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Systematic Review

Risk of gynaecologic cancers in women with metabolic syndrome: A systematic review & meta-analysis

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***Background & objectives*: Metabolic syndrome may be associated with the risk of gynaecological cancers. This systematic review aims to evaluate the risk of gynaecological cancers among women with metabolic syndrome.**

***Methods*: Studies published in English using a search strategy across PubMed, Google Scholar, and Scopus were identified from the earliest available indexing of the respective databases up to September 12-14, 2023. After removing duplicates and conducting a detailed screening by two independent reviewers, 25 studies were identified. Critical appraisal was conducted using JBI checklists for case-control and cohort studies and AXIS checklist for cross-sectional studies. Data extraction was conducted for information pertaining to study design, participant demographics, definition of metabolic syndrome, reported summary measures and type of gynaecological cancer.**

***Results*: Random effects models were employed separately for each study design, reported summary measures and the type of gynaecological cancers. In case-control, cross-sectional, and cohort studies, presence of metabolic syndrome was associated with uterine/endometrial cancer [odds ratio (OR) 1.99, $P<0.01$, OR 2.64, $P<0.01$, hazard ratio (HR) 1.45, $P=0.04$], respectively. Case-control and cohort studies in ovarian cancer suggested association (OR 3.44, $P<0.01$, OR 1.02, $P=0.79$, and HR 1.02, $P=0.80$). Cohort studies in cervical cancer patients, yielded HR 1.26, $P=0.96$ and adjusted HR 1.27, $P=0.83$. The critical appraisal of the included studies was high. GRADE reported low-quality evidence for cervical, uterine/endometrial, and ovarian cancer.**

***Interpretation & conclusions*: Women with metabolic syndrome are associated with increased risk of gynaecological cancers regardless of study design, type of gynaecological cancer and definitions of metabolic syndrome.**

Key words Cervical cancer - endometrial cancer - metabolic syndrome - ovarian cancer - risk -vaginal cancer

Metabolic syndrome is a multifactorial disorder comprising of obesity, hyperglycaemia, hypertension, high triglycerides (TG) and low high-density lipoprotein cholesterol (HDLc)[1]. Various organisations have defined

the syndrome through different thresholds and criteria for these components[2]. Despite the dissimilarities, the definitions converge on the simultaneous occurrence of three out of five components [adult treatment panel III (ATP III), harmonised definition (HD) with either obesity (International Diabetes Federation, IDF) or insulin resistance (World Health Organization, WHO)] as a mandatory component for diagnosis of metabolic syndrome[2]. The co-occurrence of these metabolic abnormalities increases the risk of cardiovascular diseases, type 2 diabetes and cancers.

Several clinical and epidemiological studies have investigated the risk of gynaecologic cancers and metabolic syndrome worldwide. These studies mainly report inconclusive findings which may be attributed to varying populations, sample size, type of definitions used for the diagnosis of metabolic syndrome and statistical adjustments. For instance, a cross-sectional study in Malaysia, investigating the association of metabolic syndrome (IDF definition) with endometrial cancer, reported a high odds ratio (OR) of 3.42[3]. In contrast, another study involving an African population in Brazil reported a low OR 0.93, implying that the odds of endometrial cancer are higher in the non-metabolic syndrome exposed group[4]. A study utilising the expansive European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, comprising over half a million participants across ten countries in Western Europe, calculated odds ratios using two distinct metabolic syndrome definitions, namely the ATP and IDF definitions. The risk of EC was 2.1-fold higher using the ATP definition as compared to 1.7-fold increased risk with IDF definition of metabolic syndrome[5]. In another single hospital-based study in Canada, the risk of endometrial cancer was associated with the IDF definition compared to ATP and HD[6]. There is a need to systematically assess the risks of gynaecological cancers in women with metabolic syndrome, duly considering factors such as study design, sample size, disease definitions, and ethnicity that can influence the study outcome.

A systematic review by Esposito *et al*[7] included five studies on metabolic syndrome and the incidence of endometrial cancer and ovarian cancer, along with other organ-specific cancers[7]. The review did not include other gynaecological cancers, such as cervical cancer, probably due to the limited availability of clinical reports at that time. Over the last decade, several publications have reported an association between gynaecological cancers and metabolic syndrome, presenting an opportunity to synthesise research findings through systematic review and meta-analysis[8-10]. We did not identify any registered protocols or in-progress reviews on this topic in Epistemonikos, PROSPERO, PubMed (MEDLINE), JBI Evidence Synthesis, and Cochrane Database of Systematic Reviews. The objective of this systematic review is to present current evidence of the risk of gynaecological cancers among women with metabolic syndrome.

Materials & Methods

This systematic review was registered with the International Prospective Registry of Systematic Reviews (PROSPERO: CRD 42022333645), and conducted following the JBI Methodology for Systematic Reviews of Etiology and Risk and Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines[11,12]. The review process and analysis are reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines[13].

Review question: What is the association of metabolic syndrome among women with gynaecological cancers?

Inclusion criteria: This review included studies on women aged ≥18 diagnosed with any three of the five components of metabolic syndrome, such as obesity, hyperglycaemia, hypertension, high triglycerides (TG) and low high-density-lipoprotein (HDL). Studies must report the risk of gynaecological cancers and/or equivalent estimates along with 95 per cent confidence interval (CI) to be considered in the review.

Sarcomas are a type of cancer that originates in the connective tissues, muscles, or bones, whereas cancers in these locations are mostly carcinomas, which arise from the epithelial cells lining the organs[14]. Sarcomas are rare in these areas, representing a small percentage of all cancers in the female reproductive system. Hence, studies reporting sarcomas were excluded.

Exposure of interest: Women with metabolic syndrome [diagnosed based on any of the standard definitions established by international consensus such as World Health Organization (WHO), International Diabetes Federation (IDF), National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III), American Heart Association, Japanese Society of Internal Medicine, Chinese Diabetes Society (CDS)]

and gynaecological cancers such as ovarian cancer, fallopian tube cancer, uterine/endometrial cancer, vaginal cancer, cervical cancer, and vulvar cancer.

Outcomes: This review presented the risk for the presence of gynaecological cancers in terms of odds ratio, relative risk, hazard ratio, and standardised incidence ratio (SIR) in women with metabolic syndrome.

Types of studies: Studies with cohort, cross-sectional and case-control study designs were included.

Search strategy:

Month and year of the study period: Research articles published in PubMed (MEDLINE), Scopus, and Google Scholar from their earliest available indexing of the respective databases up to September 2023 were searched. Query was performed without specifying a start date filter. Details of the search strategy across these databases are available in Supplementary material 1. Included articles and systematic reviews on metabolic syndrome and gynaecological cancers were referred for additional articles through their citations (forward referencing) and references (backward referencing).

Study screening: After an initial pilot, two independent reviewers (IK and IA) screened articles for inclusion/exclusion, and a third reviewer resolved the conflicts (DJ and KP). All original only English language articles were included. Studies wherein the participants had metabolic syndrome along with other comorbidities or previous history of cancers, were excluded.

Data extraction: Data related to study design, study site, ethnicity, recruitment strategy, number of participants and reported risk with 95 per cent CI were extracted by two independent reviewers (IK and IA) from the selected articles as per JBI methodology for systematic reviews of aetiology and risk[11]. Data extraction was conducted by two reviewers (IK and IA) until inter rate reliability ($k \geq 0.60$) was established. Risk estimates such as odds ratio, relative risk, hazards ratio, standardised incidence ratio, were extracted along with adjustments for age, education, and smoking.

Critical appraisal: The critical appraisal of the selected articles was assessed as per the JBI checklists for case-control and cohort and appraisal tool for cross-sectional studies (AXIS) checklist[11,15].

Data synthesis: Included studies were grouped based on study design, reported summary measure [OR, relative risk (RR), hazard ratio (HR)], and type of gynaecological cancers. Within each group, the risk estimates were pooled using the metagen (*https://rdrr.io/cran/meta/man/metagen.html*) function of meta R package. The estimation of variance within each group was calculated using DerSimonian-Laird estimator, and confidence intervals were determined based on a classic random effects model. Subgroup analysis was conducted based on the type of metabolic syndrome definition. Additionally, sensitivity analysis was carried out utilising the leave-one-out method implemented in the metainf (*https://rdrr.io/cran/meta/man/metainf.html*) function of the meta R package. As all data for meta-analysis from the included studies were available, the risk of bias due to missing results was not assessed.

Certainty of evidence: Two investigators (DJ and PK) conducted separate assessments of the certainty of evidence for each result. Any differences were settled by a third reviewer (SIT/DJ). The certainty of evidence was assessed using the grading of recommendations assessment, development and evaluation (GRADE) methodology, which categorises evidence into four degrees of certainty: very low, low, moderate, and high[12].

Results

The initial query yielded 1,590 articles. After excluding 506 duplicate studies, 1,084 titles/abstracts were screened. After excluding 25 non-English and 194 non-research articles at the title/abstract level, 862 studies were screened using full texts, and 10 studies were included. 13,732 articles were retrieved through forward and backward referencing of the included articles (n=10), and systematic reviews and meta-analysis reports (n=194), resulting in 15 included studies. A total of 25 studies[3-6,8-10,16-33] (4 cross-sectional, 8 case-control, and 13 cohort studies) were included for further analysis (Fig. 1).

The cross-sectional studies reported crude/unadjusted ORs for endometrial cancer and metabolic syndrome association in participants from Brazil, Turkey, Malaysia and China[3,4,28,32]. Two out of the eight case-control studies from the USA and China reported adjusted ORs of the association of metabolic syndrome with ovarian cancer[17,24], five studies from Europe, Canada, Italy, and the USA reported age-adjusted ORs for metabolic syndrome and endometrial

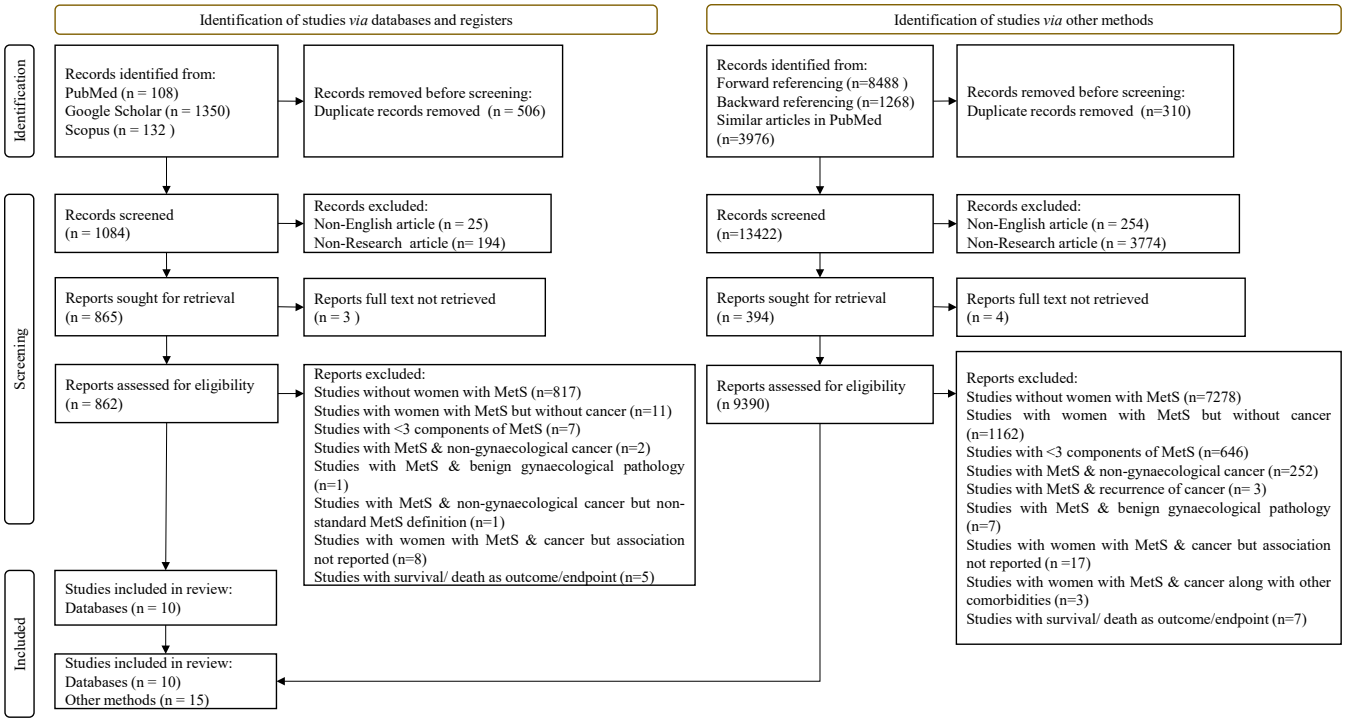

Fig. 1. PRISMA flow diagram illustrating the screening process adopted for the systematic review.

cancer[5,6,10,19,29], and one study from the USA reported an OR for risk of cervical cancer[33]. Nine cohort studies from Korea, Italy, the USA and Europe reported the association between metabolic syndrome and uterine/endometrial cancer[9,16,18,20-22,26,27,30], six studies from Europe, Korea and Italy focused on ovarian cancer[8,16,18,23,26,27], and six studies from Europe, Korea and Italy on cervical cancer[8,16,18,25-27]. Additionally, one cohort study from Europe examined the risk of rare gynaecological cancers, including vulvar and vaginal cancer, in women with metabolic syndrome[31]. Table provides the characteristics of the included studies.

Association of uterine/endometrial cancer with metabolic syndrome: Sixteen studies, comprising five case-control, four cross-sectional and nine cohort designs, reported the association of uterine/endometrial cancer with metabolic syndrome. All cross-sectional studies reported ORs, and the case-control studies reported ORs and age, diagnosis time-adjusted ORs. In case of cohort studies, OR, HR, or RR summary measures were used. Five cohort studies, with a median follow up of nine years reported both ORs and adjusted ORs, but the crude OR lacked CI; therefore, adjusted ORs were used for meta-analyses[5,6,10,19,29]. Ozdemir *et al*[32] used a cross-sectional study design and reported an OR, but the upper CI was less than the lower, hence it was recalculated, and the author was contacted for corrections. Among the cohort studies, Arthur *et al*[20] reported an age-adjusted an (OR 2.22 (95% CI:1.67-3.09), Bjorge *et al*[21] reported RR of 1.37 (95% CI: 1.28 -1.46), Ko *et al*[26] reported an HR of 1.82 (95% CI: 0.96- 3.48), Russo *et al*[27] reported an SIR 156 (95% CI: 95-241), Stocks *et al*[18] reported an adjusted RR 1.14 (95% CI: 0.95-1.38) individually for endometrium and other parts of uterus, and Stocks *et al*[16] reported an HR 1.56 (95% CI: 1.42-1.7). These studies were excluded from the meta-analysis, as there was only one study in each summary measure type. Bjorge *et al*[21] had reported risk of incidence of endometrial cancer and risk of fatal uterine corpus cancer, only the reported risk of endometrial cancer is included in the study. The study by Lopez-Jimenez *et al*[10], reported OR but did not report the CI therefore it was not included in the meta-analysis.

Meta-analyses produced an overall OR of 1.99 (95% CI: 1.61-2.45), $P<0.01$, 2.64 (95% CI: 1.26-5.52), $P<0.01$, and an HR of 1.45 (95% CI: 1.35-1.56), $P=0.043$ for case-control, cross-sectional, and cohort studies, respectively (Fig. 2A). Heterogeneity, assessed through random-effects models, was observed as 93 per cent with $P<0.01$, 77 per cent with $P<0.01$, and 63 per cent with $P< 0.0001$ in case-control, cross-sectional, and cohort studies, respectively (Fig. 2A).

In case-control studies, when stratified by metabolic syndrome definition, the risk was highest in studies with the IDF definition. The pooled OR was 2.84 (95% CI: 2.26-2.45) and 2.10 (95% CI: 1.73-2.55), *P*= 0.06, compared to studies with the HD definition: 1.56 (95% CI: 1.23-1.98), *P*= 0.77; and ATP definition: 1.91(95% CI: 1.25-2.91), *P*<0.01 (Supplementary Fig. 1).

Critical appraisal revealed high-quality evidence for the association between metabolic syndrome and endometrial cancer across case-control and cohort studies. For cross-sectional studies, except Tong *et al*[28] all other studies did not have justified sample sizes. Apart from this, the study aim, design, participant selection process, analysis and data reporting were of high quality (Supplementary material 2).

Association of ovarian cancer with metabolic syndrome: In the case of ovarian cancer, there were two case-control studies with adjusted ORs[17,24], and four cohort studies with median follow up of 11 years-two reported adjusted ORs[23,26], and two reported HR scores[16,26] (Table)[3-6,8-10,16-31]. Among cohort studies, Cao *et al*[8] reported an adjusted HR of 1.06 (CI: 0.84-1.33), and Russo *et al*[27] reported a standardised incidence ratio (SIR) of 106(CI:51-194). These studies were excluded in the meta-analysis, as only one study for each summary measure was available. Following the meta-analysis of four studies, case-control studies yielded an overall OR of 3.44 (95% CI: 1.12-10.54), *P*<0.01; cohort studies produced an OR of 1.02 (95% CI: 0.90-1.15), *P*= 0.79; and an HR of 1.02 (95% CI: 0.91-1.14), *P*=0.80 (Fig. 2B). Critical appraisal revealed high quality of evidence for the association of metabolic syndrome with ovarian cancer for case-control and cohort studies (Supplementary material 2).

Association of cervical cancer with metabolic syndrome: Russo *et al*[27] reported an SIR 59 (95% CI: 7.2-214), and Stocks *et al*[18] reported an adjusted RR 0.85 (95% CI: 0.59-1.21); both were excluded from meta-analysis. Four cohort studies, two with HRs and two with adjusted HRs were included in the meta-analysis[8,16,25,26]. The pooled estimates yielded an HR of 1.26 (95% CI: 1.09-1.46), *P*=0.96 and an adjusted HR of 1.27 (95% CI: 1.10-1.47), *P*=0.83 (Supplementary Fig. 2). Critical appraisal revealed high quality of evidence for the association of metabolic syndrome with cervical cancer for these two cohort studies (Supplementary material 2).

Association of vaginal and vulvar cancers with metabolic syndrome: There was only one study on vaginal and vulvar cancer with 11 yr of follow up, reported an adjusted HR of 1.54 (95% CI: 1.05 – 2.25) and 1.49 (95% CI: 1.2-1.84), respectively[31]. Critical appraisal revealed high quality of evidence for the association of metabolic syndrome with vaginal and vulvar cancers for these two cohort studies (Supplementary material 2).

Sensitivity analysis: The sensitivity analysis suggests a lack of large-study bias and no single study had influence on pooled estimates (Fig. 3).

Quality of evidence: The quality of evidence, assessed using the GRADE framework, indicates very low-quality evidence across all included studies (Supplementary material 3). Quality assessment of study design and imprecision parameters was not serious, but for inconsistency and indirectness, the parameters had serious concerns.

Discussion

This systematic review and meta-analysis aimed to compile existing literature on the risk factors for gynaecological cancers in women with metabolic syndrome indicates a higher risk of gynaecological cancers in women with metabolic syndrome. The pooled association remains consistently positive, irrespective of study design or the specific type of gynaecological cancers, and study quality. The pooled odds ratio (OR) in case-control studies exhibits variations across different cancer types. Notably, the risk is markedly higher in ovarian cancer[17,24] compared to endometrial cancer[5,6.19.20]. In contrast, the HR from cohort studies depicts a distinct pattern, with the highest risk in uterine/endometrial cancer[9,22,26,30] compared for ovarian[23,26] and cervical cancer[16,26].

The scarcity of studies employing analogous methodologies and summarising metrics makes it challenging to summarise the results of meta-analysis through comparison of risk scores. Since gynaecological cancers as an outcome of metabolic syndrome exposure are not rare, different summary measures were not combined in the analysis. It is essential to note the reported heterogeneity in risk. In uterine/endometrial cancer, the heterogeneity was 93, 77 and 63 per cent in case-control[5,6,19,29], cross-sectional[3,4,28,32] and cohort[9,22,26,30] studies, respectively. For ovarian cancer, among the case-control studies the heterogeneity was 99 per cent[17,24]. This substantial variability among the studies warrants caution in interpreting the pooled estimate, underscoring the

Table. Details of studies included in the review and meta-analysis

Type of cancer	Study design	Author, yr; country	Metabolic syndrome definition	Sample size				Results	Adjust-ments	Notes
				Non gynaeco-logical cancers with metabolic syndrome	Non gynaeco-logical cancers without metabolic syndrome	Gynaeco-logical cancers with metabolic syndrome	Gynaeco-logical cancers without metabolic syndrome			
Uterine/ Endometrial cancer	Case-Control	Cust *et al*[5], 2007; Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, & UK	ATP	122		102		OR 2.12 (1.51-2.97)	Yes	
			IDF	151		109		OR 1.68 (1.23-2.31)		
		Friedenreich *et al*[6], 2011; Canada	HD	367	595	318	197	OR 1.53 (1.17-2)	Yes	
			IDF	336	626	298	217	OR 2.58 (2.07-3.22)		
			ATP	417	545	335	180	OR 2.45 (1.96-3.07)		
			IDF(BMI)	296	666	285	230	OR 2.82 (2.26-3.58)		
		Rosato *et al*[29], 2011; Italy	HD	40	444	47	260	OR 1.67 (0.99 -2.81)	Yes	
		Trabert *et al* [19], 2015; Maryland	ATP	9930	90821	2505	13818	OR 1.39 (1.32-1.47)	Yes	
			IDF	2105	98646	753	15570	OR 2.03 (1.84 - 2.23)		
		Lopez-Jimenez T *et al*[10], 2022; Spain	HD	5555	15989	2011	3375	OR 1.635	No	CI is not provided, hence not included in meta-analysis
	Cross-sectional	Fernandes *et al*[4], 2022; Brazil	IDF			191	122	OR 0.93 (0.46-1.9)	No	
		Shafiee *et al*[3], 2020; Turkey	IDF(BMI)			65	54	OR 3.42 (1.12-10.46)	No	
		Tong *et al*[28], 2020; Malaysia	CDS			89	384	OR 2.86 (1.73 – 4.69)	No	

Contd...

Type of cancer	Study design	Author, yr; country	Metabolic syndrome definition	Sample size				Results	Adjust-ments	Notes
				Non gynaeco-logical cancers with metabolic syndrome	Non gynaeco-logical cancers without metabolic syndrome	Gynaeco-logical cancers with metabolic syndrome	Gynaeco-logical cancers without metabolic syndrome			
		Ozdemir *et al*[32], 2015; China	ATP	39	105	37	17	OR 5.53 (2.8-10.8)	No	Reported upper CI was 0.8; it was lower than lower CI hence recalculated & authors were contatcted
	Cohort	Tran *et al*[9], 2023; Korea (KNHIS)	ATP			768	2568	HR 1.58 (1.45-1.72)	Yes	
		Jo *et al*[30], 2022; Korea (KNHIS)	ATP	735143	2083360	1703	3901	HR 1.36 (1.28-1.45)	Yes	
		Park *et al*[22], 2022; Korea (NHID)	ATP	147825	4595064	1987	4810	HR 1.44 (1.36 -1.52)	Yes	
		Arthur *et al*[20], 2019; USA	ATP	4927	7958	99	77	OR 2.77 (1.67 – 3.09)	Yes	Only endometrial cancer cohort study with reported OR, hence excluded from meta-analysis
		Bjorge *et al*[21], 2010; Norway, Austria & Sweden (Me-Can)	HD					RR 1.37 (1.28 -1.46)	No	Excluded from meta-analysis as it was single endometrial cancer cohort study with reported unadjusted RR
		Stocks *et al*[18], 2009; Norway, Austria & Sweden (Me-Can)	WHO					RR 1.14 (0.95-1.38)	Yes	Adjusted for 1mmol/l glucose increment value, hence not included in meta-analysis
		Stocks *et al*[16], 2015; Norway, Austria & Sweden (Me-Can)	WHO					HR 1.56 (1.42 – 1.7)	No	Excluded from meta-analysis as it was single endometrial cancer cohort study with reported unadjusted HR
		Russo *et al*[7], 2008; Italy	ATP			20		SIR 156 (95-241)	No	Single study for uterine cancer with reported SIR, hence no meta-analyis could be performed
		Bjorge *et al*[21], 2010; Norway, Austria & Sweden (Me-Can)	HD					RR (1.56-1.32)	No	The uterine cancer reported in the study is not for incidence of the cancer, hence not merged with other risk reports
		Ko *et al* [26], 2016; Korea (KNHIS)	WHO			52		HR 1.82 (0.96-3.48)	No	

Contd...

Type of cancer	Study design	Author, yr; country	Metabolic syndrome definition	Sample size				Results	Adjust-ments	Notes
				Non gynaeco-logical cancers with metabolic syndrome	Non gynaeco-logical cancers without metabolic syndrome	Gynaeco-logical cancers with metabolic syndrome	Gynaeco-logical cancers without metabolic syndrome			
		Stocks *et al*[18], 2009; Norway, Austria & Sweden (Me-Can)	ATP					RR 1.14 (0.95-1.38)	Yes	Adjusted for 1mmol/l glucose increment value; hence not included in meta-analysis
Ovarian cancer	Case-control	Chen*et al*[17], 2017; Tianjin	ATP	80		159		OR 5.5 (4.09 – 7.39)	Yes	
			IDF	74		143		OR 5.25 (3.86 – 7.14)		
			CDS	79		144		OR 4.88 (3.61 – 6.59)		
		Michels *et al*[24], 2019; Rockville	ATP	64540	217338	3724	13126	OR 1.02 (0.96 – 1.07)	Yes	
	Cohort	Bjorge *et al*[23], 2011; Norway, Austria & Sweden (Me-Can)	HD			62	563	OR age >50 -1.09 (0.86-1.4) ; age >50 0.99 (0.86-1.15)	Yes	
		Ko *et al* [26], 2016; Korea (KNHIS)	ATP			82		OR 1.03 (0.53 -2.03); HR 0.94 (0.5-1.77)	Yes	
		Stocks *et al*[16], 2015; Norway, Austria & Sweden (Me-Can)	WHO					HR 1.02 (0.91-1.15)	No	Single ovarian cancer cohort study with reported HR therefore not included in meta-analysis
		Russo *et al*[27], 2008; Italy						SIR 106 (51 -194)	No	Single cohort study for ovarian cancer with reported SIR; hence not included in meta-analysis
		Cao *et al*[8], 2020; England, Scotland and Wales (UK Biobank)						HR 1.17 (0.9-1.51)	Yes	Single study of ovarian cancer to report adjusted HR; hence not included in meta-analysis
		Stocks *et al*[18], 2009; Norway, Austria & Sweden (Me-Can)						RR 0.85 (0.66 – 1.1)	Yes	Adjusted for 1mmol/l glucose increment value; hence not included in meta-analysis

Contd...

Type of cancer	Study design	Author, yr; country	Metabolic syndrome definition	Sample size				Results	Adjust-ments	Notes
				Non gynaeco-logical cancers with metabolic syndrome	Non gynaeco-logical cancers without metabolic syndrome	Gynaeco-logical cancers with metabolic syndrome	Gynaeco-logical cancers without metabolic syndrome			
Cervical cancer	Case-control	Penaranda *et al*[33], 2013; USA	HD					OR 1.9 (1.06-3.42)	No	Single case-control study for cervical cancer; hence not included in meta-analysis
	Cohort	Ko *et al* [26], 2016; Korea (KNHIS)	ATP			94		HR 1.27 (1.09 -1.47)	No	
		Stocks *et al*[16], 2015; Norway, Austria & Sweden (Me-Can)	WHO					HR 1.27 (1.09-1.47)	No	
		Cao *et al*[8], 2020; England, Scotland & Wales (UK Biobank)	ATP					HR 1.36 (0.69 -2.7)	Yes	
		Ulmer *et al*[25], 2012; Norway, Austria, & Sweden (Me-Can)	WHO					HR 1.26 (1.09-1.47)	Yes	
		Stocks *et al*[18], 2009; Norway, Austria & Sweden (Me-Can)	WHO					RR 0.85 (0.59 – 1.21)	Yes	Single cohort study for cervical cancer with reported RR; hence not included in meta-analysis
		Russo *et al*[27], 2008; Italy	ATP					SIR 59 (7.2 -214)	No	Single cohort study for cervical cancer with reported SIR; hence not included in meta-analysis
Vulvar cancer	Cohort	Nagel *et al*[31], 2011; Norway, Austria & Sweden (Me-Can)	WHO					HR 1.49 (1.2 -1.84)	Yes	Single study for vulvar cancer, hence no meta-analyis could be performed
Vaginal cancer	Cohort	Nagel *et al*[31], 2011; Norway, Austria & Sweden (Me-Can)	WHO					HR 1.54 (1.05 – 2.25)	Yes	Single study for vaginal cancer, hence no meta-analyis could be performed

KNHIS, Korean National Health Insurance Service; Me-Can, Metabolic syndrome and cancer project cohort; NHID, Korea National Health Information Database; ATP, adult treatment panel; WHO, World Health Organisation; IDF, International Diabetes Federation; HD, harmonised definition for metabolic syndrome diagnosis; OR, odds ratio; HR, hazards ratio; RR, risk ratio; SIR, standard incidence ratio; CI, confidence interval

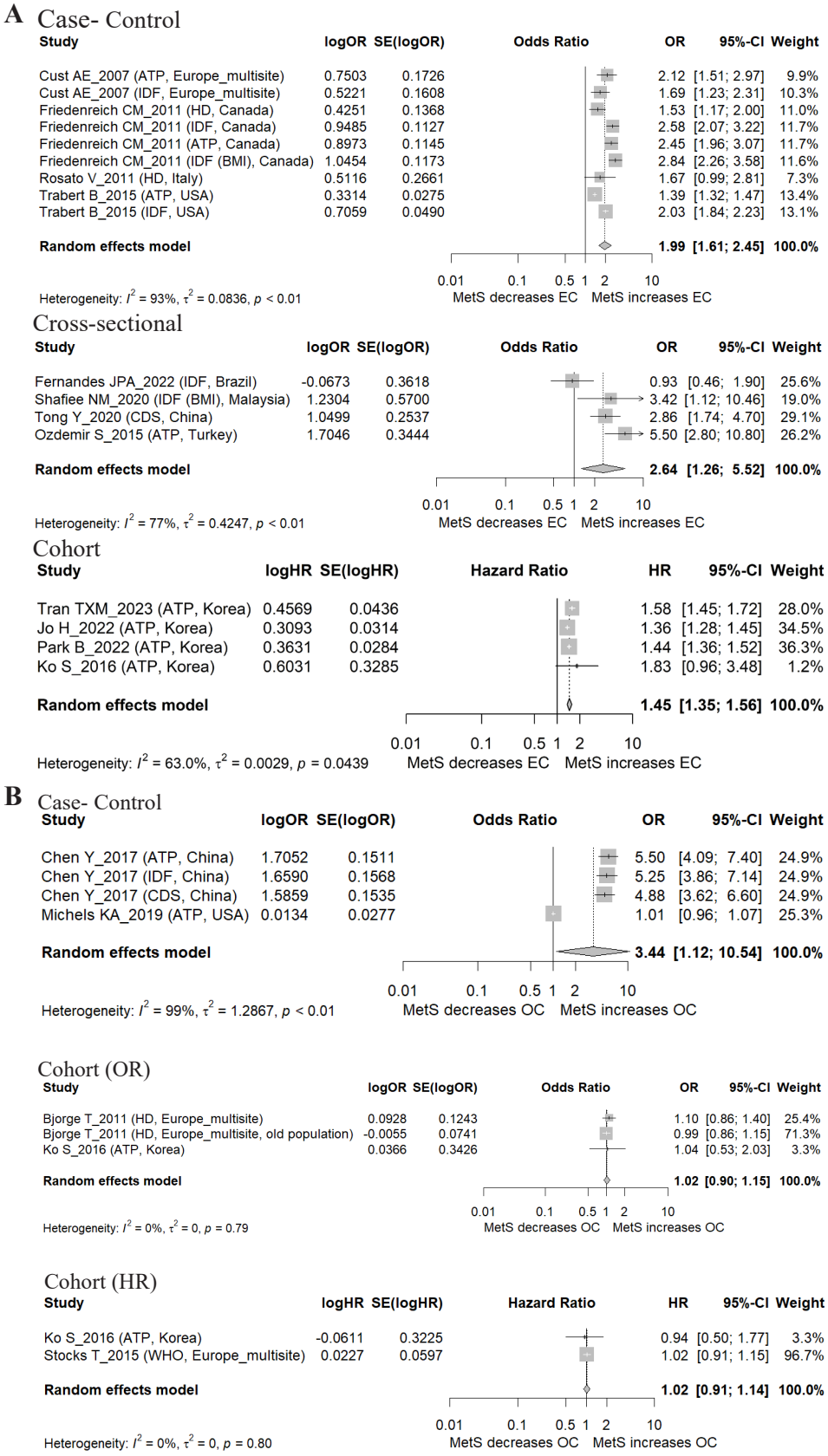

Fig. 2. Meta-analysis of association of metabolic syndrome with (**A**) uterine/endometrial cancer, and (**B**) ovarian cancer.

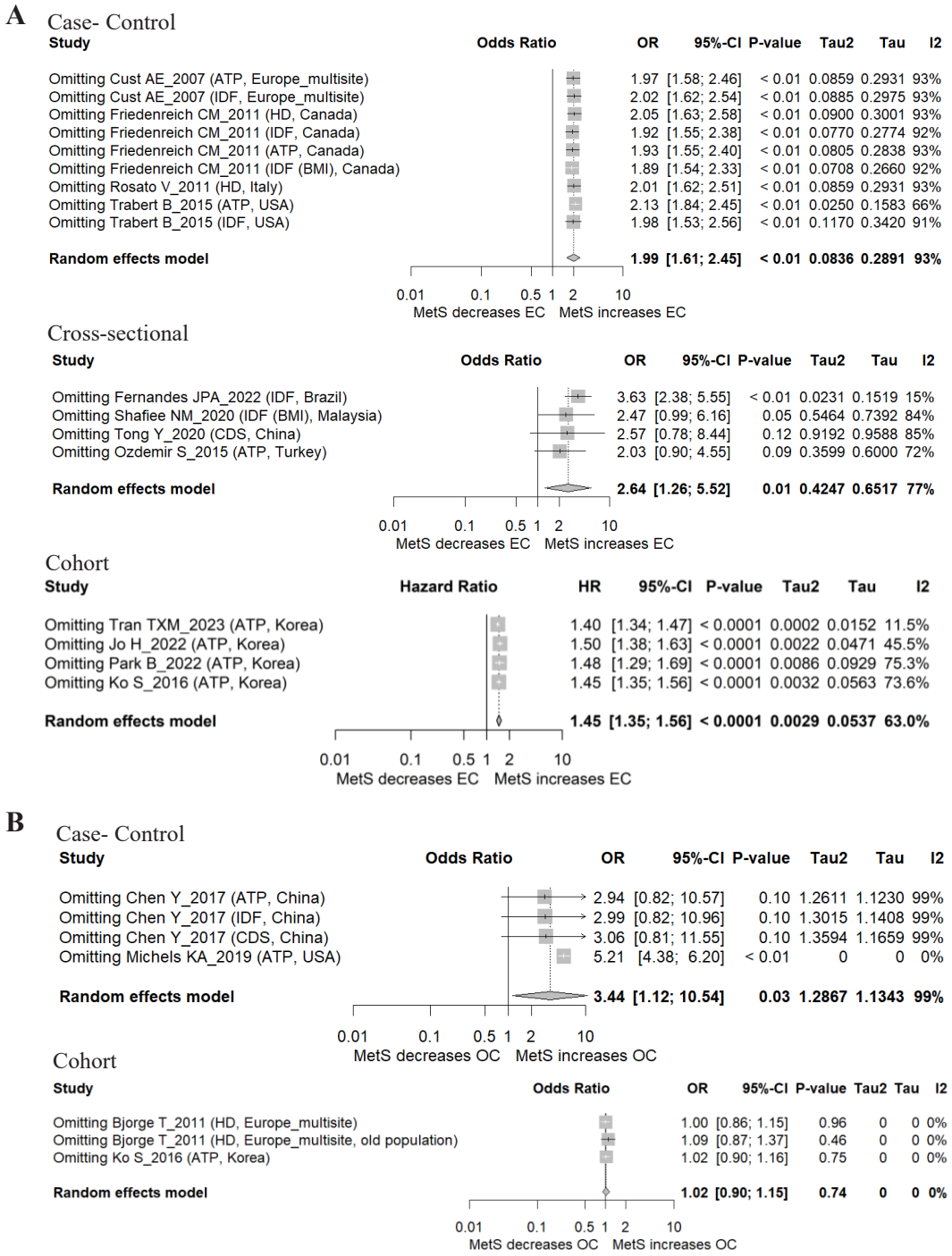

Fig. 3. Sensitivity analysis of association of metabolic syndrome with (**A**) uterine/endometrial cancer, and (**B**) ovarian cancer.

need for a nuanced understanding of these complex relationships.

Based on the findings from these systematic reviews, the elevated risk of gynaecological cancers in women with metabolic syndrome could be explained based on the interlinked pathophysiologies of the diseases. The key contributors of metabolic syndrome such as insulin resistance, inflammation and obesity can support increased proliferative, anti-apoptotic, and metastatic activities conducive to cancer development[34]. Insulin, recognised as a pivotal component of the growth factor system, can modify proliferation signals *via* the PI3K/Akt and MAPK/ERK pathways, exerting anti-apoptotic influence on cancer cells[35]. Elevated

circulating insulin levels indirectly reduce the hepatic synthesis of sex hormone-binding globulin, leading to increase serum oestrogen and testosterone levels, thereby escalating the risk of ovarian cancer and endometrial cancer[36]. Obesity significantly influences the sex hormone *milieu*. It is linked to increased serum androgen levels in women[37]. Adipose tissue expansion also results in the secretion of adipokines and pro-inflammatory factors, potentially influencing the regulation of cell growth and apoptosis in uterine and ovarian tissues, thereby impacting gynaecological cancers risk.

The strengths of our analysis include the use of primary endpoints based on prospective analyses with adjustments wherever necessary, and uniform methods to better define associations across gynaecological cancers, between cancer subsites, and definitions of metabolic syndrome.

This systematic review has several limitations. First, included studies were restricted to those written in English, potentially excluding studies from regions with high prevalence of gynaecological cancers, such as Asia and Eastern Europe[38,39]. Apart from language restrictions, the search for articles was limited to freely accessible databases such as PubMed and Google Scholar. However, a substantial number of additional papers were identified through forward and backward citation tracking, which likely mitigated this limitation. Secondly, significant heterogeneity in recruitment strategies resulted in a wide range of sample sizes, ranging from 1,000 in a hospital-based recruitment to 600,000 in a registry-based recruitment, which complicated the accurate estimation of the true risk. Smaller studies may lack statistical power, while larger studies could introduce variability and confounding factors[40]. Variations in diagnostic criteria for metabolic syndrome and a lack of individual patient data hindered detailed meta-regression analysis. Moreover, the lack of consistent reporting across studies regarding adjustments for confounding variables, such as lifestyle factors, socioeconomic status, and other relevant covariates, introduces uncertainty in the interpretation of the pooled estimates. Additionally, due to the limited number of studies on each gynaecological cancer, meta-regression, publication bias, and subgroup analyses could not be performed. The included studies were predominantly from South/North Korea, Europe and the Americas, therefore, there is a possibility of population bias, which may affect the applicability of the findings to more diverse or underrepresented populations from African and South Asia, and other low-and middle-income countries.

In our systematic review, a total of 54 studies from India were screened for inclusion, of which 31 studies were excluded because they did not include women with metabolic syndrome, and 20 were non-cancerous related studies. One study was on oral cancer, a non-gynaecological cancer, hence not included. Three studies had fewer than three components of metabolic syndrome and, therefore, could not be diagnosed as having metabolic syndrome according to any of the standard definitions; consequently, they were excluded.

Additionally, it is well documented that medications used to manage metabolic syndrome, including metformin, statins may have a preventive effect on cancer development[41-43]. In light of these existing findings, addressing and managing metabolic syndrome should be an integral part of the strategies employed to prevent and treat gynaecologic cancer. So far, only limited data are available regarding risk of gynaecological cancers and metabolic syndrome in developing countries, and further research is required for robust conclusions.

The results of this comprehensive study, which incorporates numerous recently published studies, indicate that there is a relatively low to moderate heightened susceptibility to gynaecological malignancies in women with metabolic syndrome. There is a pressing need for preventive techniques, specifically primary prevention and early identification of cancer. This need has also been indicated for people with fully developed disorders like diabetes[44]. Furthermore, it is advisable for women with metabolic syndrome to undergo the recommended cancer tests appropriate for their age. Crucially, we require information regarding the therapies that reduce metabolic syndrome in women also lower the risk of developing cancer.

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