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The Global Burden and Causal Associations of Risk Factors with Ovarian Cancer: A Combined GBD and Mendelian Randomization Analysis

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KEYWORDS

Ovarian Cancer;
Global Burden of Disease;
Mendelian Randomization;
Obesity;
Waist Circumference;
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ABSTRACT

Ovarian cancer (OC) remains a major cause of gynecologic cancer mortality worldwide, with incidence continuing to rise in low- and middle-SDI regions. Metabolic risk factors may be reshaping OC epidemiology. This study quantifies global OC burden from 1990 to 2023 and examines causal relationships between metabolic and behavioral factors and OC using Mendelian randomization (MR). Using GBD 2023 data, we assessed OC incidence, mortality, DALYs, and estimated annual percentage changes (EAPCs) across regions and SDI levels. A two-sample MR analysis was conducted to evaluate causal effects of multiple exposures, with sensitivity tests including MR-Egger, weighted median, and Cochran's Q. From 1990 to 2023, global OC incidence increased by 111%, deaths by 100.7%, and DALYs by 97.4%. Age-standardized incidence and mortality rates declined until 2014 but have risen over the past decade, particularly in low- and middle-SDI settings. Women aged 30–49 years experienced the fastest growth in EAPC. MR results indicated significant associations between OC risk and HIP (OR = 1.29, 95% CI: 1.13–1.48), childhood BMI (OR = 1.22, 95% CI: 1.07–1.39), and waist circumference (OR = 1.28, 95% CI: 1.07–1.51), with consistent findings across sensitivity analyses and no evidence of pleiotropy. These results indicate a rising global OC burden and support a causal link between central adiposity, early-life obesity, and OC risk, emphasizing the need for targeted metabolic interventions and early detection strategies.

INTRODUCTION

Ovarian cancer (OC) remains one of the most lethal gynecological malignancies, significantly contributing to global female morbidity and mortality[1]. In 2022, an estimated 313,000 new cases and 207,000 deaths were reported worldwide, ranking OC as the eighth most common cancer and the fifth leading cause of cancer-related deaths in women[2]. Despite advances in imaging, surgical techniques, and targeted therapies, the prognosis for patients remains poor. Five-year survival rates are reported to below 45% in most regions, primarily due to late-stage diagnosis and the frequent occurrence of resistance to therapies[3, 4]. The substantial clinical and biological heterogeneity of OC—including epithelial, germ cell, and stromal subtypes—continues to hinder early detection and prevention[5, 6]. High-grade serous OC, responsible for over 70% of OC deaths, is characterised by

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rapid progression, extensive peritoneal spread, and frequent TP53 mutations[5]. Although OC predominantly affects postmenopausal women, it increasingly poses a hidden burden among women of reproductive age.

A large-scale data from the 2021 Global Burden of Disease (GBD) study reveal that the age-standardized incidence and mortality rates of OC have shown divergent trends across regions[1]. Temporal decomposition analysis indicate that the observed discrepancies are closely linked to several critical determinants, including accelerated population aging, which increases the number of older individuals at risk for developing OC.[1].The shifting demographic landscape, characterized by increasing life expectancy and declining fertility, suggests that the global burden of OC will likely continue to escalate in the coming decades without effective prevention strategies[1].

OC is a multifactorial disease influenced by a complex interplay of genetic susceptibility, hormonal exposure, chronic inflammation, and metabolic dysregulation[7, 8]. Previous studies have confirmed that reproductive factors (e.g., childlessness, early menarche, late menopause, and endometriosis) are well-established risk for OC[9]. more recent evidence suggests that metabolic factors (including obesity, type 2 diabetes mellitus, and dyslipidaemia) have a significant association with the risk of developing the disease[10, 11]. Obesity and insulin resistance foster a pro-inflammatory environment, hyperinsulinemia, and elevated estrogen bioavailability, all of which may promote ovarian carcinogenesis[12]. Furthermore, poor lifestyle factors such as high intake of saturated fats, physical inactivity, and alcohol use have been associated with increased OC risk in several cohort studies[13]. Mounting observational data have also linked OC risk with biomarkers like leptin, adiponectin, sex hormone-binding globulin, and C-reactive protein, suggesting a modifiable inflammatory–metabolic axis[14, 15]. However, these associations are prone to confounding and reverse causation, limiting their utility in establishing causal relationships or guiding interventions. In this context, Mendelian randomization (MR) offers a powerful framework to disentangle causality from correlation[16]. By using genetic variants as instrumental variables (IVs) for modifiable exposures (e.g., adiposity, glucose levels, hormone regulation), MR simulates the design of a natural randomized controlled trial, minimizing residual confounding and reverse causality bias[16]. Furthermore, MR has been employed to test the inverse association between oral contraceptive use and OC risk, revealing subtype-specific protection against HGSOC and endometrioid tumors[17, 18]. Nonetheless, these analyses have often focused on single exposures and European-ancestry populations, underscoring the need for expanded, integrative MR analyses across diverse genomic and epidemiological settings.

To address these gaps, our study leverages the latest GBD 2023 data to quantify the spatiotemporal burden of OC among women globally, particularly those of reproductive age. By coupling GBD metrics with two-sample MR analyses, this study aim to explore the causal impact of lifestyle, metabolic, and hormonal factors on OC risk using large-scale GWAS summary data. This integrated approach not only enriches the descriptive epidemiology of OC and provides mechanistic clarity that may inform targeted prevention strategies.

METHODS

GBD Analysis

Data Sources

The GBD database, the world's largest platform for quantifying health losses, is led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. Serving as a cornerstone of global health assessment, it systematically integrating data from censuses, vital registration systems, disease surveillance networks, healthcare facility records, and multidisciplinary research. The latest GBD 2023 iteration encompasses 204 countries and territories (including dozens of subnational regions), evaluating 370 distinct diseases and injuries alongside 88 risk factors, providing a comprehensive framework for analyzing health outcomes and risk attribution multiple levels (https://ghdx.healthdata.org/series/global-burden-disease-gbd)[16, 19-22].

Study Design and Statistical Analysis

This study extracted OC data from the GBD 2023 database to conduct a multi-dimensional burden analysis. The temporal trends in the total number of cases and age-standardized rates (ASRs) were systematically evaluated from 1990 to 2023. This assessment focused on key metrics such as disability-adjusted life years (DALYs), mortality rates, prevalence, morbidity, years lived with disability (YLDs), and years of life lost (YLLs). To highlight the spatial variation in disease burden, stratified analyses were conducted based on age group, socio-demographic index (SDI), GBD region, and country. To elucidate underlying drivers of burden variation, we conducted a demographic decomposition analysis. Furthermore, a combination of time-series forecasting models—namely autoregressive integrated moving average (ARIMA), exponential smoothing (ES), and Bayesian Bayesian age-period-cohort (BAPC) models—were employed to project OC burden trajectories from 2024 to 2050. This integrative analytical framework constructs a comprehensive evidence chain, offering critical data to guide the development of precisely targeted, time-sensitive public health intervention strategies.

Mendelian Randomization Analysis

Exposure and Outcome Data Sources

This study systematically investigated the causal relationships between OC and multi-dimensional risk exposures across three key domains: socioeconomic factors, behaviors factors, and nutritional-metabolic factors, employing a causal inference framework[23-32].

In this study, we systematically characterized the genetic susceptibility profile of epithelial ovarian cancer (EOC) using data from the world’s largest GWAS of OC conducted by Phelan et al[33]. This large-scale study integrated multicenter genome-wide genotyping data, assembling a comprehensive sample bank comprising 25,509 EOC cases and 40,941 healthy controls. The analysis identified 9 novel susceptibility loci associated with distinct EOC histological subtypes: six associated with serous EOC, two with mucinous EOC, and one with endometrioid EOC. Futhermore, an integrative analysis incorporating data from 31,448 BRCA1 and BRCA2 mutation carriers revealed three additional susceptibility loci located at chromosomal regions 2q13, 8q24.1, and 12q24.31.

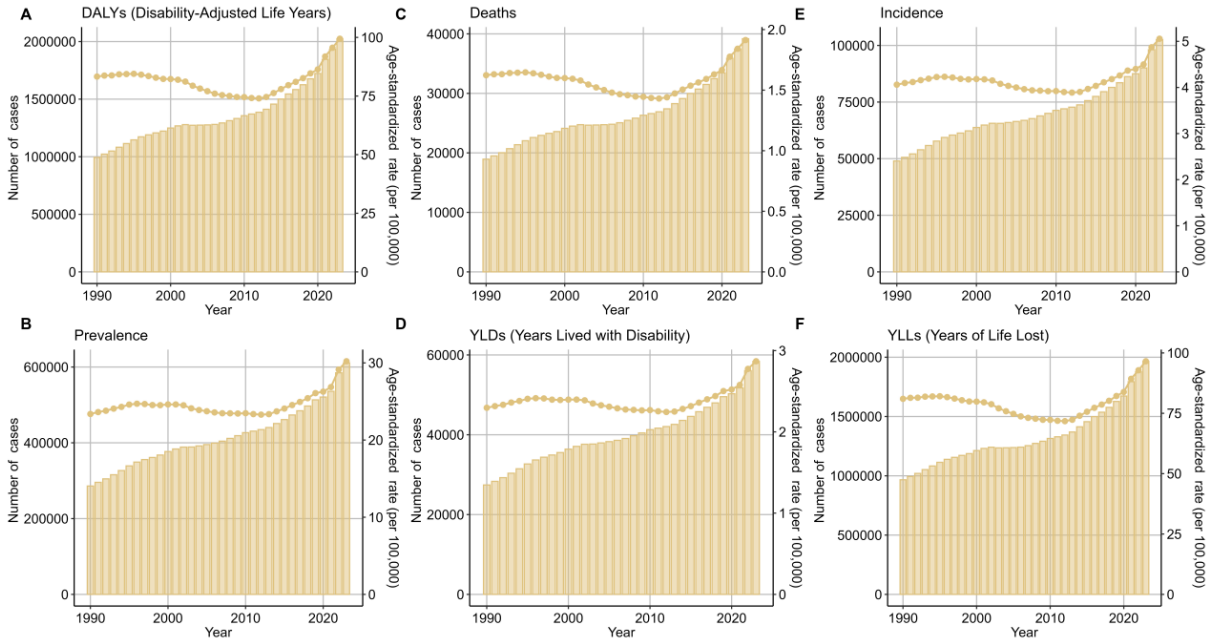


Figure 1 | The trend of ovarian cancer-related GBD of Deaths, YLDs, YLLs, DALYs, Prevalence and Incidence between 1990 and 2023. Abbreviations: ASR, age-standardized rate; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; DALYs, disability-adjusted-life-years.

MR Study Design and Statistical Analysis

To minimize bias in MR analysis, this study adhered to three core MR assumptions [34]: 1) strong association between instrumental variables (IVs) and target exposures; 2) independence of IVs from observed/unobserved confounders; and 3) exclusion restriction - IVs influence outcomes only through the specified exposure pathway. The genetic instrument selection followed a dual-quality control protocol [35-37]: 1) genome-wide significant SNPs ($P < 5\times10^{-8}$) associated with target exposures were selected as IV candidates; 2) linkage disequilibrium (LD) clumping ($r^2 < 0.001$, window size: 10,000 kb) ensured instrumental independence by eliminating genetic correlations among SNPs. To strengthen causal inference robustness, this study adopted four complementary MR methods were concurrently applied: weighted median estimator (tolerating ≤50% invalid instruments), simple median method (non-parametric), and maximum-likelihood estimation, enabling methodological triangulation[39]. Within the MR framework, the inverse-variance weighted (IVW) method served as the principal approach for estimating exposure-outcome causal effects[38]. Sensitivity analysis included MR-Egger intercept testing to quantify and adjust for directional pleiotropy[40]. All effect estimates were subsequently standardized as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Temporal Trend for GBD of Ovarian Cancer From 1990 to 2023

Globally, from 1990 to 2023, OC cases exhibited a consistent upward trend. The absolute numbers of DALYs increased from 993,999.33 (95% UI: 832,708.12–1,156,042.18) in 1990 to 2,024,514.33 (95% UI: 1,619,308.65–2,571,768.29) in 2023; Deaths from 18,946.1 (95% UI: 15,915.1–21,940.42) to 39,181.47 (95% UI: 31,487.95–49,788.19); Incidence from 48,990.6 (95% UI: 41,452.56–58,394.84) to 102,549.03 (95% UI: 82,058.4–128,422.75); Prevalence from 285,991.53 (95% UI: 237,190.6–345,777.95) to 610,765.17 (95% UI: 473,999.13–778,592.52); YLDs from 27,418.94 (95% UI: 18,978.43–39,187.97) to 58,377.3 (95% UI: 39,468.34–80,876.23); and YLLs from 966,580.39 (95% UI: 806,536.25–1,128,260.41) to 1,966,137.03 (95% UI: 1,570,390.77–2,515,999.87). Conversely, the ASR showed a distinct pattern with 2014 as the inflection point: declining before 2014 and rising afterward. The EAPC for each metric was: DALYs: 0.08 (95% CI: -0.17 to 0.32); Deaths: 0.04 (95% CI: -0.21 to 0.28); Incidence: 0.20 (95% CI: 0.01 to 0.39); Prevalence: 0.32 (95% CI: 0.14 to 0.49); YLDs: 0.23 (95% CI: 0.05 to 0.40); and YLLs: 0.07 (95% CI: -0.17 to 0.32). Consequently, ASR values changed from 1990 to 2023 as follows: DALYs from 83.3 (95% UI: 70.14–97.65) to 99.43 (95% UI: 78.05–127.78); Deaths from 1.62 (95% UI: 1.37–1.89) to 1.91 (95% UI: 1.51–2.45); Incidence from 4.06 (95% UI: 3.41–4.81) to 5.06 (95% UI: 3.98–6.51); Prevalence from 23.38 (95% UI: 19.26–28.16) to 30.22 (95% UI: 23.51–39.10); YLDs from 2.30 (95% UI: 1.57–3.26) to 2.87 (95% UI: 1.92–4.02); and YLLs from 81.00 (95% UI: 68.11–95.00) to 96.56 (95% UI: 75.65–124.37) (**Figure 1**).

Since the ovaries are organs unique to females, we focused solely on the disease burden in women. Furthermore, considering that women of childbearing age represent a high-risk group for OC, we specifically analyzed the burden in the 15-49-year age group. From 1990 to 2023, the trends across age groups paralleled the global pattern. Notably, the steepness of change increased proportionally with age, with the 30-34-year age group exhibiting the most pronounced trends. The EAPC values for DALYs, Deaths, Incidence, Prevalence,

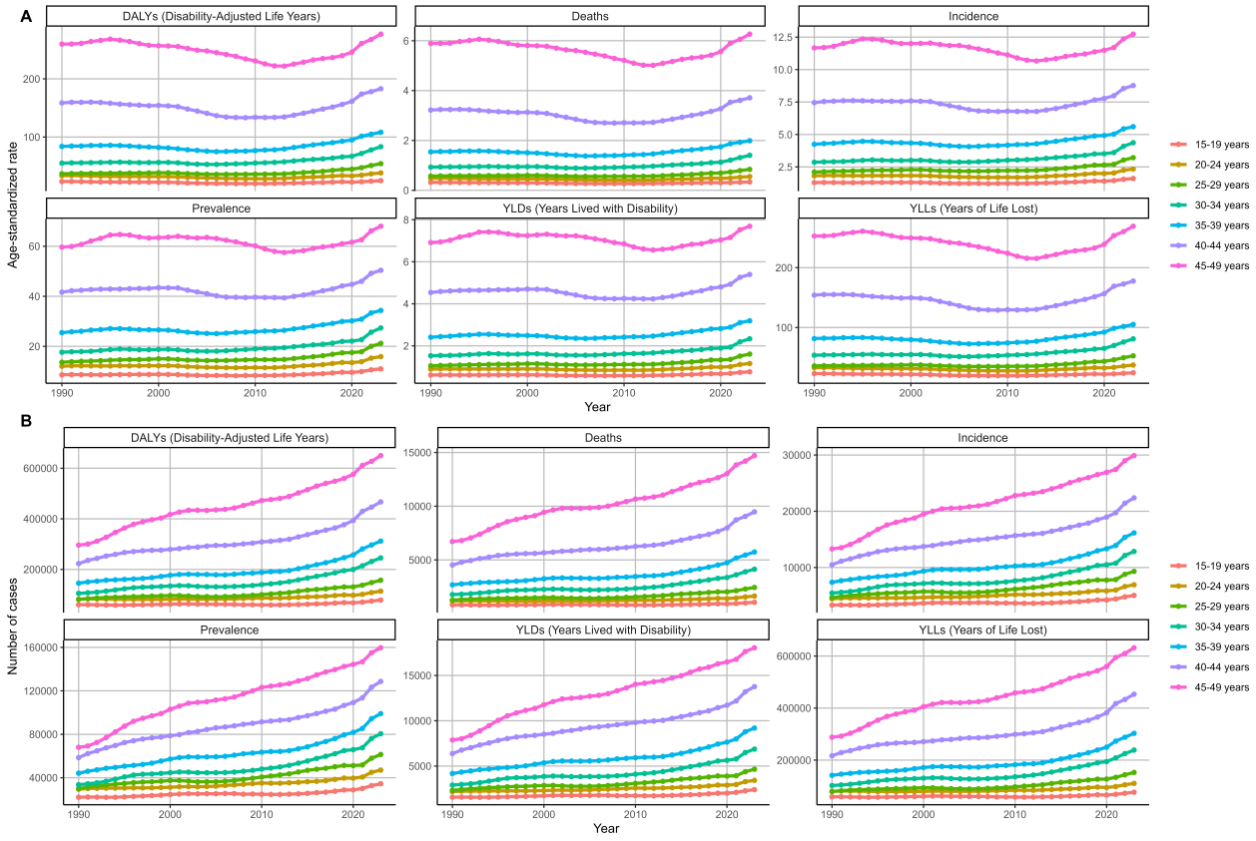


Figure 2 | The trend of ovarian cancer-related GBD of Deaths, YLDs, YLLs, DALYs, Prevalence and Incidence for different age groups between 1990 and 2023. Abbreviations: ASR, age-standardized rate; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; DALYs, disability-adjusted-life-years.

YLDs, and YLLs in this age group were 0.75 (95% CI: 0.48 to 1.02), 0.75 (95% CI: 0.48 to 1.03), 0.76 (95% CI: 0.54 to 0.99), 0.81 (95% CI: 0.60 to 1.03), 0.78 (95% CI: 0.56 to 0.99), and 0.75 (95% CI: 0.48 to 1.02), respectively (**Figure 2**).

OC burden trends varied significantly across regions with different SDI levels. For ASR, DALYs, Deaths, and YLLs declined in High SDI and High-middle SDI regions but increased in all other regions; while Incidence, Prevalence, and YLDs decreased only in High SDI regions and rose elsewhere. Regarding the number of cases, all regions except High SDI showed increasing trends consistent with global patterns, whereas the High SDI region exhibited an initial increase followed by decline (**Figure 3**).

To visually understand trend variations across GBD regions, we performed hierarchical cluster analysis on the ASR of all metrics. The structural results revealed that regions with significantly decreased burden included Oceania, Central Sub-Saharan Africa, Southern Sub-Saharan Africa, and Andean Latin America; while regions with significantly increased burden encompassed Western Sub-Saharan Africa, Eastern Sub-Saharan Africa, North Africa and Middle East, South Asia, Central Latin America, and Southeast Asia (**Figure 4**).

Trends in the burden of OC varied substantially between countries from 1990 to 2023. Guam exhibited the largest increases across all metrics, with EAPC values of 6.63 (95% CI: 4.96 to 8.23) for DALYs, 6.59 (95% CI: 4.92 to 8.28) for deaths, 6.97 (95% CI: 5.24 to 8.73) for incidence, 7.13 (95% CI: 5.36 to 8.93) for prevalence, 6.89 (95% CI: 5.16 to 8.65) for YLDs, and 6.62 (95% CI: 4.95 to 8.32) for YLLs. Conversely, Qatar showed the greatest reductions in DALYs (EAPC: -3.20, 95% CI: -3.71 to -2.68), Deaths (-3.26, 95% CI: -3.78 to -2.74), and YLLs (-3.26 ,95% CI: -3.77 to -2.74); while Luxembourg had the largest declines in Incidence (EAPC: -2.42 ,95% CI: -2.69 to -2.15), Prevalence (-2.18 ,95% CI: -2.48 to -1.88), and YLDs [-2.17 (95% CI: -2.46 to -1.88)] (**Figure 5**).

The Disease Burden of Ovarian Cancer in 2023

To assess the most recent OC burden, we conducted an in-depth analysis of 2023 data. Both absolute case counts and ASR demonstrated a progressive increase with age, peaking in the 45-49-year age group. The absolute burden metrics were: 649,847.17 (95% UI: 532,080.47–810,722.75) for DALYs, 14,708.82 (95% UI: 12,046.59–18,399.76) for deaths, 29,891.71 (95% UI: 24,830.1–36,682.38) for Incidence, 159,644.86 (95% UI: 132,178.52–197,106.21) for prevalence, 18,053.75 (95% UI: 12,691.2–24,454.88) for prevalence, 631,793.42 (95% UI: 517,447.2–790,508.8) for YLLs. Corresponding ASR values were 276.79 (95% UI: 226.63–345.31), 6.26 (95% UI: 5.13–7.84), 12.73 (95% UI: 10.58–15.62), 68.00 (95% UI: 56.30–83.95), 7.69 (95% UI: 5.41–10.42) and 269.10 (95% UI: 220.39–336.70), respectively.

The burden of OC by SDI level revealed distinct patterns. For ASR, DALYs, Deaths and YLLs, negative correlations were observed with SDI, peaking in Low SDI regions at

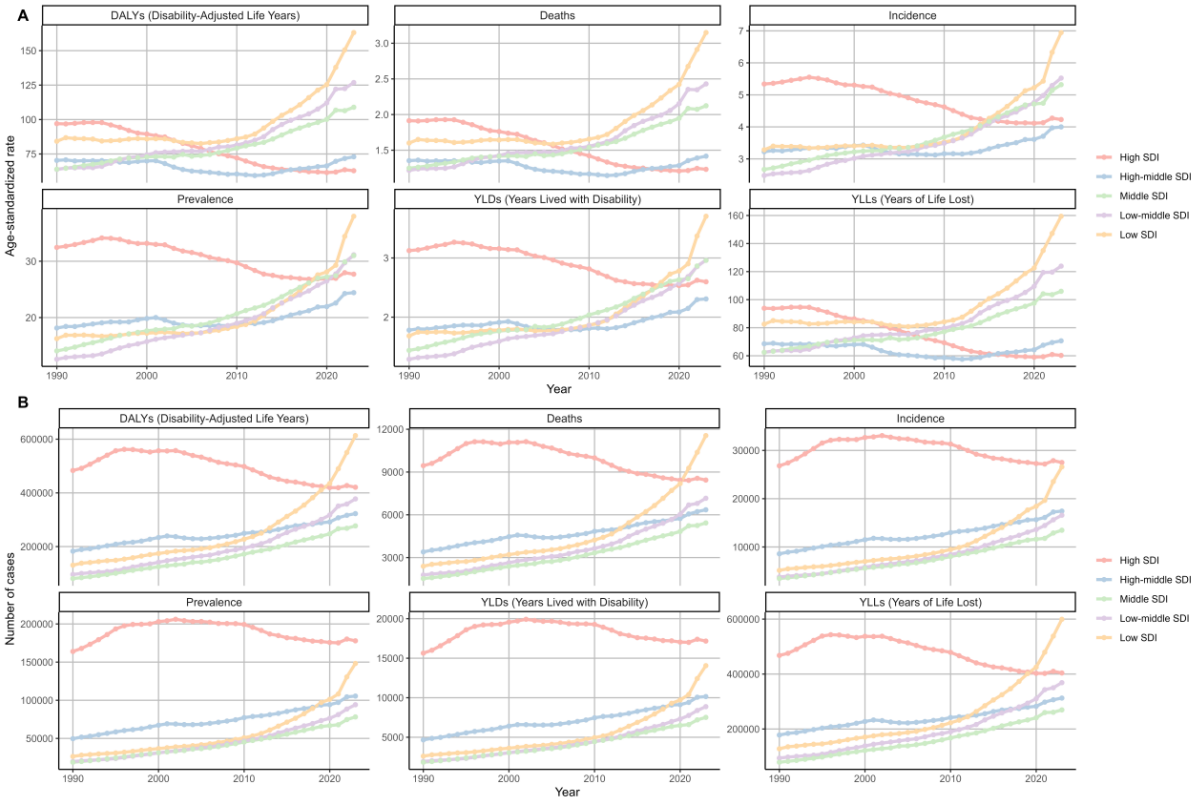


Figure 3 | The trend of ovarian cancer-related GBD of Deaths, YLDs, YLLs, DALYs, Prevalence and Incidence for different SDI regions between 1990 and 2023. Abbreviations: ASR, age-standardized rate; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; DALYs, disability-adjusted-life-years.

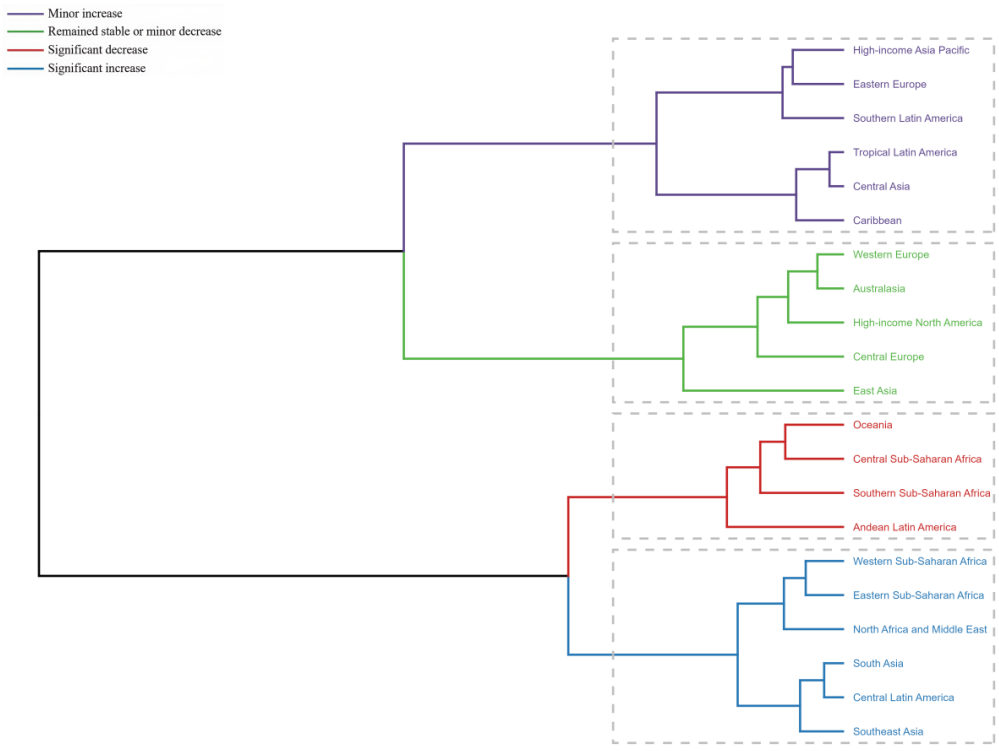


Figure 4 | Results of cluster analysis based on the EAPC values of ovarian cancer-related age-standardized rates from 1990 to 2023. Abbreviations: EAPC, estimated annual percentage change; DALYs, disability-adjusted-life-years.

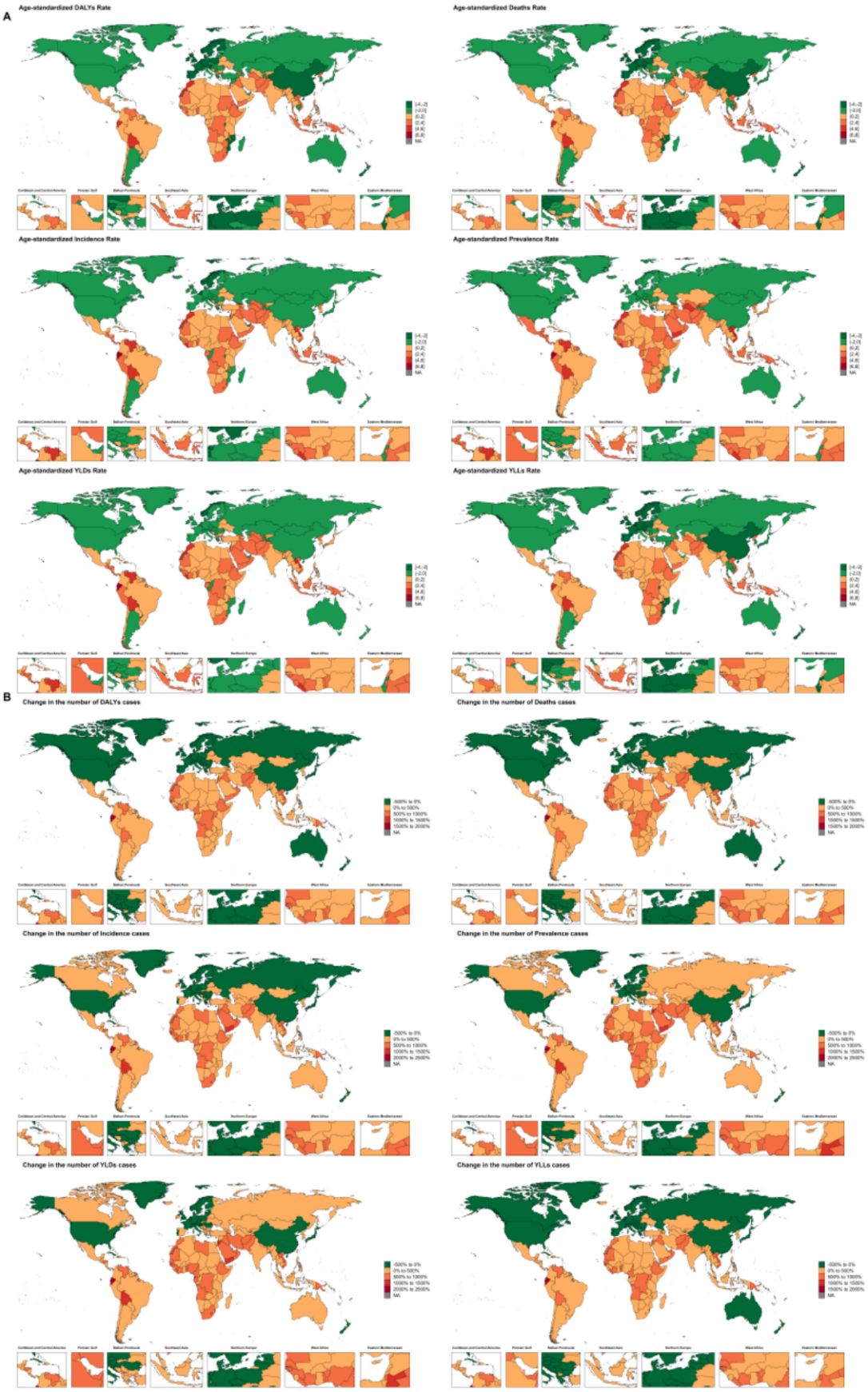


Figure 5 | The trend of ovarian cancer-related numbers and ASRs of Deaths, YLDs, YLLs, DALYs, Prevalence and Incidence between for different countries between 1990 and 2023. Abbreviations: ASR, age-standardized rate; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; DALYs, disability-adjusted-life-years.

163.14 (95% UI: 110.5–228.02), 3.15 (95% UI: 2.13–4.39), and 159.43 (95% UI: 107.99–222.80) per 100,000 respectively. Conversely, Incidence, Prevalence, and YLDs demonstrated U-shaped relationships with SDI but also peaked in Low SDI regions at 6.95 (95% UI: 4.61–9.92), 37.98 (95% UI: 24.78–54.73), and 3.70 (95% UI: 2.10–5.70) per 100,000. Regarding absolute case counts, all metrics followed U-shaped trajectories against SDI. DALYs [613,392.89 (95% UI: 414,749.78–838,907.05)], deaths [11,555.31 (95% UI: 7,835.69–15,812.80)], and YLLs [599,338.60 (95% UI: 405,138.01–823,123.04)] reached maxima in low SDI regions, whereas incidence [27,500.35 (95% UI: 24,489.77–30,864.43)], prevalence [177,940.57 (95% UI: 154,179.45–205,495.94)], and YLDs [17,167.04 (95% UI: 12,192.90–22,700.07)] peaked in high SDI regions.

The burden of OC exhibited substantial disparities across GBD regions. Notably, South Asia recorded the highest absolute numbers for all metrics: DALYs at 592,191.5 (95% UI: 422,329.42–818,170.5), Deaths at 11,395.52 (95% UI: 8,143.24–15,520.88), Incidence at 26,128.31 (95% UI: 17,579.17–36,298.87), Prevalence at 148,569.55 (95% UI: 98,965.07–209,447.6), YLDs at 14,159.5 (95% UI: 8,481.22–21,593.68), and YLLs at 578,032.01 (95% UI: 413,340.11–794,551.84). Conversely, Oceania showed the lowest absolute burden: DALYs: 1,660.9 (95% UI: 1,030.74–2,536.79); Deaths: 31.72 (95% UI: 19.77–48.51); Incidence: 72.91 (95% UI: 45.27–109.82); Prevalence: 406.21 (95% UI: 252.06–618.77); YLDs: 39.73 (95% UI: 22.33–69.11); YLLs: 1,621.17 (95% UI: 1,004.03–2,474.62). For ASR, Eastern Sub-Saharan Africa consistently demonstrated the highest values: 243.77 (95% UI: 160.32–346.86) for DALYs, 4.67 (95% UI: 3.08–6.62) for Deaths, 10.30 (95% UI: 6.79–14.78) for Incidence, 55.76 (95% UI: 35.96–81.85) for Prevalence, 5.40 (95% UI: 2.98–8.36) for YLDs, 238.37 (95% UI: 156.99–339.61) for YLLs. The lowest ASR values were regionally stratified: East Asia had minima for DALYs, Deaths and YLLs, while Oceania showed the lowest incidence, prevalence, and YLDs.

The OC burden varied considerably across countries. Regarding absolute case counts, India consistently exhibited the highest values for all metrics. The corresponding figures were DALYs at 311,445 (95% UI: 217,795.67–425,375.87), deaths at 6,136.51 (95% UI: 4,299.93–8,438.06), incidence at 13,871.93 (95% UI: 9,308.33–19,247.01), prevalence at 78,400.59 (95% UI: 52,410.81–110,781.71), YLDs at 7,694.35 (95% UI: 4,598.94–12,073.19), and YLLs at 303,750.65 (95% UI: 211,899.43–415,375.54). Conversely, Tokelau consistently recorded the smallest case counts across all metrics. For ASR, Uganda showed the highest values for all indicators: 387.06 (95% UI: 223.08–625.30) for DALYs, 7.35 (95% UI: 4.23–11.86) for Deaths, 18.55 (95% UI: 10.64–30.45) for Incidence, 102.42 (95% UI: 58.32–169.95) for Prevalence, 9.52 (95% UI: 3.79–18.64) for YLDs, and 377.54 (95% UI: 217.02–610.77) for YLLs. Kiribati demonstrated the lowest ASR values: 15.16 (95% UI: 9.02–22.81) for DALYs, 0.30 (95% UI: 0.18–0.45) for deaths, 0.58 (95% UI: 0.34–0.89) for incidence, 3.00 (95% UI: 1.76–4.64) for prevalence, 0.32 (95% UI: 0.17–0.54) for YLDs and 14.85 (95% UI: 8.83–22.33) for YLLs.

Drivers of Ovarian Cancer Epidemiology – Ageing, Population, and Epidemiological Change

To investigate the drivers of changes in the global burden of OC from 1990 to 2023, we conducted a decomposition analysis revealing that all three factors contributed to increased global burden. Aging accounted for increases of 6.97% in DALYs, 8.46% in deaths, 5.83% in incidence, 4.82% in prevalence, 6.30% in YLDs and 6.99% in YLLs. Population growth contributed 65.01% to DALYs, 65.33% to deaths, 61.24% to incidence, 58.53% to prevalence, 60.64% to YLDs and 65.15% to YLLs. Epidemiological changes accounted for increases of 28.02% for DALYs, 26.21% for deaths, 32.92% for incidence, 36.65% for prevalence, 33.05% for YLDs and 27.86% for YLLs.

The Predicted Results of Disease Burden for Ovarian Cancer From 2024 to 2050

To inform evidence-based policies for reducing OC burden, we projected future trends using three modeling approaches. The ARIMA model indicated aggressive surges in absolute case counts across all six metrics, while ASR remained largely stable except for increases in prevalence ASR and YLDs ASR. In contrast, the ES model projected more gradual increases in both absolute numbers and ASR for all metrics. The BAPC analysis consistently predicted rising burden trajectories. Despite the methodological heterogeneity among these projections, all models converge on acritical conclusion: the OC burden will continue its upward trajectory, underscoring the urgent need for effective interventions to mitigate this concerning trend (**Figure 6**).

MR Analysis

Among the risk factors examined, a significant causal with OC risk was identified for three adiposity-related traits. Specifically, HIP (OR=1.29 95% CI: 1.13-1.48, p=0.0002), childhood BMI [OR=1.22 ,95% CI: 1.07-1.39, p=0.0037] and WC [OR=1.28, 95% CI: 1.07-1.51, p=0.0054] were all positively associated with increased OC risk. Supplementary analyses (weighted median, simple median, maximum-likelihood method, and MR-Egger) detected no pleiotropy and the results remained robust. Detailed results are presented in **Table 1**.

DISCUSSION

This study presents a comprehensive evaluation of the global burden of OC among women of reproductive age from 1990 to 2023, integrating GBD estimates with MR evidence. We observed a significant resurgence in OC incidence, mortality, and DALYs in the past decade, especially in low- and middle-SDI regions. Concomitantly, the MR analysis identified central adiposity and childhood BMI as causal risk factors for OC, reinforcing the relevance of metabolic pathways in ovarian tumorigenesis. These findings highlight the shifting global epidemiological landscape of OC, with rising burden in younger women and increasing disparities between high- and low-resource settings.

Our study systematically characterizes the dynamic evolution of the global OC burden from 1990 to 2023. Although ASRs declined until 2014, a reversal has emerged over past decade, resulting in an increased burden of global public health concern, particularly among women of reproductive

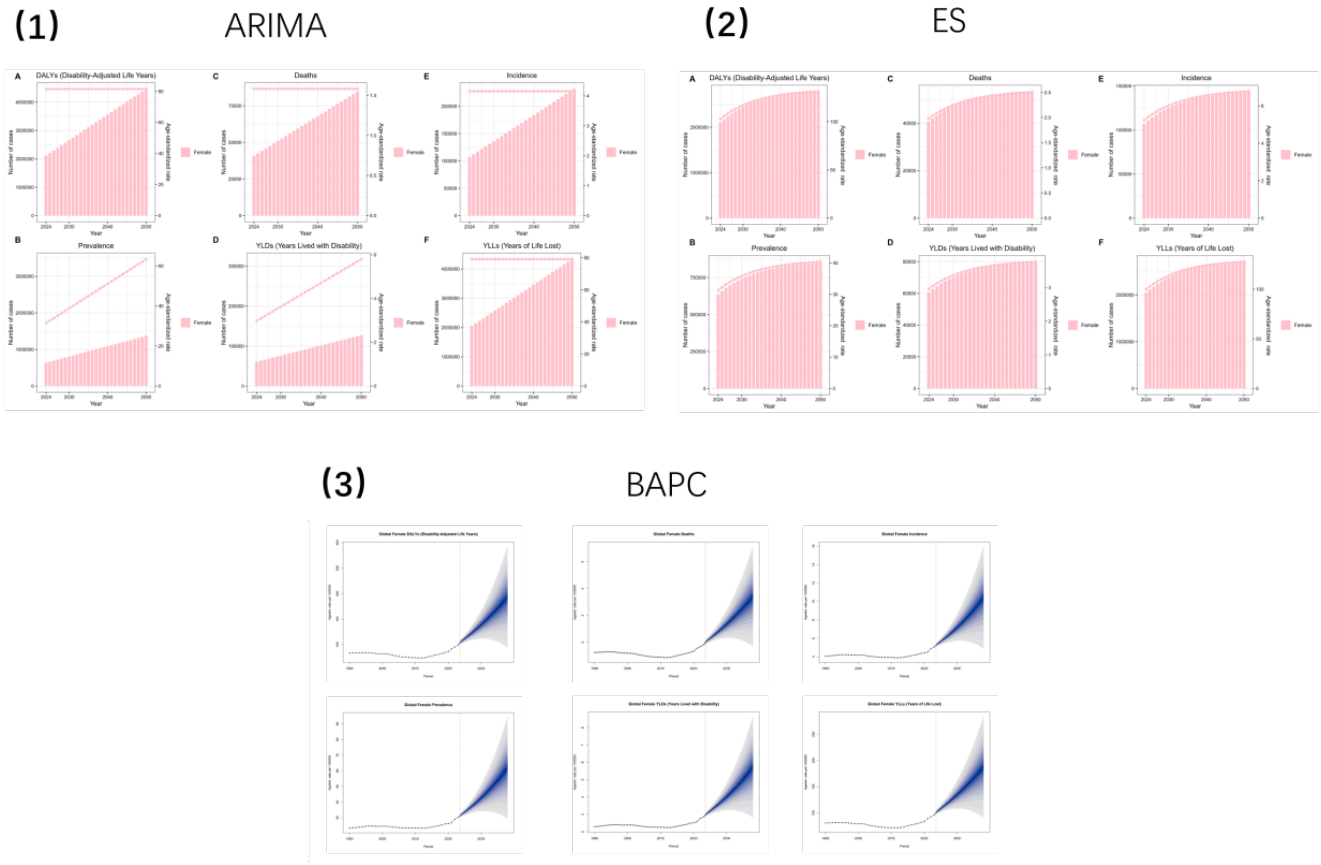
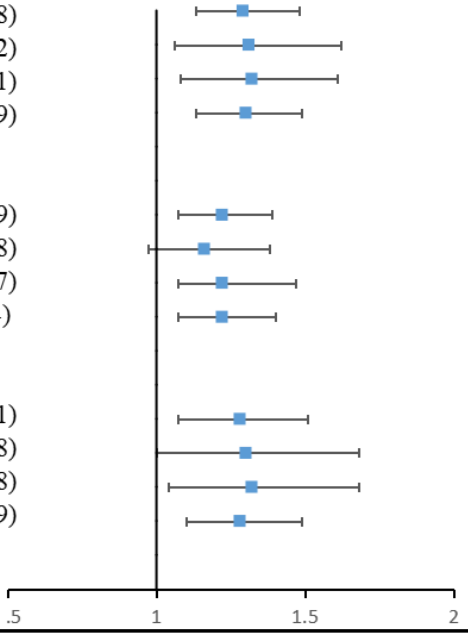


Figure 6 | The predicted results in ovarian cancer-related GBD of Deaths, YLDs, YLLs, DALYs, Prevalence and Incidence from 2024 to 2050. Abbreviations: ASR, age-standardized rate; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; DALYs, disability-adjusted-life-years.

Table. 1 | Results of Mendelian randomization analyses between multiple exposure and ovarian cancer.

Characteristics	SNPs	OR (95%CI)	*P* value	*P* intercept
HIP				
Inverse-variance weighted	53	1.29(1.13-1.48)	0.000	
Weighted median	53	1.31(1.06-1.62)	0.013	
Simple median	53	1.32(1.08-1.61)	0.008	
Maximum-likelihood method	53	1.30(1.13-1.49)	0.000	
MR-Egger	53			0.781
Childhood BMI				
Inverse-variance weighted	17	1.22(1.07-1.39)	0.004	
Weighted median	17	1.16(0.97-1.38)	0.112	
Simple median	17	1.22(1.07-1.47)	0.039	
Maximum-likelihood method	17	1.22(1.07-1.4)	0.003	
MR-Egger	17			0.254
WC				
Inverse-variance weighted	43	1.28(1.07-1.51)	0.005	
Weighted median	43	1.30(1.00-1.68)	0.049	
Simple median	43	1.32(1.04-1.68)	0.020	
Maximum-likelihood method	43	1.28(1.10-1.49)	0.001	
MR-Egger	43			0.875



age. This trend reversal is particularly pronounced in low- and middle-SDI regions, highlighting structural deficiencies in cancer early screening, treatment accessibility, and prevention systems[41]. Key drivers include escalating metabolic and reproductive risk factors, lagging screening programs, and the rising prevalence of endocrine-related diseases such as obesity and diabetes in emerging economies[1]. In 2023, south Asia contributed the highest absolute burden, whereas eastern sub-Saharan Africa recorded the highest ASRs, attributable to the combined effects of rapid population growth and under-resourced healthcare systems. In such low-resource settings, the lack of pathology services, late-stage diagnosis, and inadequate treatment options create a vicious cycle that further exacerbates the disease burden.

This study reveals a peak in the estimated annual EPIC for OC incidence, mortality, and DALYs among women aged 30 to 49 years. This indicates a notable shift of OC burden toward younger age groups, with profound implications for reproductive healath, psychological, and economic consequences[42, 43]. The rising incidence in this age group may be attributed to multiple factors, including increased metabolic risk linked to lifestyle modernization, delayed childbearing age, greater exposure to exogenous hormonal agents, and a high rate of underdiagnosis of hereditary ovarian cancer syndromes, especially in resource-constrained settings[44]. Importantly, in low-resource environments, these risk factors often co-occur alongside weak primary healthcare systems, amplifying the intergenerational transmission of disease burden. These findings provide critical evidence for reorienting ovarian cancer prevention and control strategies, emphasizing the need to enhance risk communication targeting young women, optimize reproductive health management, and establish genetic testing and early screening programs in resource-limited regions.

Furthermore, the marked rise in DALYs associated with OC is largely driven by ongoing epidemiologic transitions and population ageing, particularly in regions insufficient gynecologic oncology services. This underscores the urgent need for context-specific prevention strategies to be deployed in tandem with the expansion of early detection and diagnostic programs. Forecasting analyses indicate that, without coordinated and targeted intervention, the global burden of OC is expected to rise steadily through 2050. These projections are primarily influenced by demographic factor such as population growth and ageing, but also shaped by cancer subtype heterogeneity, emerging drug resistance, and diagnostic delays[45].

In this study, HIP, childhood BMI, and WC were identidied as significant risk factors for OC through MR analysis, aligning wtihresults from large-scale perspective cohorts, such as the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Nurses' Health Study[46, 47]. Notably, childhood BMI emerged as a risk factor, suggesting that early-life obesity may initiate long-tern distruptions in the metabolic-endeocrine-inflammatory axis via metabolic programming effects, therby creating a tissue microenvironment conducive to the malignant transformation of ovarian cells[48]. Mechanistically, excessive adiposity in both early and adult life can promote a state of chronic low-grade inflammation, hyperinsulinemia, and increased circulating estrogen levels through peripheral aromatization, collectively contributing to epithelial proliferation and genomic instability in the ovaries[49, 50]. Additionally, central obesity—as indicated by increased WC—is closely associated with insulin resistance and altered adipokine secretion (e.g., elevated leptin and reduced adiponectin), both of which have been implicated in tumorigenesis and poor prognosis in OC[51]. The robust association between HIP and OC may also reflect a hormonally regulated pattern of fat distribution that modulates local and systemic estrogenic signaling[52]. These findings reinforce the importance of considering life-course adiposity as a critical determinant in OC prevention and highlight the potential utility of early metabolic risk modification strategies.

Several limitations of this study must be acknowledged. First, the GBD estimates are derived from statistical modeling based on heterogeneous data sources, and their accuracy depends on the completeness and quality of cancer surveillance systems. Second, our MR analyses relied primarily on GWAS from populations of European ancestry, which may limit the generalizability of causal inferences to other ethnic groups, especially in regions where OC incidence is rising but genetic data remain scarce. Third, the univariable MR employed, while robust for detecting direct causal effects, does not account for potential mediation effects, gene-environment interactions, or horizontal pleiotropy. Given that OC is multifactorial disease, complex interdependencies among metabolic, hormonal, and reproductive factors may

influence effect estimates and causal pathways. Moreover, although the biological mechanisms linking adiposity-related traits to OC risk are plausible, they remain incompletely understood. Finally, our MR findings should be interpreted as hypothesis-generating rather than confirmatory. Further experimental and longitudinal studies, including multi-omics profiling and life-course cohorts, are needed to validate these associations and elucidate underlying mechanisms.

CONCLUSION

In summary, our findings underscore the increasing global burden of OC among women of reproductive age and establish a causal link between early-life and central adiposity and OC risk. These insights emphasize the need for age- and context-specific interventions that integrate metabolic health, reproductive counseling, and access to early detection. As OC increasingly affects younger women across diverse regions, it is imperative to translate epidemiologic and genetic insights into scalable, equity-focused public health strategies.

References

1. Li T, Zhang H, Lian M, He Q, Lv M, Zhai L, Zhou J, Wu K, Yi M: Global status and attributable risk factors of breast, cervical, ovarian, and uterine cancers from 1990 to 2021. J Hematol Oncol 2025, 18(1):5.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024, 74(3):229-263.
3. Lheureux S, Braunstein M, Oza AM: Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin 2019, 69(4):280-304.
4. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL: Ovarian cancer statistics, 2018. CA Cancer J Clin 2018, 68(4):284-296.
5. Kurman RJ, Shih Ie M: The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. Am J Pathol 2016, 186(4):733-747.
6. Bowtell DD, Bohm S, Ahmed AA, Aspuria PJ, Bast RC, Jr., Beral V, Berek JS, Birrer MJ, Blagden S, Bookman MA et al: Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer 2015, 15(11):668-679.
7. Tavares V, Marques IS, Melo IG, Assis J, Pereira D, Medeiros R: Paradigm Shift: A Comprehensive Review of Ovarian Cancer Management in

an Era of Advancements. Int J Mol Sci 2024, 25(3).
8. Stewart C, Ralyea C, Lockwood S: Ovarian Cancer: An Integrated Review. Semin Oncol Nurs 2019, 35(2):151-156.
9. Moorman PG, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, Funkhouser E, Peters ES, Schwartz AG, Terry P et al: Reproductive factors and ovarian cancer risk in African-American women. Ann Epidemiol 2016, 26(9):654-662.
10. Lin Y, Liang X, Zhang X, Ni Y, Zhou X, Zhao X: Metabolic cross-talk between ovarian cancer and the tumor microenvironment-providing potential targets for cancer therapy. Front Biosci (Landmark Ed) 2022, 27(4):139.
11. Chia ML, Bulat F, Gaunt A, Ros S, Wright AJ, Sawle A, Porcu L, Vias M, Brenton JD, Brindle KM: Metabolic imaging distinguishes ovarian cancer subtypes and detects their early and variable responses to treatment. Oncogene 2025, 44(9):563-574.
12. Khandekar MJ, Cohen P, Spiegelman BM: Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011, 11(12):886-895.
13. Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson GL, Beresford SA, Pettinger M, Lane DS, Lessin L, Yasmeen S et al: Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2007, 99(20):1534-1543.
14. Khanlarkhani N, Azizi E, Amidi F, Khodarahmian M, Salehi E, Pazhohan A, Farhood B, Mortezae K, Goradel NH, Nashtaei MS: Metabolic risk factors of ovarian cancer: a review. JBRA Assist Reprod 2022, 26(2):335-347.
15. Jin JH, Kim HJ, Kim CY, Kim YH, Ju W, Kim SC: Association of plasma adiponectin and leptin levels with the development and progression of ovarian cancer. Obstet Gynecol Sci 2016, 59(4):279-285.
16. Davies NM, Holmes MV, Davey Smith G: Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018, 362:k601.
17. Wang L, Li X, Wang Y, Li G, Dai S, Cao M, Meng Z, Ren S: Endometriosis and epithelial ovarian cancer: a two-sample Mendelian randomization analysis. Sci Rep 2023, 13(1):21992.
18. Harris HR, Cushing-Haugen KL, Webb PM, Nagle CM, Jordan SJ, Australian Ovarian Cancer Study G, Risch HA, Rossing MA, Doherty JA, Goodman MT et al: Association between genetically predicted polycystic ovary syndrome and ovarian cancer: a Mendelian randomization study. Int J Epidemiol 2019, 48(3):822-830.
19. Choi YJ, Myung SK, Lee JH: Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies. Cancer research and treatment 2018, 50(2):474-487.
20. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 2018, 392(10159):1789-1858.
21. Mangum KD, Farber MA: Genetic and epigenetic regulation of abdominal aortic aneurysms. Clinical genetics 2020, 97(6):815-826.
22. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England) 2020, 396(10258):1204-1222.
23. Li Y, Zheng Q, Sun D, Cui X, Chen S, Bulbul A, Liu S, Yan Q: Dehydroepiandrosterone stimulates inflammation and impairs ovarian functions of polycystic ovary syndrome. J Cell Physiol 2019, 234(5):7435-7447.
24. Wootton RE, Richmond RC, Stuijfzand BG, Lawn RB, Sallis HM, Taylor GMJ, Hemani G, Jones HJ, Zammit S, Davey Smith G et al: Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. Psychological medicine 2020, 50(14):2435-2443.
25. Kranzler HR, Zhou H, Kember RL, Vickers Smith R, Justice AC, Damrauer S, Tsao PS, Klarin D, Baras A, Reid J et al: Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. Nat Commun 2019, 10(1):1499.
26. Cornelis MC, Byrne EM, Esko T, Nalls MA, Ganna A, Paynter N, Monda KL, Amin N, Fischer K, Renstrom F et al: Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. Molecular psychiatry 2015, 20(5):647-656.
27. Jones SE, Lane JM, Wood AR, van Hees VT, Tyrrell J, Beaumont RN, Jeffries AR, Dashti HS, Hillsdon M, Ruth KS et al: Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun 2019, 10(1):343.
28. Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, Strand LB, Winsvold BS, Wang H, Bowden J et al: Biological and clinical insights from genetics of insomnia symptoms. Nature genetics 2019, 51(3):387-393.
29. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG 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.
30. Klimentidis YC, Raichlen DA, Bea J, Garcia DO, Wineinger NE, Mandarino LJ, Alexander GE, Chen Z, Going SB: Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including CADM2 and APOE. International journal of obesity (2005) 2018, 42(6):1161-1176.
31. van de Vegte YJ, Said MA, Rienstra M, van der Harst P, Verweij N: Genome-wide association studies and Mendelian randomization analyses for leisure sedentary behaviours. Nature communications 2020, 11(1):1770.
32. Phelan CM, Kuchenbaecker KB, Tyrer JP, Kar SP, Lawrenson K, Winham SJ, Dennis J, Pirie A, Riggan MJ, Chornokur G et al: Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nature genetics 2017, 49(5):680-691.
33. Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, Smoller JW, Major Depressive Disorder Working Group of the Psychiatric Genomics C: Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry 2019, 76(4):399-408.
34. Cai J, Li X, Wu S, Tian Y, Zhang Y, Wei Z, Jin Z, Li X, Chen X, Chen WX: Assessing the causal association between human blood metabolites and the risk of epilepsy. Journal of translational medicine 2022, 20(1):437.
35. Sun J, Zhao J, Jiang F, Wang L, Xiao Q, Han F, Chen J, Yuan S, Wei J, Larsson SC et al: Identification of novel protein biomarkers and drug targets for colorectal cancer by integrating human plasma proteome with genome. Genome Med 2023, 15(1):75.
36. Chen J, Xu F, Ruan X, Sun J, Zhang Y, Zhang H, Zhao J, Zheng J, Larsson SC, Wang X et al: Therapeutic targets for inflammatory bowel disease: proteome-wide Mendelian randomization and colocalization analyses. EBioMedicine 2023, 89:104494.
37. Sun J, Luo J, Jiang F, Zhao J, Zhou S, Wang L, Zhang D, Ding Y, Li X: Exploring the cross-cancer effect of circulating proteins and discovering potential intervention targets for 13 site-specific cancers. J Natl Cancer Inst 2024, 116(4):565-573.
38. Bowden J, Davey Smith G, Haycock PC, Burgess S: Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic epidemiology 2016, 40(4):304-314.
39. Bowden J, Davey Smith G, Burgess S: Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. International journal of epidemiology 2015, 44(2):512-525.
40. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I et al: Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2019, 5(12):1749-1768.
41. Yuk JS, Kim M: Incidence and prevalence of primary ovarian insufficiency in South Korea: a population-based study. Arch Gynecol Obstet 2021, 304(3):823-831.
42. Armidie TA, Bandera EV, Johnson CE, Peres LC, Haller K, Terry P, Akonde M, Peters ES, Cote ML, Hastert TA et al: Diet and Survival in Black Women With Epithelial Ovarian Cancer. JAMA Netw Open 2024, 7(10):e2440279.
43. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021, 71(3):209-249.
44. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A: Cancer statistics, 2025. CA Cancer J Clin 2025, 75(1):10-45.
45. Kotsopoulos J, Baer HJ, Tworoger SS: Anthropometric measures and risk of epithelial ovarian cancer: results from the nurses' health study. Obesity (Silver Spring) 2010, 18(8):1625-1631.
46. Huang T, Tworoger SS, Willett WC, Stampfer MJ, Rosner BA: Associations of early life and adulthood adiposity with risk of epithelial ovarian cancer. Ann Oncol 2019, 30(2):303-309.
47. Llewellyn A, Simmonds M, Owen CG, Woolacott N: Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev 2016, 17(1):56-67.
48. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA: Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. J Clin Oncol 2016, 34(35):4270-4276.
49. Quail DF, Dannenberg AJ: The obese adipose tissue microenvironment in cancer development and progression. Nat Rev Endocrinol 2019, 15(3):139-154.
50. Craig ER, Londono AI, Norian LA, Arend RC: Metabolic risk factors and mechanisms of disease in epithelial ovarian cancer: A review. Gynecol Oncol 2016, 143(3):674-683.
51. Pasquali R: Obesity and androgens: facts and perspectives. Fertil Steril 2006, 85(5):1319-1340.