alcohol intake were not significantly associated.

Table 2 Metabolic factor F statistic and R^2

Metabolic factors	Outcomes	Mean F (min,max)	R^2
BMI	ALL-EC	73.37 (28.62–1426.17)	0.049
BMI	EC	73.37 (28.62–1426.17)	0.049
BMI	NEC	73.37 (28.62–1426.17)	0.049
Systolic blood pressure	ALL-EC	67.09 (27–514.87)	0.052
Systolic blood pressure	EC	67.09 (27–514.87)	0.052
Systolic blood pressure	NEC	67.63 (27–514.87)	0.053
Diastolic blood pressure	ALL-EC	69.42 (26.67–496.7)	0.052
Diastolic blood pressure	EC	69.33 (26.67–496.7)	0.052
Diastolic blood pressure	NEC	71.12 (26.67–668.05)	0.053
Type 1 diabetes	ALL-EC	201.72 (30.1–1402.98)	0.007
Type 1 diabetes	EC	201.72 (30.1–1402.98)	0.007
Type 1 diabetes	NEC	192.71 (30.1–1402.98)	0.007
Type 2 diabetes	ALL-EC	78.92 (29.61–1066.63)	0.028
Type 2 diabetes	EC	78.92 (29.61–1066.63)	0.028
Type 2 diabetes	NEC	78.64 (29.61–1066.63)	0.027
Fasting glucose	ALL-EC	136.48 (24.53–1650.91)	0.043
Fasting glucose	EC	136.48 (24.53–1650.91)	0.043
Fasting glucose	NEC	136.48 (24.53–1650.91)	0.043
Fasting insulin	ALL-EC	51.8 (22.44–173.13)	0.013
Fasting insulin	EC	51.8 (22.44–173.13)	0.013
Fasting insulin	NEC	51.8 (22.44–173.13)	0.013
Glycated hemoglobin levels	ALL-EC	106.74 (25–1391.6)	0.051
Glycated hemoglobin levels	EC	106.74 (25–1391.6)	0.051
Glycated hemoglobin levels	NEC	107.29 (25–1391.6)	0.051
Total cholesterol levels	ALL-EC	148.98 (30.87–3063.03)	0.076
Total cholesterol levels	EC	148.98 (30.87–3063.03)	0.076
Total cholesterol levels	NEC	145.01 (30.87–3063.03)	0.072
HDL	ALL-EC	137.54 (30.39–2806.33)	0.097
HDL	EC	137.54 (30.39–2806.33)	0.097
HDL	NEC	136.2 (30.39–2806.33)	0.095
LDL	ALL-EC	209.52 (30.78–4531.38)	0.082
LDL	EC	209.52 (30.78–4531.38)	0.082
LDL	NEC	205.85 (30.78–4531.38)	0.079
Apolipoprotein A1	ALL-EC	131.74 (29.98–1859.31)	0.080
Apolipoprotein A1	EC	131.74 (29.98–1859.31)	0.080
Apolipoprotein A1	NEC	128.33 (29.98–1859.31)	0.077
Apolipoprotein B	ALL-EC	176.86 (30.2–3528.44)	0.082
Apolipoprotein B	EC	176.86 (30.2–3528.44)	0.082
Apolipoprotein B	NEC	172.17 (30.2–3528.44)	0.078
Griglycerides	ALL-EC	135.98 (30.32–1393.58)	0.076
Griglycerides	EC	135.98 (30.32–1393.58)	0.076
Griglycerides	NEC	137.55 (30.32–1393.58)	0.076

Additionally, Higher education level continued to be protective (OR: 0.66, 95% CI 0.55–0.78), while moderate-intensity physical activity showed a significant reduction in risk (OR: 0.35, 95% CI 0.15–0.84).

The results revealed that higher education attainment (OR: 0.66; 95% CI 0.55–0.78) and engagement in moderate to vigorous physical activity (OR:0.35; 95% CI 0.15–0.84) were observed to correlate with decreased risks of endometrioid EC. Nevertheless, intense physical activity did not show a significant effect on EC.

For NEC, the associations with life styles were less pronounced. No associations were observed between lifestyle factors and non-endometrioid EC. These findings highlight that NEC may have a different etiological profile compared to

Table 3 Heterogeneity and pleiotropy assessment

Exposure	Outcome	SNP	Cochran's Q	Intercept	P for intercept	Outliers
Age of smoking initiation	ALL-EC	13	3.96	0.00	0.83	0
Age of smoking initiation	EC	13	2.12	0.00	0.89	0
Age of smoking initiation	NEC	13	9.79	− 0.05	0.42	0
Smoking initiation	ALL-EC	85	99.56	0.01	0.38	0
Smoking initiation	EC	85	82.84	0.01	0.58	0
Smoking initiation	NEC	85	89.69	− 0.01	0.78	0
Cigarettes per day	ALL-EC	21	26.37	− 0.01	0.56	1
Cigarettes per day	EC	22	28.13	− 0.02	0.11	0
Cigarettes per day	NEC	21	23.25	0.02	0.25	0
Lifetime smoking index	ALL-EC	108	116.43	0.02	0.02	0
Lifetime smoking index	EC	108	110.77	0.01	0.19	0
Lifetime smoking index	NEC	106	112.78	0.02	0.32	0
Alcohol intake frequency	ALL-EC	93	122.92	0.00	0.83	2
Alcohol intake frequency	EC	93	118.32	0.00	0.55	2
Alcohol intake frequency	NEC	95	90.32	− 0.03	0.02	0
Alcoholic drinks per week	ALL-EC	33	54.90	0.00	0.81	0
Alcoholic drinks per week	EC	33	38.77	− 0.01	0.41	0
Alcoholic drinks per week	NEC	32	43.81	0.04	0.01	0
Coffee intake	ALL-EC	37	50.62	0.00	0.62	1
Coffee intake	EC	38	51.57	0.00	0.77	0
Coffee intake	NEC	38	28.38	0.03	0.08	0
Years of schooling	ALL-EC	306	329.71	0.00	0.42	0
Years of schooling	EC	306	323.81	0.01	0.09	0
Years of schooling	NEC	305	280.96	− 0.02	0.11	0
Moderate to vigorous physical activity	ALL-EC	18	31.25	0.01	0.69	1
Moderate to vigorous physical activity	EC	18	29.99	0.02	0.70	1
Moderate to vigorous physical activity	NEC	19	19.91	0.06	0.25	0
Vigorous physical activity	ALL-EC	7	5.47	0.05	0.42	0
Vigorous physical activity	EC	7	6.69	0.04	0.62	0
Vigorous physical activity	NEC	7	1.95	− 0.06	0.69	0
BMI	ALL-EC	489	547.52	0.00	0.20	3
BMI	EC	490	598.67	0.00	0.45	2
BMI	NEC	492	474.35	− 0.01	0.17	0
Systolic blood pressure	ALL-EC	323	369.06	0.00	0.24	6
Systolic blood pressure	EC	326	381.33	0.00	0.64	3
Systolic blood pressure	NEC	329	370.02	0.01	0.28	0
Diastolic blood pressure	ALL-EC	314	379.57	0.00	0.22	3
Diastolic blood pressure	EC	315	369.15	0.01	0.16	3
Diastolic blood pressure	NEC	316	403.20	0.01	0.37	1
Type 1 diabetes	ALL-EC	14	23.44	− 0.01	0.61	1
Type 1 diabetes	EC	14	23.97	0.00	0.96	1
Type 1 diabetes	NEC	16	12.52	0.00	0.84	0
Type 2 diabetes	ALL-EC	169	242.65	0.00	0.37	3
Type 2 diabetes	EC	171	245.06	0.01	0.00	1
Type 2 diabetes	NEC	169	199.59	0.00	0.88	1
Fasting glucose	ALL-EC	62	88.38	− 0.01	0.02	2
Fasting glucose	EC	63	104.72	− 0.01	0.07	1
Fasting glucose	NEC	64	49.62	− 0.02	0.06	0
Fasting insulin	ALL-EC	37	49.90	− 0.02	0.16	1
Fasting insulin	EC	36	38.53	0.00	0.77	2
Fasting insulin	NEC	38	40.56	− 0.01	0.74	0

Table 3 (continued)

Exposure	Outcome	SNP	Cochran's Q	Intercept	P for intercept	Outliers
Glycated hemoglobin levels	ALL-EC	71	120.23	0.00	0.82	0
Glycated hemoglobin levels	EC	71	111.29	0.00	0.49	0
Glycated hemoglobin levels	NEC	70	56.97	0.01	0.63	0
Total cholesterol levels	ALL-EC	59	74.74	0.00	0.45	0
Total cholesterol levels	EC	59	63.52	0.00	0.85	0
Total cholesterol levels	NEC	58	77.24	0.02	0.10	0
HDL	ALL-EC	81	110.74	0.00	0.34	1
HDL	EC	81	107.75	0.00	0.82	1
HDL	NEC	81	101.39	− 0.01	0.27	0
LDL	ALL-EC	44	51.40	0.00	0.89	2
LDL	EC	46	56.48	0.00	0.77	0
LDL	NEC	45	56.67	0.01	0.61	0
Apolipoprotein A1	ALL-EC	70	109.13	0.00	0.72	0
Apolipoprotein A1	EC	69	97.88	0.00	0.74	1
Apolipoprotein A1	NEC	68	89.08	− 0.02	0.13	1
Apolipoprotein B	ALL-EC	54	75.51	0.01	0.16	0
Apolipoprotein B	EC	54	53.34	0.01	0.21	0
Apolipoprotein B	NEC	53	68.37	0.02	0.09	0
Griglycerides	ALL-EC	65	85.00	0.01	0.30	0
Griglycerides	EC	65	80.54	0.00	0.77	0
Griglycerides	NEC	64	77.02	0.02	0.16	0

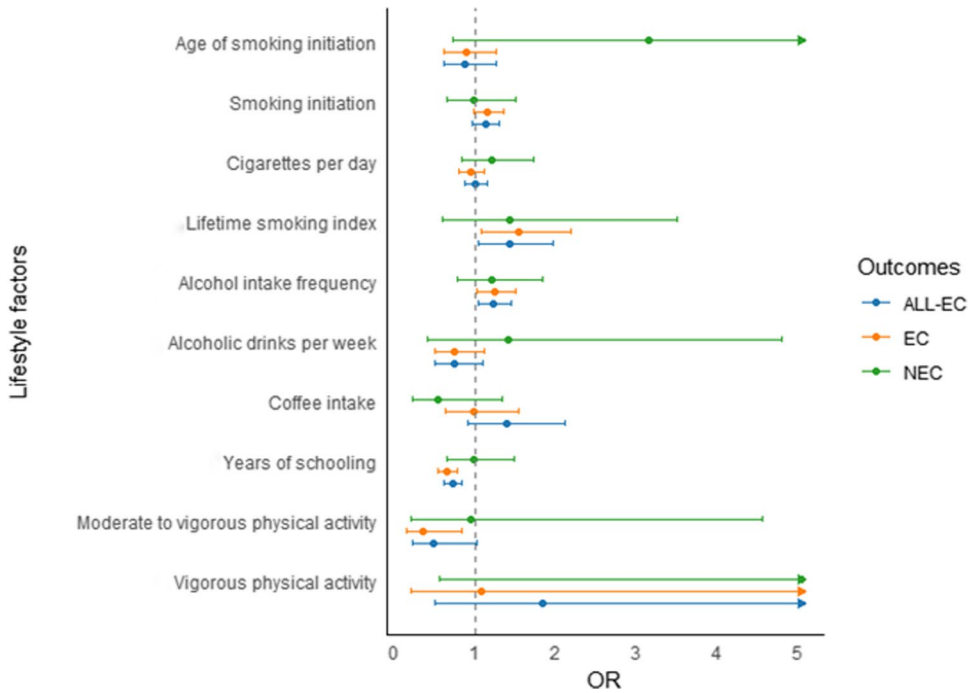

Fig. 2 Associations of lifestyle factors and genetic predisposition with endometrial cancer risk by histological subtypes

EC, with fewer lifestyle factors exerting a significant influence. However, the underlying mechanisms need to explore in future studies.

3.2 Metabolic factors and endometrial cancer

In the primary inverse-variance weighting (IVW) analyses, genetic predisposition to elevated body mass index (BMI) (OR: 1.82; 95% CI 1.64–2.01), type 2 diabetes (OR: 1.06; 95% CI 1.00–1.12), and fasting insulin levels (OR:1.97; 95% CI 1.30–2.98) were associated with an increased risk of EC (Fig. 3 and supplemental Table S2). However, systolic, diastolic blood pressure, Type 1 diabetes, fasting blood glucose and glycosylated hemoglobin were not significantly associated with ALL-EC risk. In terms of lipid profiles, higher levels of LDL (OR: 0.91; 95% CI 0.84–0.99) were linked to a decreased risk of EC, while systolic, diastolic blood pressure, Type 1 diabetes, fasting blood glucose and glycosylated hemoglobin were not significantly associated with ALL-EC risk.

In secondary analyses, the associations between metabolism factors and EC histological subtypes were observed. For EC, the results were consistent with ALL-EC. BMI remained a strong risk factor (OR: 1.86, 95% CI 1.65–2.11), and fasting insulin was again associated with increased risk (OR: 2.16, 95% CI 1.39–3.36). Additionally, higher levels of apolipoprotein B (OR: 0.77; 95% CI 0.60–0.98) and LDL (OR: 0.71; 95% CI 0.55–0.90) were associated with a reduced risk of endometrioid EC. For NEC, BMI was again associated with increased risk though less strongly (OR: 1.61, 95% CI 1.23–2.10) and increased glycated hemoglobin levels (OR: 2.30; 95% CI 1.14–4.64) were linked to an augmented risk. These results highlights a potential distinct metabolic pathway involved in EC and NEC.

4 Discussion

Our MR analyses revealed significant associations between EC risk and various lifestyle and metabolic factors based on large-scale GWAS summary statistics. We found compelling genetic evidence suggesting that higher lifetime smoking index, alcohol intake frequency, BMI, T2DM, and fasting insulin are associated with an increased risk of EC, particularly for endometrioid EC. Conversely, higher education attainment, engagement in moderate to high intensity exercise, and lower levels of triglycerides may reduce the risk of EC.

Our findings regarding the association between smoking and EC risk align with existing literature. Smoking, characterized by its carcinogenic properties, has been linked to cancer incidence and poorer long-term outcome [25, 26]. Nicotine, a prominent component of tobacco, acts as a cancer promoter, facilitating cancer cell division epithelial-mesenchymal transformation, and angiogenesis [27–30], thereby potentially contributing to a more aggressive phenotype conducive to metastasis. However, it is noteworthy that some studies [31], such as those by NIKI Dimiou, have reported inverse associations between

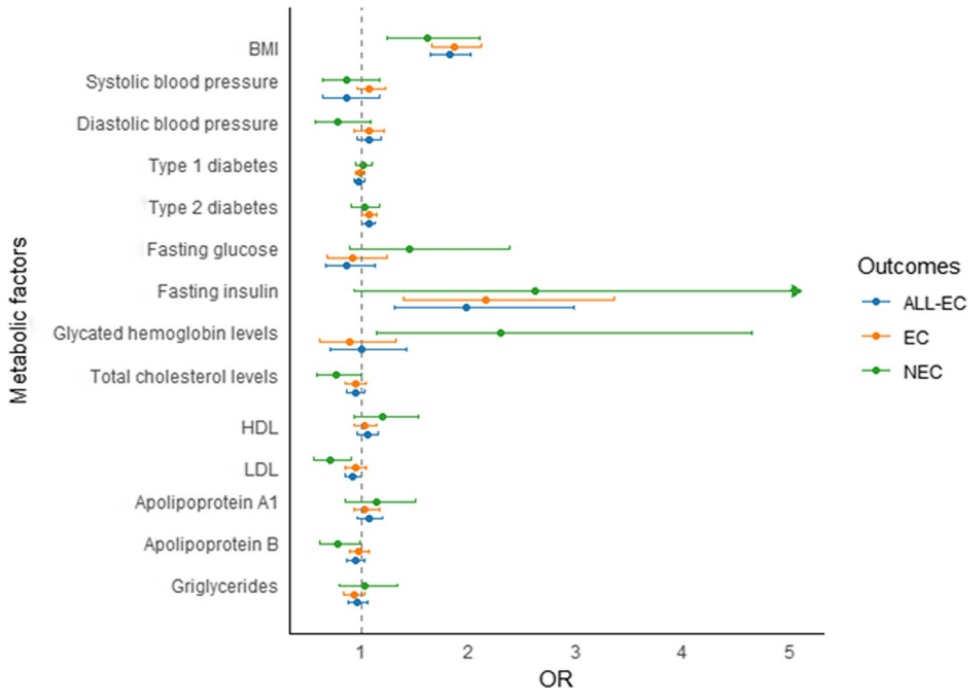

Fig. 3 Associations of metabolic factors and genetic predisposition with endometrial cancer risk by histological subtypes

lifetime smoking and EC risk [18], suggesting the necessity for further confirmation through larger Mendelian randomization studies.

Regarding alcohol intake frequency, our analysis revealed suggestive evidence of its association with EC, including both endometrioid and non-endometrioid subtypes. However, the precise biological mechanisms underlying this relationship remain unclear. Nonetheless, alcohol intake may lead to elevated cumulative estrogen burden, thereby promoting epithelial cell genotoxicity and mitosis [16], which could contribute to EC progression. Notably, our findings did not establish a significant association between weekly alcohol consumption and EC risk, consistent with previous cohort studies.

Additionally, we did not reveal a statistically significant relationship between coffee intake and the risk of developing EC, irrespective of coffee type. Nonetheless, prior research has indicated that caffeine consumption among premenopausal women may be associated with increased EC risk, while such an association is negligible among postmenopausal women [9, 32].

Educational attainment emerged as a noteworthy factor associated with EC risk reduction in our study, particularly for endometrioid EC. This finding is consistent with previous cohort studies, including one by Qi Xia Wang, which suggested that longer educational attainment could predict a significant reduction in EC risk [33]. The exact mechanisms mediating this association remain elusive, although various intermediate phenotypes may play mediating roles.

In terms of physical activity, our study revealed an association between moderate physical activity and reduced risk of endometrioid EC, whereas no significant relationship was observed with vigorous physical activity. Promoting physical activity and reducing sedentary behaviors are recognized as effective strategies for cancer prevention, independently of body fat [34], through various mechanisms.

Moreover, our Mendelian randomization study provided genetic support for the causal relationship between BMI, fasting insulin, type 2 diabetes, LDL cholesterol, and EC risk, particularly for endometrioid EC, with associations reported by observational and MR analyses [2, 35–37].However, no statistically significant associations were found between hypertension, type 1 diabetes, fasting blood glucose, glycated hemoglobin, HDL cholesterol, total cholesterol, and EC risk.

In conclusion, our comprehensive analysis sheds light on the complex interplay between lifestyle, metabolic factors, and EC risk. While certain factors demonstrate clear associations, further research is warranted to elucidate underlying mechanisms and confirm observed relationships, particularly those with conflicting findings across different studies.

Several strengths characterize our Mendelian randomization (MR) study. Foremost among them is the MR design, which effectively mitigates confounding and reverse causality biases to a significant extent [38, 39]. Through the application of Mendelian randomization, we comprehensively investigated the associations between 5 lifestyle factors, 14 metabolic factors, and EC and its subtypes. Furthermore, our study specifically targeted individuals of European descent, minimizing potential biases arising from population structure.

5 Limitation

Certain limitations warrant consideration when interpreting our findings. Firstly, our MR analysis predominantly focused on individuals of European ancestry, potentially limiting the generalizability of our results to other populations. This underscores the importance of conducting genomic studies encompassing diverse ancestral groups to capture broader insights into EC etiology. Secondly, the utilization of summarized data restricted the scope of analyses that could be performed, precluding non-linear MR investigations. Lastly, sample overlap was observed between several exposure genome-wide association studies (GWASs) and the outcome dataset in our MR analysis. While sample overlap is a common limitation in two-sample MR studies employing large genetic consortia, it may introduce weak instrument bias. Nevertheless, our stringent selection criteria for single-nucleotide polymorphisms (SNPs) at the genome-wide threshold, along with consistently high estimated F statistics (ranging from 33.45 to 209.52, all exceeding 10), suggest that significant weak instrument bias is unlikely, despite the consortia overlap.

6 Conclusions

Our study yields compelling evidence for a favorable causal association between genetically factors such as lifetime smoking index, alcohol intake frequency, BMI, T2DM, fasting insulin levels, and the risk of EC. Conversely, our findings suggest that higher education levels, engagement in moderate-intensity physical exercise, and lower levels of LDL cholesterol may reduce the risk of EC.

The comprehensive MR analysis conducted in this study offers valuable insights into potential causal mechanisms underpinning the relationship between lifestyle and metabolic factors and EC risk. Furthermore, the findings revealed a basis for developing potential strategies aimed at the prevention of EC.

Author contributions X.Z., C.P., and J.W. conceptualized and designed the study; X.Z. and C.P. analyzed the data; X.Z., C.P., L.W., X.L., H.L., S.W., and L.W. interpreted the data; X.Z. and C.P. wrote the original draft; All authors commented on the manuscript; X.L., and J.W. reviewed and improved the manuscript; J.W. supervised all research work. All authors have read and agreed to the published version of the manuscript.

Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Competing interests The authors declare no competing interests.

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