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Association between metabolic syndrome and risk of endometrial cancer; a systematic review and meta-analysis

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Abstract

Introduction: Endometrial cancer is one of the most prevalent female malignancies, with various factors, including metabolic syndrome, contributing to its incidence. Thus, this study aims to evaluate the association between metabolic syndrome and the risk of endometrial carcinoma.

Materials and Methods: In this systematic review and meta-analysis, two independent authors searched electronic databases, including Cochrane, PubMed, ProQuest, Web of Science, and the Google Scholar search engine up to May 16, 2024. Data analysis was conducted using STATA 14 software with a significance level of $P < 0.05$ for all tests.

Results: A pooled analysis of 12 observational studies found that metabolic syndrome elevated the risk of endometrial carcinoma by 37% overall (OR: 1.37, 95% CI: 1.33, 1.42), 35% in cohort studies (OR: 1.35, 95% CI: 1.29, 1.42), and 40% in case-control studies (OR: 1.40, 95% CI: 1.33, 1.48). However, hypertension increased the risk of endometrial carcinoma by 25% (OR: 1.25, 95% CI: 1.18, 1.33), fasting hyperglycemia by 25% (OR: 1.25, 95% CI: 1.15, 1.37), hypertriglyceridemia by 17% (OR: 1.17, 95% CI: 1.13, 1.21), low high density lipoprotein (HDL) by 20% (OR:1.20, 95% CI: 1.12, 1.28), increased waist circumference by 59% (OR:1.59, 95% CI: 1.43, 1.77), pre-menopausal period by 67% (OR:1.67, 95% CI: 1.38, 2.02), and post-menopausal period by 61% (OR: 1.61, 95% CI: 1.17, 2.21). Likewise, obesity almost doubled the risk of endometrial carcinoma (OR: 2.13, 95% CI: 1.65, 2.75).

Conclusion: Metabolic syndrome increases the risk of endometrial carcinoma, with obesity being the most dangerous risk factor for endometrial cancer. Thus, managing metabolic disorders in women can be an important step toward reducing the incidence of endometrial cancer.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024551509) and Research Registry (UIN: reviewregistry1838).

Introduction

Metabolic syndrome is a pathological condition characterized by abdominal obesity, insulin resistance, dyslipidemia, hypertension, and hyperglycemia (1,2). It is a common clinical condition in countries with a high obesity prevalence and Western dietary patterns (3), affecting over 20% of adults in most Asian-Pacific countries (4) and nearly one-third of the adult population in the US (5). Chronic kidney disease and metabolic syndrome are significant public health problems worldwide. Diabetes and hypertension are the most important risk factors for chronic kidney disease. In addition, obesity and metabolic syndrome are independent predictors of chronic kidney disease (6).

According to the most recent GLOBOCAN data, endometrial cancer ranks second in the global incidence rate. In 2020, 417 000 new cases and 97 000 deaths of endometrial carcinoma have been reported (7), with early

Key point

In this study, we found that metabolic syndrome significantly elevates the risk of endometrial carcinoma, with obesity being the most critical risk factor for endometrial cancer. Healthcare providers should prioritize identifying and managing metabolic disorders, particularly obesity, in women to reduce the risk of endometrial carcinoma, educate patients on the importance of maintaining a healthy weight, and provide resources for weight management, such as nutrition counseling and support groups. By addressing metabolic disorders through these interventions, healthcare providers can play a crucial role in reducing the incidence of endometrial cancer and improving overall women's health outcomes.

menstruation (menarche), late menopause, infertility, post-menopausal hormone therapy, and obesity identified as risk factors. These risk factors are primarily associated with unopposed estrogen, as well as a family history of endometrial carcinoma, type 2 diabetes, hypertension, physical activity, and dietary factors (8). With changes in lifestyle and a rise in the occurrence of metabolic disorders, the incidence and mortality of endometrial carcinoma have grown globally. In the United States alone, its incidence is expected to reach 42.13 cases per 100 000 individuals by 2030 (9). Endometrial carcinoma is more likely to be diagnosed post-menopause and after the age of 60 years. However, obesity is linked with endometrial carcinoma diagnosis at younger ages (10,11).

Various studies have suggested a significant relationship between metabolic syndrome and increased risk of carcinomas, including prostate, colorectal, and breast carcinoma (12-14). However, contradicting results have been reported regarding the association between metabolic syndrome and endometrial carcinoma. Some studies have identified metabolic syndrome as a strong risk factor for endometrial cancer occurrence (15-17), while others found no significant statistical relationship between metabolic syndrome and endometrial carcinoma (18,19). Moreover, a previous meta-analysis conducted on this subject reviewed the studies published up to 2019 (20). However, the present systematic review and meta-analysis involves more up-to-date studies until 2024 and presents an updated comprehensive conclusion.

Materials and Methods

This study was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (21). The study protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) and Research Registry websites.

Search strategy

Two qualified researchers independently searched electronic databases, including Cochrane, PubMed, ProQuest, Web of Science, and the Google Scholar search engine from inception until May 16, 2024. The following keywords were used in search strategies: "Metabolic Syndrome," "Endometrial Neoplasms," "Endometrial Carcinoma," "Reaven Syndrome X," "Insulin Resistance Syndrome X," and "Endometrium Cancer." A simple search was conducted using Medical Subject Headings (Mesh) terms and their equivalents. For advanced searches, a combination of keywords using Boolean operators ("AND" and "OR") was utilized. The reference list of primary studies was manually searched to ensure a thorough query and minimize the chance of missing relevant sources and errors in the search phase. The following search strategy in the PubMed database was adopted: ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrial"[All Fields] AND "carcinoma"[All Fields]) OR "endometrial carcinoma"[All Fields]) OR ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrium"[All Fields] AND "cancer"[All Fields]) OR "endometrium cancer"[All Fields])) AND ("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields] OR ("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields] OR "reaven syndrome x"[All Fields]) OR ("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields] OR "insulin resistance syndrome x"[All Fields])).

PICO framework

Population: Studies that assessed the relationship between metabolic syndrome and endometrial cancer in women.
Exposure: Metabolic syndrome development.
Comparison: The comparison group involved women without endometrial cancer or metabolic syndrome.
Outcome: Odds ratio (OR) of the relationship between metabolic syndrome and the risk of endometrial carcinoma.

Inclusion criteria

Observational studies that evaluated the association between metabolic syndrome and the risk of endometrial carcinoma in women.

Exclusion criteria

Duplicate studies (only one study from each category was retained); non-observational studies; review articles and meta-analyses; studies that reported qualitative results; conference and symposium articles; journal articles published as abstracts; studies with a quality score of less than five based on Newcastle-Ottawa Scale (NOS) instrument; studies examining the relationship between

metabolic syndrome and other endometrial disorders (other than endometrial carcinoma); studies whose full-text was unavailable; studies lacking adequate data for analysis.

Quality assessment

Two authors independently assessed the quality of studies using the 9-item NOS instrument. The NOS scoring ranges from zero to 10, with 0 indicating the lowest quality and 10 indicating the highest quality. A NOS cut-off score of 5 was set in this study, and articles with a score of ≥5 were considered high-quality (22).

Data extraction

Two researchers independently completed the data checklist. The following data were extracted: the author's name, number of patients, publication year, study duration, the average age of patients, study design, the country of study, the OR of the relationship between hypertension and endometrial carcinoma, the OR of the relationship between fasting blood sugar and endometrial carcinoma, the OR of the relationship between elevated triglyceride and endometrial cancer, the OR of the relationship between reduced high density lipoprotein (HDL) and endometrial cancer, the OR of the relationship between overweight and endometrial cancer, the OR of the relationship between obesity and endometrial cancer, the OR of the relationship between menopause and endometrial carcinoma, the OR of the relationship between waist circumference and endometrial cancer, the OR of the relationship between metabolic syndrome and endometrial carcinoma, along with its upper and lower limits.

Statistical analysis

The indices analyzed in the articles included OR, hazard ratio (HR), risk ratio (RR), and standard incidence ratio (SIR). The logarithm of indices for each study was applied, and studies were pooled for data analysis. The between-studies heterogeneity was assessed using the I^2 index. A fixed-effects model was adopted for low heterogeneity between studies, and a random-effects model was utilized for high heterogeneity between studies. Data were analyzed in STATA 14 software. The significance level was set at $P < 0.05$ for all tests.

Results

Of the 529 articles initially retrieved from the database search, 213 duplicates were discarded. The abstracts of the remaining 316 articles were screened, and 23 studies whose full texts were inaccessible were eliminated. From the remaining 293 articles, another 42 were excluded due to inadequate data for analysis. 239 out of 251 remaining articles that met other exclusion criteria were removed. Eventually, 12 articles entered the systematic review and meta-analysis process (Figure 1).

This meta-analysis involved twelve observational

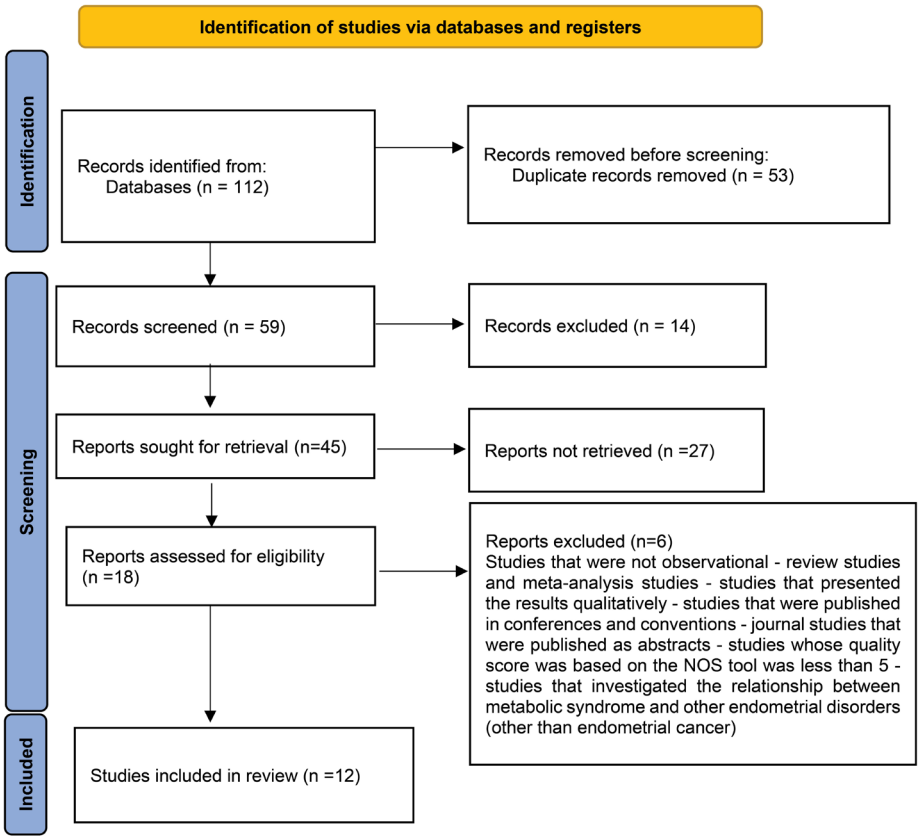

Figure 1. The PRISMA flow chart of study selection.

Table 1. Summarized information of the studies

Author, year	Country	Type of Study	Sample size	Mean age (year)	Index	Duration of study	Association between metabolic syndrome and risk of endometrial carcinoma		
							Risk	Low	Up
Tran TX, 2023 (15)	South Korea	Cohort	3031980	≥ 40	HR	2009-2012	1.22	1.11	1.34
Park B, 2022(17)	South Korea	Cohort	6097686	≥40	HR	between 2009 and 2010	1.42	1.34	1.5
Jo H, 2022 (16)	South Korea	Cohort	2824107	54.02	HR	From Jan 1 to Dec 31, 2009	1.36	1.28	1.44
Lopez-Jimenez T, 2022 (23)	Spain	Case-control	NR	NR	OR	between Jan. 2008 and Dec 2017	NR	NR	NR
Cao Z, 2020 (18)	UK	Cohort	390575	37-73	HR	2006–2016	1.14	0.81	1.61
Arthur RS, 2019 (19)	USA	Cohort	24210	50-79	HR	between 1993 and 1998	1.34	0.97	1.84
Trabert B, 2015 (24)	USA	Case-control	NR	NR	OR	from 1993 through 2007	1.39	1.32	1.47
Friedenreich CM, 2011 (25)	Canada	Case-control	NR	NR	OR	2002–2006	1.53	1.17	2
Rosato V, 2011 (26)	Italy	Case-control	NR	NR	OR	between 1992 and 2006	1.98	1.14	3.44
Bjorge T, 2010 (27)	Austria, Norway and Sweden	Cohort	290000	NR	RR	1974–2005	1.37	1.28	1.46
Russo A, 2008 (28)	Italy	Cohort	16677	≥40	SIR	between 1 Jan 1999 and 31 Dec 2005	1.56	0.95	2.41
Cust AE, 2007 (29)	Europe	Case-control	NR	NR	RR	between Jun 1999 and Dec 2003	1.62	1.08	2.41

NR: not reported.

studies (seven cohort and five case-control studies). Table 1 provides detailed information on the reviewed articles.

Overall, regardless of the study type, metabolic syndrome increased the risk of endometrial cancer by 37% (OR: 1.37, 95% CI: 1.33, 1.42) (Figure 2). When stratified by study design, metabolic syndrome elevated the risk of endometrial carcinoma by 35% in cohort studies (OR: 1.35, 95% CI: 1.29, 1.42) and by 40% in case-control studies (OR: 1.40, 95% CI: 1.33, 1.48) (Figure 3). Thus, from these observations, metabolic syndrome can be considered a serious risk factor for endometrial carcinoma development.

In subgroup analyses by metabolic syndrome components, hypertension elevated the risk of endometrial cancer in women by 25% (OR: 1.25, 95% CI: 1.18, 1.33), fasting hyperglycemia by 25% (OR: 1.25, 95% CI: 1.15, 1.37), hypertriglyceridemia by 17% (OR: 1.17, 95% CI: 1.13, 1.21), and reduced HDL by 20% (OR: 1.20, 95% CI: 1.12, 1.28) (Figures 4-7).

No statistically significant association was noted between overweight and the risk of endometrial carcinoma (OR: 1.38, 95% CI: 0.91, 2.08) (Figure 8).

However, increased waist circumference was associated with a 59% (OR: 1.59, 95% CI: 1.43, 1.77), pre-menopausal status with a 67% (OR: 1.67, 95% CI: 1.38, 2.02), post-menopausal status with a 61% (OR: 1.61, 95% CI: 1.17, 2.21), and obesity with a nearly twofold increase in the risk of endometrial carcinoma (OR: 2.13, 95% CI: 1.65, 2.75) (Figures 9-12).

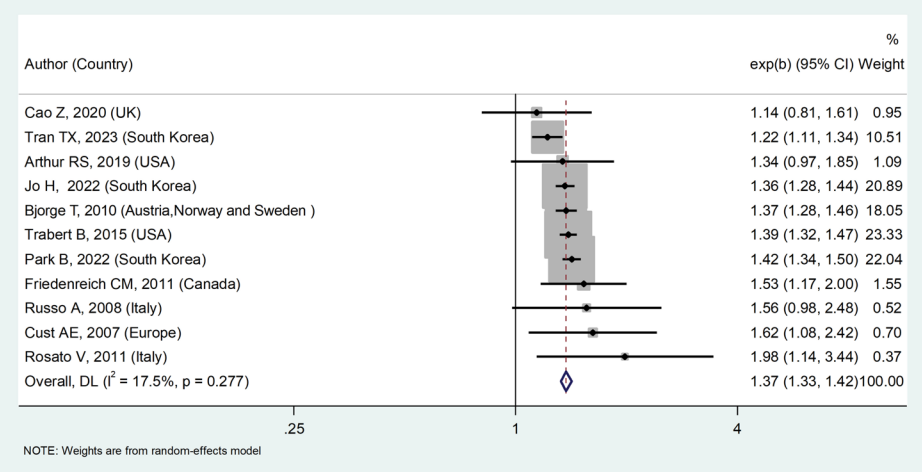

Figure 2. Forest plot showing the association between metabolic syndrome and risk of endometrial cancer.

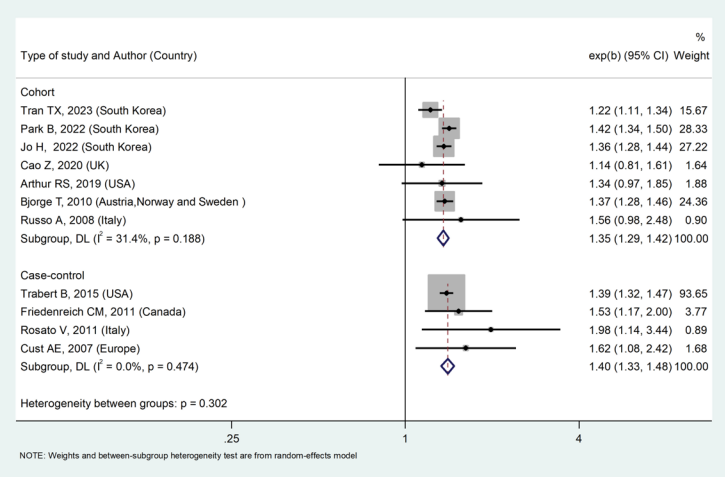

Figure 3. Forest plot showing the association between metabolic syndrome and risk of endometrial cancer by type of studies.

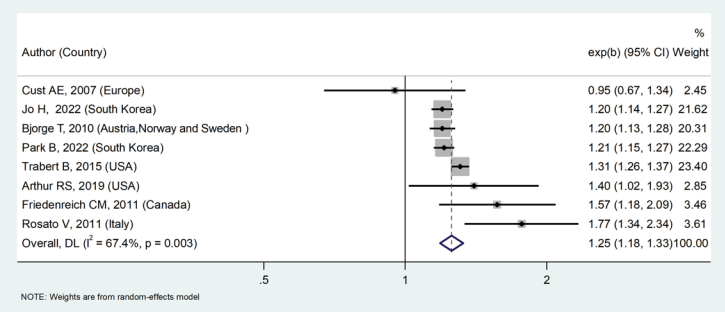

Figure 4. Forest plot showing the association between blood pressure and risk of endometrial cancer.

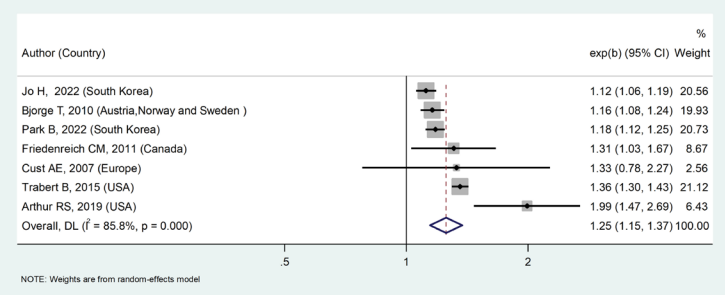

Figure 5. Forest plot showing the association between fasting blood glucose and risk of endometrial cancer.

Discussion

The pooled results of 12 cohort and case-control studies indicated that metabolic syndrome increased the risk of endometrial carcinoma by 37%.

A meta-analysis by Wang et al involving six studies revealed that women with metabolic syndrome are at a higher risk of endometrial carcinoma compared to healthy women (OR: 1.45, 95% CI: 1.16, 1.81) (20). In another meta-analysis by Esposito et al, metabolic syndrome was associated with an elevated risk of endometrial carcinoma (RR: 1.89, 95 % CI: 1.34, 2.67) (30). Esposito et al conducted a meta-analysis to evaluate the relationship between metabolic syndrome and the risk of some cancers. By pooling the results of cohort studies, the authors showed that metabolic syndrome elevates the risk of endometrial cancer (RR: 1.61, 95% CI: 1.2, 2.15) (31). The findings of these meta-analyses are consistent with our results in that the present meta-analysis also identified metabolic syndrome as a significant risk factor for endometrial cancer by pooling the results of 12 observational studies. However, our meta-analysis was more comprehensive and up-to-date than previous ones.

Several studies have highlighted metabolic syndrome as a risk factor not only for endometrial carcinoma but also for breast carcinoma in women. In their meta-analysis, Gue et al found that metabolic syndrome was associated with an increased risk of breast carcinoma incidence (RR: 1.15, 95% CI: 1.05, 1.26) (32). Another meta-analysis

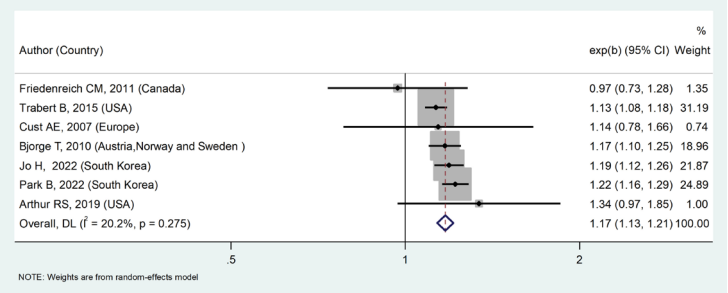

Figure 6. Forest plot showing the association between TG and risk of endometrial cancer.

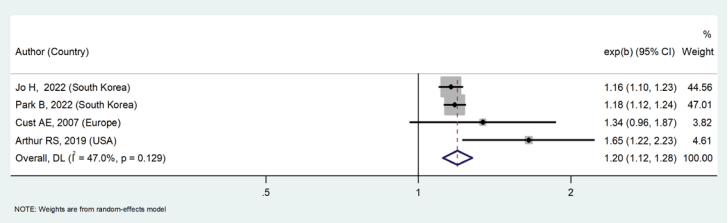

Figure 7. Forest plot showing the association between HDL and risk of endometrial cancer.

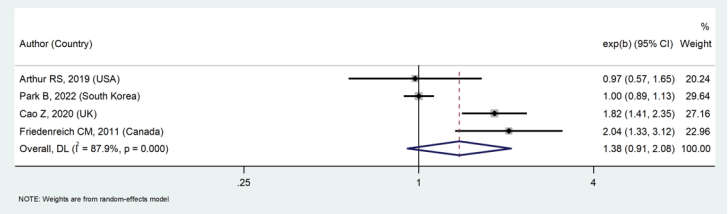

Figure 8. Forest plot showing the association between overweight and risk of endometrial cancer.

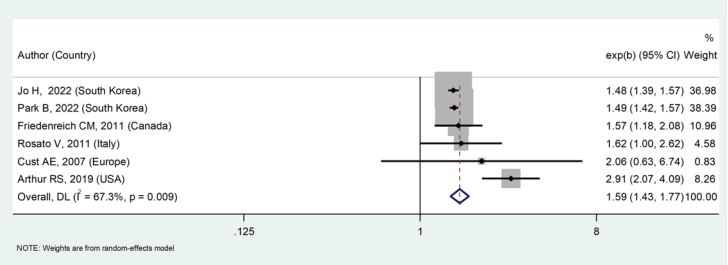

Figure 9. Forest plot showing the association between waist circumference and risk of endometrial cancer.

by Bhandari et al supported this result and suggested a positive correlation between metabolic syndrome and the elevated risk of breast carcinoma in women (RR: 1.47, 95% CI: 1.15, 1.87) (33).

Chen et al conducted a meta-analysis to explore the association between metabolic syndrome and ovarian cancer in women and found no statistically significant relationship (OR: 1.29, 95% CI: 0.90, 1.84) (34). Despite increasing the risk of endometrial cancer, metabolic syndrome had no association with ovarian cancer, which contradicts the results of the present meta-analysis.

Du et al performed a meta-analysis and concluded that metabolic syndrome was linked with an increased risk of renal cell carcinoma in adults (RR: 1.62, 95% CI: 1.41, 1.87) (35). In a meta-analysis by Jinjuvadia et al, metabolic syndrome resulted in a marked increase in the risk of liver carcinoma (RR: 1.81, 95% CI: 1.37, 2.41) (36). Another meta-analysis by Shen et al reported that metabolic syndrome significantly elevated the risk of colon carcinoma in both males and females (RR: 1.36, 95% CI: 1.26, 1.47) (37). The mentioned studies corroborate the findings of the current meta-analysis, suggesting that metabolic syndrome not only elevates the risk of female carcinomas (endometrial and breast carcinoma) but also the risk of liver, kidney, and colorectal cancers. These results are not surprising given the metabolic

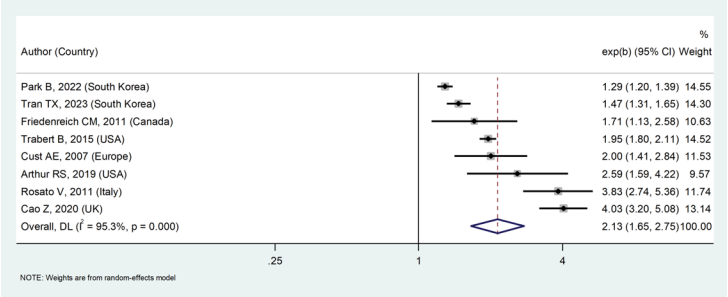

Figure 10. Forest plot showing the association between obese and risk of endometrial cancer.

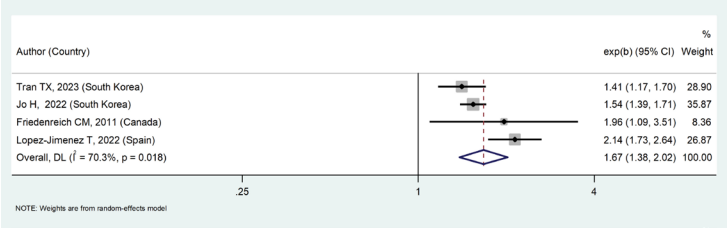

Figure 11. Forest plot showing the association between premenopausal and risk of endometrial cancer.

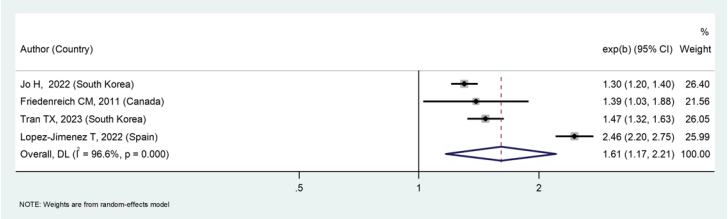

Figure 12. Forest plot showing the association between postmenopausal and risk of endometrial cancer.

syndrome constituent components because hyperglycemia, hypertriglyceridemia, and hypertension are the underlying causes of many diseases, including cancers.

Results of a meta-analysis by Mariani et al indicated no relationship between metabolic syndrome and the risk of gastric cancer (HR: 1.05, 95% CI: 0.92, 1.18) (38). In another meta-analysis by Qiao et al, neither the metabolic syndrome defined by the revised NCEP-ATP III criteria (HR: 0.94, 95% CI: 0.84, 1.05) nor the metabolic syndrome defined by the IDF criteria (HR: 0.82, 95% CI: 0.61, 1.11) were significantly associated with lung cancer (39). While the findings of these studies contrast with the present meta-analysis, these inconsistencies can be explained by differences in the type of disease and the statistical population across these studies.

Conclusion

Metabolic syndrome significantly elevated the risk of endometrial carcinoma. The most significant risk factors of endometrial carcinoma were obesity, pre-menopausal period, post-menopausal period, increased waist circumference, hypertension, fasting hyperglycemia, decreased HDL, and increased triglyceride. In addition, overweight did not change the likelihood of endometrial cancer incidence in women. Given the rising occurrence of endometrial cancer and considering the metabolic syndrome components as significant risk factors of endometrial cancer, the effective management of metabolic disorders in women can substantially lower the risk of endometrial cancer.

Limitations of the study

The present meta-analysis faces some limitations. First, it was not possible to analyze the relationship between metabolic syndrome and endometrial cancer risk by age in women. Moreover, only a limited number of studies were included in the meta-analysis, and studies were conducted unevenly across various geographical regions worldwide. Further research is suggested to address these limitations.

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Authors' contribution

Conceptualization: Sheida Abbasi and Fariba Bazi.
Data curation: Elmira Hosseini and Zahra Hamidi Madani.
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Investigation: Zeinab Zamanpour and Sheida Abbasi.
Methodology: Jalal Rezaei and Sadaf Rassouli.

Project Management: Zahra Hamidi Madani.
Resources: All authors.
Supervision: Sheida Abbasi.
Validation: Moloud Alsadat Mousavi.
Visualization: Marziyeh Noori.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical considerations

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42024551509) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1838). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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