Hypertension and Ovarian Cancer Risk: a Meta-Analysis of Observational Studies with 2,497,898 participants

Keywords
hypertension, meta-analysis, cardiovascular disease, ovarian cancer

Abstract

Introduction

Ovarian cancer is the eighth most common cancer in women, and is an important source of cancer-related mortality, particularly in developed countries. Scientific studies show that hypertension may play a significant role in the initiation of cancer. Therefore, we carried out the first meta-analysis to comprehensively examine the association between hypertension and ovarian cancer risk.

Material and methods

We performed a literature search of all of the observational studies published as original articles from inception to July 2024 and we searched the following databases: PubMed, EMBASE and Cochrane Library. Finally, we included ten full-text cohort and case-control studies addressing the effect of hypertension on ovarian cancer in this meta-analysis. The our study was preregistered with the PROSPERO:CRD42024565574 and followed the PRISMA statement. Effect size was presented as risk ratios(RRs). Heterogeneity test evaluation was performed using Cochran's Q test and I2 statistics.

Results

The meta-analysis included a total of 2,497,898 women. There was a statistically significant association (RR=1.10,1.02–1.23, p<0.011) between hypertension and ovarian cancer risk. Subgroup analysis showed that parity may significantly reduce the ovarian cancer risk, which was higher among woman who had never given birth (RR=1.43,p<0.002), while a body mass index >25 increased the risk of ovarian cancer (RR=1.12,p<0.001).

Conclusions

Findings of this comprehensive review and meta-analysis indicate that hypertension is associated with higher overall risk of ovarian cancer. The data presented in our study are novel, but from a future perspective, we hope that this meta-analysis will encourage researchers to conduct further studies to assess the effect of hypertension on ovarian cancer.

Hypertension and Ovarian Cancer Risk: a Meta-Analysis of Observational Studies with 2,497,898 participants

Abstract

Background: Ovarian cancer is the eighth most common cancer in women, and is an important source of cancer–related mortality, particularly in developed countries. Scientific studies show that hypertension may play a significant role in the initiation of cancer. Therefore, we carried out the first meta-analysis to comprehensively examine the association between hypertension and ovarian cancer risk.

Materials and Methods: We performed a literature search of all of the observational studies published as original articles from inception to July 2024 and we searched the following electronic databases: PubMed, EMBASE and Cochrane Library. Finally, we included ten full-text cohort and case-control studies addressing the effect of hypertension on ovarian cancer in this meta-analysis. Our study was preregistered with International Prospective Register of Systematic Reviews (PROSPERO CRD42024565574) and followed the PRISMA statement. Effect size was presented as risk ratios (RRs) and 95% confidence interval (CI). Heterogeneity test evaluation was performed using Cochran's Q test and I^2 statistics.

Results: The meta-analysis included a total of 2,497,898 women. There was a statistically significant association (RR = 1.10, 95% CI: 1.02 – 1.23, $p < 0.011$) between hypertension and ovarian cancer risk.

Subgroup analysis showed that parity may significantly reduce the ovarian cancer risk, which was higher among woman who had never given birth (RR = 1.43, $p < 0.0025$), while a body mass index (BMI) > 25 increased the risk of ovarian cancer (RR = 1.12, $p < 0.0001$).

Conclusion: Findings of this comprehensive review and meta-analysis indicate that hypertension is associated with higher overall risk of ovarian cancer. The data presented in our study are novel, but from a future perspective, we hope that this meta-analysis will

encourage researchers to conduct further studies to assess the effect of hypertension on ovarian cancer.

Keywords: ovarian cancer, hypertension, cardiovascular disease, meta-analysis

Introduction

Ovarian cancer is the eighth most common cancer in women [1], but among the most common cancers leading to death in this gender, it ranks fifth [2]. Sadly, it is also the most poorly prognostic cancer of the female reproductive system [3,4]. Since the 1990s, a global annual decrease in mortality from this cancer has been observed, ranging from approximately 1 to 2.4%. However, considering the incidence of ovarian cancer on a regional scale, it should be noted that in well-developed countries and those that have undergone economic transformation, an increase in the incidence of this cancer is observed (e.g., Eastern and Southern Europe, Japan), which may be due to a decrease in the number of pregnancies and shorter breastfeeding durations [3–6].

Since the vast majority of ovarian cancers originate from epithelial cells, it has been divided into five types: high-grade serous carcinoma (70%), low-grade serous carcinoma (3%), endometrioid carcinoma (12%), clear cell carcinoma (12%), and mucinous carcinoma (3%) [7,8]. The above-mentioned frequency of occurrence of each type of ovarian cancer is similar worldwide, except for Asian countries, where clear cell carcinoma and endometrioid carcinoma are more common, while serous carcinoma is less common [5]. The symptoms of ovarian cancer are nonspecific, and there is no screening test that can unambiguously detect this cancer, resulting in an unfavorable prognosis in the majority of cases at the time of diagnosis [6,9,10]. Among the clearly proven risk factors for ovarian cancer are greater height and BMI [11], older age [12], mutations in the BRCA1 and BRCA2 genes [13], nulliparity [15], tobacco smoking [16], endometriosis [11], and diabetes [11]. Studies suggests a diverse

effect of hormone replacement therapy (HRT) on ovarian cancer risk [11,14,17]. However, meta-analysis Xiang et al. show that the risk of ovarian cancer associated with HRT has been decreasing over time [18], but previous meta-analyses have reported conflicting findings [19,20]. Factors that may have a preventive effect include pregnancy [21], breastfeeding [22] and combined oral contraceptive pills use that may act as chemoprevention through the impact on the epigenome of the cells of origin of ovarian cancer [23].

Hypertension is one of the most common causes of death worldwide, affecting about 45% of the American population, while in other regions of the world, its prevalence is increasing year by year (e.g., about 22% of all people in European Union countries) [24,25]. Hypertension plays a significant role in the development of numerous cancers and also affects their prognosis [24,26]. Mechanisms through which this disease may contribute to the development of cancers include remodeling of the extracellular matrix [27], influencing VEGF (Vascular Endothelial Growth Factor Regulation) secretion [28], ROS (Reactive Oxygen Species) [24], the functioning of the RAA (Renin–Angiotensin–Aldosterone System) [29,30] and the functioning of MMPs (matrix metalloproteinases) [31].

Although many scientific studies have attempted to investigate the relationship between hypertension and ovarian cancer, the results of these studies have not provided a clear answer to this question. Thus, the authors of the article have conducted a systematic review of this topic via meta-analysis.

Materials and Methods

This meta-analysis strictly followed the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (Supplement Table S1), [32], and was designed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines to identify observational studies examining the effect of hypertension on ovarian

cancer. Protocol was preregistered with the PROSPERO platform with ID: CRD42024565574.

Search Strategy and Selection Criteria

The comprehensive literature search was conducted on July 21th, 2024 using the following bibliographic databases: MEDLINE, Embase, and the Cochrane Library to identify articles examining the association between hypertension and ovarian cancer. The medical databases search was limited to English papers and was conducted from inception until July 20th 2024. In the computer search, we used the following keywords in various combinations: "hypertension" OR "blood pressure" OR "high blood pressure" AND "ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "ovarian tumor" OR "ovarian malignancy" OR "ovarian dysplasia".

Eligibility Criteria

Eligibility focused on patients with ovarian cancer. Included in our meta-analysis were only original studies published in English to July 2024, assessing the risk of ovarian cancer in relation to hypertension and matched the following criteria: i) prospective and retrospective cohort and case-control studies; ii) provided risk estimates (relative risks, odds ratios, hazard ratios) and 95% confidence intervals; iii) containing the following data: number of women with hypertension who developed ovarian cancer and number of women with hypertension who did not develop ovarian cancer and number of patients without hypertension who developed ovarian cancer and number of patients without hypertension who did not develop ovarian cancer.

Data Extraction

Two researchers, respectively, extracted the basic data of the included literature and characteristics of the studied populations. Data extraction from the included studies was performed independently by the lead author (AD) and co-author (WK). Next, data were subsequently reviewed by the co-authors for accuracy (MM and UR). Disagreements between reviewers were resolved through discussions after an additional publications review.

Study Quality Assessment

The Newcastle–Ottawa Scale (NOS) [33] was used to assess risk of bias of the studies. We evaluated the methodological quality of cohort studies based on the following issues: study design, data comparability and outcome assessment [33]. In the methodological evaluation process, scores from 0 to 3, from 4 to 6 and from 7 to 9 were given for low, medium and high quality, respectively.

Assessing the case-control studies, the NOS includes following aspects: selection, comparability, and exposure. The comparability category can receive a maximum of 2 stars, while each point in the selection and exposure categories can receive up to 1 star. A maximum of 9 stars (or points) can be awarded to determine the risk of studies bias. We considered a study to be of high quality when the total score was ≥7 points.

Data synthesis and Statistical analyses

STATISTICA 13.3 program (StatSoft, Cracow, Poland, https://www.statsoft.pl/) by way of employing the Medical Package program was used for all statistical analyses. For each study, we created separate two-by-two crosstabs. A similar approach was taken to analyze subgroups for selected variables. The risk ratios (RRs) and the 95% confidence intervals (CIs) were assessed as effective measures for the risk based on the reported data. A DerSimonian-Laird random-effects model was used to calculate the combining RR from various studies [34]. We

126 employed I^2 and Cochrane Q to evaluate heterogeneity, by utilizing the following criteria:
127 high heterogeneity, I^2 >75%; moderate heterogeneity, I^2 = 50% to 75%; and low
128 heterogeneity, I^2 < 50% [35,36]. The risk of publication bias was assessed by applying
129 Egger's linear regression test [37] and Begg's rank correlation test [38]. We assessed
130 publication bias using funnel plots. In the absence of bias, the plots resemble a symmetrical
131 funnel and was tested using Egger's test and Begg's test [39].
132
133 Subgroup analysis
134 We performed subgroup analyses by study design (case–control; cohort), and study
135 quality NOS score (≥7; <7 stars). Additionally, for our exploratory analyses, subgroups were
136 created based on categorical variables of interest collected from studies herein. Additional
137 stratified analysis was performed according to parity (gave birth vs. nulliparous), diabetes
138 (yes vs. no), menopausal status (premenopausal vs. postmenopausal), body mass index (≥25
139 vs. <25), cigarette smoking (yes vs. no).
140
141 Results
142 We identified 2047 references through the medical databases Embase, MEDLINE, and
143 the Cochrane Library to July 2024. In accordance with inclusion criteria, 1699 articles were
144 excluded by title or abstract, and the 312 duplicate studies were removed. As an outcome,
145 total of 36 articles were identified for full text review. Subsequently, the comprehensive
146 evaluation of publications resulted in the exclusion of 27 articles. Finally, 10 studies (9
147 articles) were considered for inclusion in this meta-analysis [40–48]. These consisted of 6
148 case-control studies and 4 cohort studies. One publication provided results from two cohorts
149 [44]. All other publications were rejected due to lack of raw data (adjusted data were
150 available), or there was no access to the control group data (no information on hypertension or

ovarian cancer), or the articles were unrelated to the topic (the outcome was mortality, taking antihypertensive drugs, prognosis for ovarian cancer). A flow-chart of the selection procedure for the included studies is provided in Figure 1.

Table 1 gives an overview of the study characteristics. A total of 2,497,898 patients were included in the study, with ovarian cancer cases sizes ranging from 133 to 16,850. All the included patients in this meta-analysis were females over 20 years.

Three studies were conducted in the USA [43,44,46], three in European countries [40–42], one in the People's Republic of China [45], one study was conducted in Saudi Arabia [48], and one was a multicenter study [47]. All studies were observational studies - case-controls or cohort in design. The NOS quality rating was between 6 and 8 stars, and the average NOS score was 7.1 for the included studies (Supplement Table S2, Table S3).

The results of a meta-analysis of observational studies comparing the risk of ovarian cancer in patients diagnosed with hypertension to the risk of ovarian cancer in patients without hypertension are shown in Figure 1. Accordingly, the risk of ovarian cancer in patients with hypertension is significantly higher (RR = 1.10, 95% CI: 1.02–1.23, $p < 0.011$). The I^2 value was 95.68%, which indicates high heterogeneity of studies, while the Egger's test indicated no publication bias (b0 = 0.181, 95% CI: -3.651–4.014, t = 0.107, p = 0.095).

The overall heterogeneity of the pooled result was considered high, and therefore additional subgroup analysis was performed (Table 2). Subgroup analysis indicated that study design and NOS score had no clear impact on the heterogeneity based on high variability of I^2 within the subgroup. On the other hand, the risk of developing ovarian cancer was 1.12 times higher in patients with BMI ≥25 kg/m^2 than in those with BMI ≤25 kg/m2 (95% CI: 1.07, 1.18, $p < 0.0001$), and 1.43 times higher among woman who had never given birth (95% CI: 1.05, 1.96, $p < 0.0025$). In turn, diabetes, menopausal status and cigarette smoking did not significantly affect the risk of ovarian cancer.

Discussion

The relationship between hypertension and ovarian cancer has been explored in numerous scientific studies [40–48], but they have not allowed for a definitive determination of the relationship between these conditions. Based on a pooled analysis regarding the risk of developing ovarian cancer in people with hypertension, we found that this condition significantly increases the risk of this cancer (RR 1.10, 95% CI 1.02–1.23, $p < 0.011$), but this result is characterized by statistically significant heterogeneity ($p < 0.0001$, $I^2 = 95.68\%$). Since this is the first meta-analysis on this topic, it is not possible to compare its results with previous studies. The study also verified the impact of other risk factors for ovarian cancer: parity (RR = 1.43, $p < 0.0025$), diabetes (RR = 1.27, $p < 0.1155$), menopausal status (RR = 1.20, $p < 0.2242$), BMI (RR = 0.89, $p < 0.0001$) and cigarette smoking (RR = 2.20, $p < 0.2791$).

Recently, there has been a growing number of publications considering the significance of antihypertensive drugs in cancer therapy [49]. Their role in treatment is directly related to the hypotensive effect or results from a pleiotropic effect (e.g., β-blockers and CCBs) [50,52].

Hypertension is a proven risk factor for numerous cancers [24]. A strong correlation is observed between hypertension and kidney cancer, renal cell carcinoma (RCC), breast cancer, colorectal cancer, endometrial cancer and bladder cancer [52–66]. This list may be expanded in the coming years, as the relationship between hypertension and many cancers has not yet been well studied, opening a broad field for further research. Numerous scientific studies have also shown that hypertension worsens the prognosis for various cancers [67–76]. The literature indicates several mechanisms by which hypertension may contribute to the development of cancer, which should be discussed in the paper [24,27,29–31].

Remodeling of the extracellular matrix is caused by the inflammation associated with hypertension [24]. The remodeling of the blood vessel wall resulting from hypertension leads to stiffening of the ECM, which disrupts the production of adhesive molecules that regulate cell-cell interactions, resulting in faster tumor growth [27,77].

VEGF is an important factor in the process of physiological and pathological angiogenesis, facilitating it by increasing blood vessel permeability and regulating endothelial cell proliferation [28]. It has been shown that people with hypertension have higher levels of VEGF, which translates into faster tumor progression and poorer prognosis [78].

Metabolic syndrome components (including hypertension) lead to cancer development primarily by increasing the formation of ROS, estrogen, IGF–1 and adipokines in the body [24]. Hypertension has been linked to insulin resistance, and thus increased IGF-1 production in the body, indicating its possible involvement in carcinogenesis through this mechanism [79]. Hypertension is also associated with excessive activity of the RAA system. Indeed, some studies have shown a link between mutations in genes encoding the angiotensin II receptor and the development of certain cancers [29,55,64].

MMPs are enzymes that degrade the collagen present in the ECM. One of the best-studied enzymes in this group is MMP–2, which can exhibit both pro– and anti–inflammatory effects [80]. MMPs are responsible for changes in the structure of blood vessels typical of hypertension, yet hypertension itself, in an as–yet–unknown way, leads to increased activation of MMP–2 [81]. This phenomenon, among other issues, disrupts the structure of cadherin, one of the adhesive molecules, which may impact cancer development [81]. Increased MMP activity is also observed in many cancers, suggesting a need for further research into the link between hypertension and carcinogenesis through the mechanism of MMP activity modification, as this relationship is not yet fully understood [24].

We are aware that drawing final conclusions from the results of our meta-analysis requires caution given the number of limitations such as risk measures and high heterogeneity, as well as the population differences. It should be noted that we limited the search to English-language literature. The number of studies that could be included is limited, and most of them were case-control studies, which are more susceptible to biases such as recall and selection. Additionally, it should be noted that the study did not account for the presence and type of antihypertensive treatment. It is also worth remembering that in this study, all types of ovarian cancer are considered together, while the risk factors for ovarian cancer seem to depend on the histological type, so the impact of hypertension on the development and course of the disease may vary for different types [82,83].

Conclusions

In summary, the above meta–analysis shows a positive association between hypertension and the development of ovarian cancer. Future studies should focus on better understanding the pathophysiological mechanisms connecting hypertension with ovarian cancer, and on deepening the analysis by distinguishing between different types of ovarian cancer, as well as conducting subgroup analyses by geographical regions of the world.

Conflict of Interest: The authors declare no potential conflicts of interest.
Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.
Consent to Participate declaration: Not applicable.
Institutional Review Board Statement: Systematic review registration: www.crd.york.ac.uk/prospero/, identifier: CRD42024565574

References

1. Webb PM, Jordan SJ. Global epidemiology of epithelial ovarian cancer. Nat Rev Clin Oncol. 2024;21(5):389-400.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024 [published correction appears in CA Cancer J Clin. 2024;74(2):203. CA Cancer J Clin. 2024;74(1):12-49.
3. Ali AT, Al-Ani O, Al-Ani F. Epidemiology and risk factors for ovarian cancer. Menopause Review 2023;22(2):93-104.
4. Feeney L, Harley IJ, McCluggage WG, et al. Liquid biopsy in ovarian cancer: Catching the silent killer before it strikes. World J Clin Oncol. 2020;11(11):868-889.
5. Coburn SB, Bray F, Sherman ME, et al. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer. 2017;140(11):2451-2460.
6. Ali AT. Towards Prevention of Ovarian Cancer. Curr Cancer Drug Targets. 2018;18(6):522-537.
7. Köbel M, Kang EY. The Evolution of Ovarian Carcinoma Subclassification. Cancers (Basel) 2022;14(2):416.
8. Köbel M, Kalloger SE, Lee S, et al. Biomarker-based ovarian carcinoma typing: a histologic investigation in the ovarian tumor tissue analysis consortium. Cancer Epidemiol Biomarkers Prev. 2013;22(10):1677-1686.
9. Sideris M, Menon U, Manchanda R. Screening and prevention of ovarian cancer. Med J Aust. 2024;220(5):264-274.
10. Pavlik EJ, van Nagell JR Jr, Dietrich CS 3rd, et al. Compelling Story of Ovarian Cancer Screening. J Clin Oncol. 2024;42(10):1091-1094.
11. Whelan E, Kalliala I, Semertzidou A, et al. Risk Factors for Ovarian Cancer: An Umbrella Review of the Literature. Cancers (Basel). 2022;14(11):2708.
12. Bandera EV, Lee VS, Rodriguez-Rodriguez L, et al. Racial/ethnic disparities in ovarian cancer treatment and survival. Clin Cancer Res 2016; 22:5909-5914.
13. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017; 317:2402-2416.
14. Lee AW, Ness RB, Roman LD, et al. Ovarian Cancer Association Consortium. Association between menopausal estrogen-only therapy and ovarian carcinoma risk. Obstet Gynecol 2016; 127: 828-836.
15. Gaitskell K, Green J, Pirie K, et al.. Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. Int J Cancer 2018; 142: 281-9.
16. Wang T, Read SH, Moino D, et al. Tobacco Smoking and Survival Following a Diagnosis with Ovarian Cancer. Cancer Epidemiol Biomarkers Prev. 2022;31(7):1376-1382.
17. Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer. 2004; 112(1):130-4.
18. Xiang H, Wang L, Sun L, Xu S. The risk of ovarian cancer in hormone replacement therapy users: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2024; 15:1414968.
19. Garg PP, Kerlikowske K, Subak L, et al. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. Obstet Gynecol. 1998, 92:472–9.
20. Coughlin SS, Giustozzi A, Smith SJ, Lee NC. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. J Clin Epidemiol. 2000, 53:367–75.

21. Husby A, Wohlfahrt J, Melbye M. Pregnancy duration and ovarian cancer risk: A 50-year nationwide cohort study. Int J Cancer. 2022;151(10):1717-1725.
22. Babic A, Sasamoto N, Rosner BA, et al. Association Between Breastfeeding and Ovarian Cancer Risk. JAMA Oncol. 2020; 6(6):e200421.
23. Avramenko, A.S., Flanagan, J.M. An epigenetic hypothesis for ovarian cancer prevention by oral contraceptive pill use. Clin Epigenet 2023, 15, 165.
24. Connaughton M, Dabagh M. Association of Hypertension and Organ-Specific Cancer: A Meta-Analysis. Healthcare 2022;10(6):1074.
25. European Comission, EuroStat Data. 22% of people in the EU have high blood pressure. ec.europa.eu. [available online: https://ec.europa.eu/eurostat/web/products-eurostat-news/-/edn-20210929-1, 13.01.2025)
26. Drab A, Kanadys W, Malm M, Wdowiak K, Dolar-Szczasny J, Barczyński B. Association of endometrial cancer risk with hypertension- an updated meta-analysis of observational studies. Sci Rep. 2024, 22;14(1):24884.
27. Gkretsi V, Stylianopoulos T. Cell Adhesion and Matrix Stiffness: Coordinating Cancer Cell Invasion and Metastasis. Front Oncol. 2018;8:145.
28. Yang P, Elhalawani H, Shi Y, et al. A large-scale retrospective study of the overall survival outcome in nasopharyngeal carcinoma with hypertension in Chinese population. Oncotarget. 2017;8:75577–75586.
29. Deckers IA, van den Brandt PA, van Engeland M, et al. Polymorphisms in genes of the renin-angiotensin-aldosterone system and renal cell cancer risk: Interplay with hypertension and intakes of sodium, potassium and fluid: RAAS Polymorphisms and RCC Risk: Interplay with Hypertension and Diet. Int. J. Cancer. 2015;136:1104–1116.
30. Sobczuk P, Szczylik C, Porta C, et al. Renin angiotensin system deregulation as renal cancer risk factor. Oncol. Lett. 2017;14:5059–5068. doi: 10.3892/ol.2017.6826.
31. Jabłońska-Trypuć A, Matejczyk M, Rosochnowlei S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J. Enzyme Inhib. Med. Chem. 2016;31:177–183.
32. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
33. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, (Online). 2011; (cited 31 July 2024; available from: URL http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
34. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp. Clin. Trials 2015, 45, 139–145.
35. Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions, 2nd ed.; John Wiley and Sons, Ltd.: Chichester, UK, 2019; pp. 143–176.
36. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002, 21, 1539–1558.
37. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315: 629–634.
38. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994, 50: 1088–1101.
39. Hayden JA, van der Windt DA, Cartwright JL P, et al. Assessing bias in studies of prognostic factors. Ann. Intern. Med. 2013, 158: 280-286.
40. Parazzini F, Moron, S, La Vecchia C, et al. Ovarian cancer risk and history of selected medical conditions linked with female hormones. European Journal of Cancer 1997, 33(10): 1634–1637.

41. Soler M, Chatenoud L, Negri E, et al. Hypertension and Hormone-Related Neoplasms in Women. Hypertension 1999, 34(2): 320–325.
42. Brinton LA, Sakoda LC, Frederiksen K, et al. Relationships of uterine and ovarian tumors to pre-existing chronic conditions. Gynecol Oncol. 2007;107(3):487-94.
43. Chia VM, O'Malley CD, Danese MD, et al. Prevalence and incidence of comorbidities in elderly women with ovarian cancer. Gynecol Oncol. 2013;129(2):346-52
44. Huang T, Poole EM, Eliassen AH, Okereke OI, Kubzansky LD, Sood AK, Forman JP, Tworoger SS. Hypertension, use of antihypertensive medications, and risk of epithelial ovarian cancer. Int J Cancer. 2016;139(2):291-9.
45. Chen Y, Zhang L, Liu W, Wang K. Case-control study of metabolic syndrome and ovarian cancer in Chinese population. Nutr Metab (Lond). 2017:14:21.
46. Michels KA, McNeel TS, Trabert B. Metabolic syndrome and risk of ovarian and fallopian tube cancer in the United States: An analysis of linked SEER-Medicare data. Gynecol Oncol. 2019;155(2):294-300.
47. Staples JN, Peres LC, Camacho F, et al. Cardiometabolic comorbidities and epithelial ovarian cancer risk among African-American women in the African-American Cancer Epidemiology Study (AACES). Gynecol Oncol. 2020;158(1):123-129.
48. Alrobaiq BM, Alharbi RS, Alhoshan FS, Alnasyan MA, Alahideb A, Omair A. Hypertension and Ovarian Cancer: A Case-Control Study in Saudi Arabia. Cureus. 2023; 15(2):e35294.
49. Carlos-Escalante JA, de Jesús-Sánchez M, Rivas-Castro A, et al. The Use of Antihypertensive Drugs as Coadjuvant Therapy in Cancer. Front Oncol. 2021;11:660943.
50. Mravec B, Horvathova L, Hunakova L. Neurobiology of Cancer: The Role of β-Adrenergic Receptor Signaling in Various Tumor Environments. Int J Mol Sci, 2020, 21(21):1–24.
51. Wegman-Ostrosky T, Soto-Reyes E, Vidal-Millán S, Sánchez-Corona J. The Renin-Angiotensin System Meets the Hallmarks of Cancer. JRAAS - J Renin-Angiotensin-Aldosterone Syst 2015, 16(2):227–33.
52. Stocks T, Van Hemelrijck ., Manjer J, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. Hypertension. 2012;59:802–810.
53. Lindgren AM, Nissinen AM, Tuomilehto JO,et al. Cancer pattern among hypertensive patients in North Karelia, Finland. J. Hum. Hypertens. 2005;19:373–379.
54. Behrens I, Basit S, Jensen A, Lykke JA, et al. Hypertensive disorders of pregnancy and subsequent risk of solid cancer—A nationwide cohort study: Hypertensive disorders of pregnancy and solid cancer. Int. J. Cancer. 2016;139:58–64.
55. Lofterød T, Frydenberg H, Flote V, et al. Exploring the effects of lifestyle on breast cancer risk, age at diagnosis, and survival: The EBBA-Life study. Breast Cancer Res. Treat. 2020;182:215–227.
56. Sun L-M, Kuo H-T, Jeng L-B, et al. Hypertension and subsequent genitourinary and gynecologic cancers risk: A population-based cohort study. Medicine 2015;94:e753.
57. Yassin S, Younis M, Abuzerr S, et al. Extrinsic risk factors for women breast cancer in Gaza strip, Palestine: Associations and interactions in a case-control study. Adv. Breast Cancer Res. 2019;08:11–30.
58. Pereira A, Garmendia ML, Alvarado M., et al. Hypertension and the risk of breast cancer in Chilean women: A case-control study. Asian Pac. J. Cancer Prev. 2012;13:5829–5834.

59. Chuang S-C, Wu G-J, Lu Y-S, et al. Associations between medical conditions and breast cancer risk in Asians: A nationwide population-based study in Taiwan. PLoS ONE. 2015;10:e0143410.
60. Beji NK, Reis N. Risk factors for breast cancer in Turkish women: A hospital-based case-control study. Eur. J. Cancer Care. 2007;16:178–184.
61. Jung SJ, Song ., Choi J-Y, Song N, et al. Association of selected medical conditions with breast cancer risk in Korea. J. Prev. Med. Public Health. 2013;46:346–352.
62. Lee SH, Lee HA, Lee SS, et al. Clinical impact of pre-hypertension on the risk of cancer in male and female subjects. Sci. Rep. 2020;10:9974.
63. Ko S, Yoon S-J, Kim D, et al. Metabolic risk profile and cancer in Korean men and women. J. Prev. Med. Public Health. 2016;49:143–152.
64. Hirai HW, Ching JYL, Wu JCY, et al. Risk factors for advanced colorectal neoplasms in the proximal colon in 6218 subjects undergoing complete colonoscopy: Risk factor of proximal colonic lesions. J. Gastroenterol. Hepatol. 2019;34:113–119.
65. Samarakoon YM, Gunawardena NS, Pathirana A. Behavioral, familial and comorbid illness risk factors of colorectal cancer: A case control study. Ceylon Med. J. 2018;63:113–118.
66. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, et al. Midlife metabolic factors and prostate cancer risk in later life. Int. J. Cancer. 2018;142:1166–1173.
67. Teleka S, Jochems SHJ, Häggström C, et al. Association between blood pressure and BMI with bladder cancer risk and mortality in 340,000 men in three Swedish cohorts. Cancer Med. 2021;10:1431–1438.
68. Peeters PH, van Noord PAHoes AW, Grobbee DE. Hypertension, antihypertensive drugs, and mortality from cancer among women. J. Hypertens. 1998;16:941–947.
69. Navin S, Ioffe V. The association between hypertension and prostate cancer. Rev. Urol. 2017;19:113–118.
70. Azzam N, AlRuthia Y, Alharbi O, et al. Predictors of survival among colorectal cancer patients in a low incidence area. Cancer Manag. Res. 2020;12:451–459.
71. Dibaba D, Ogunsina K, Braithwaite D, et al. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. Breast Cancer Res. Treat. 2019;174:209–218.
72. Tini G, Sarocchi M, Tocci G, et al. Arterial hypertension in cancer: The elephant in the room. Int. J. Cardiol. 2019;281:133–139.
73. Harding JL, Sooriyakumaran M, Anstey KJ, et al. Hypertension, antihypertensive treatment and cancer incidence and mortality: A pooled collaborative analysis of 12 Australian and New Zealand cohorts. J. Hypertens. 2016;34:149–155.
74. Emaus A, Veierød MB, Tretli S, Finstad S.E., Selmer R., Furberg A.-S., Bernstein L., Schlichting E., Thune I. Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Res. Treat. 2010;121:651–660.
75. Hu D, Jia R, Zhang X, et al. Identification of optimal baseline blood pressure predicting postoperative digestive tract cancer-specific mortality in the FIESTA cohort involving 6865 patients. J. Cancer. 2019;10:1794–1799.
76. Yang P, Elhalawani H, Shi Y, et al. A large-scale retrospective study of the overall survival outcome in nasopharyngeal carcinoma with hypertension in Chinese population. Oncotarget. 2017;8:75577–75586.
77. Mumby S, Perros F, Hui C, et al. Extracellular matrix degradation pathways and fatty acid metabolism regulate distinct pulmonary vascular cell types in pulmonary arterial hypertension. Pulm Circ. 2021;11(1):2045894021996190.

78. Duco MR, Murdock JL, Reeves DJ. Vascular endothelial growth factor inhibitor induced hypertension: Retrospective analysis of the impact of blood pressure elevations on outcomes. J Oncol Pharm Pract. 2022;28(2):265-273.
79. Li F, Du H, Li S, Liu J. The Association Between Metabolic Syndrome and Gastric Cancer in Chinese. Front Oncol. 2018;8:326.
80. Gobin E, Bagwell K, Wagner J, et al. A pan-cancer perspective of matrix metalloproteases (MMP) gene expression profile and their diagnostic/prognostic potential. BMC Cancer. 2019;19(1):581.
81. Belo VA, Guimarães DA, Castro MM. Matrix Metalloproteinase 2 as a Potential Mediator of Vascular Smooth Muscle Cell Migration and Chronic Vascular Remodeling in Hypertension. J Vasc Res. 2015;52(4):221-231.
82. Minlikeeva AN, Freudenheim JL, Cannioto RA, et al. History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium. Cancer Causes Control. 2017;28(5):469-486.
83. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. J Clin Oncol. 2016;34(24):2888-2898.

493

494 Table 1. Characteristics of the studies included in the meta-analysis.

495 Table 2. Subgroup analysis.

496

497 Figure 1. Flowchart of inclusion process in accordance with the PRISMA.

498 Figure 2. Forest plot for association between hypertension and ovarian cancer risk.

499

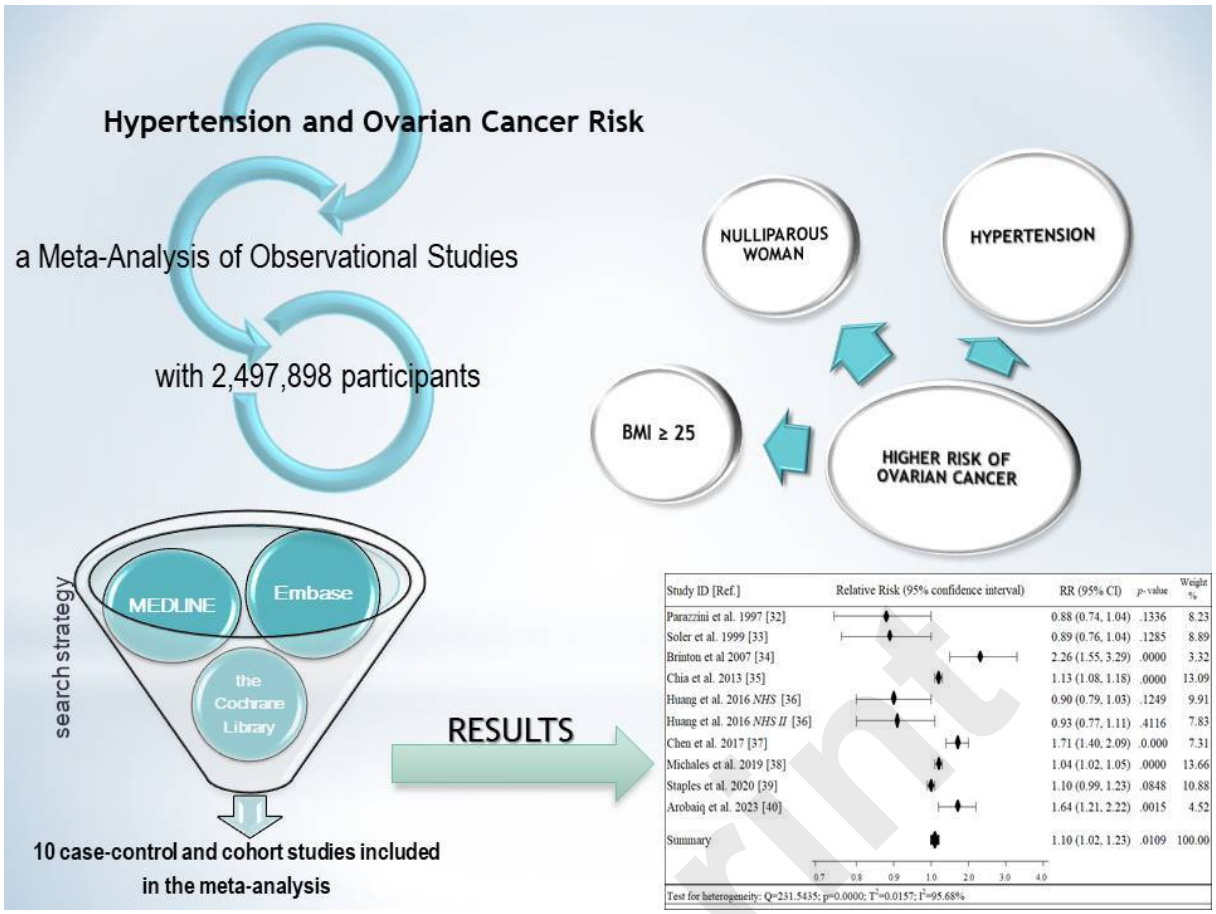

Hypertension and Ovarian Cancer Risk
a Meta-Analysis of Observational Studies
with 2,497,898 participants
NULLIPAROUS WOMAN
HYPERTENSION
BMI ≥ 25
HIGHER RISK OF OVARIAN CANCER
search strategy
MEDLINE
Embase
the Cochrane Library
10 case-control and cohort studies included in the meta-analysis
RESULTS
Study ID [Ref.]
Relative Risk (95% confidence interval)
RR (95% CI)
p-value
Weight %
Parazzini et al. 1997 [32] 0.88 (0.74, 1.04) .1336 8.23
Soler et al. 1999 [33] 0.89 (0.76, 1.04) .1285 8.89
Brinton et al 2007 [34] 2.26 (1.55, 3.29) .0000 3.32
Chia et al. 2013 [35] 1.13 (1.08, 1.18) .0000 13.09
Huang et al. 2016 NHS [36] 0.90 (0.79, 1.03) .1249 9.91
Huang et al. 2016 NHS II [36] 0.93 (0.77, 1.11) .4116 7.83
Chen et al. 2017 [37] 1.71 (1.40, 2.09) .0.000 7.31
Michales et al. 2019 [38] 1.04 (1.02, 1.05) .0000 13.66
Staples et al. 2020 [39] 1.10 (0.99, 1.23) .0848 10.88
Arobaiq et al. 2023 [40] 1.64 (1.21, 2.22) .0015 4.52
Summary 1.10 (1.02, 1.23) .0109 100.00
0.7 0.8 0.9 1.0 2.0 3.0 4.0
Test for heterogeneity: Q=231.5435; p=0.0000; T²=0.0157; I²=95.68%

Table 1. Characteristics of the studies included in the meta-analysis.

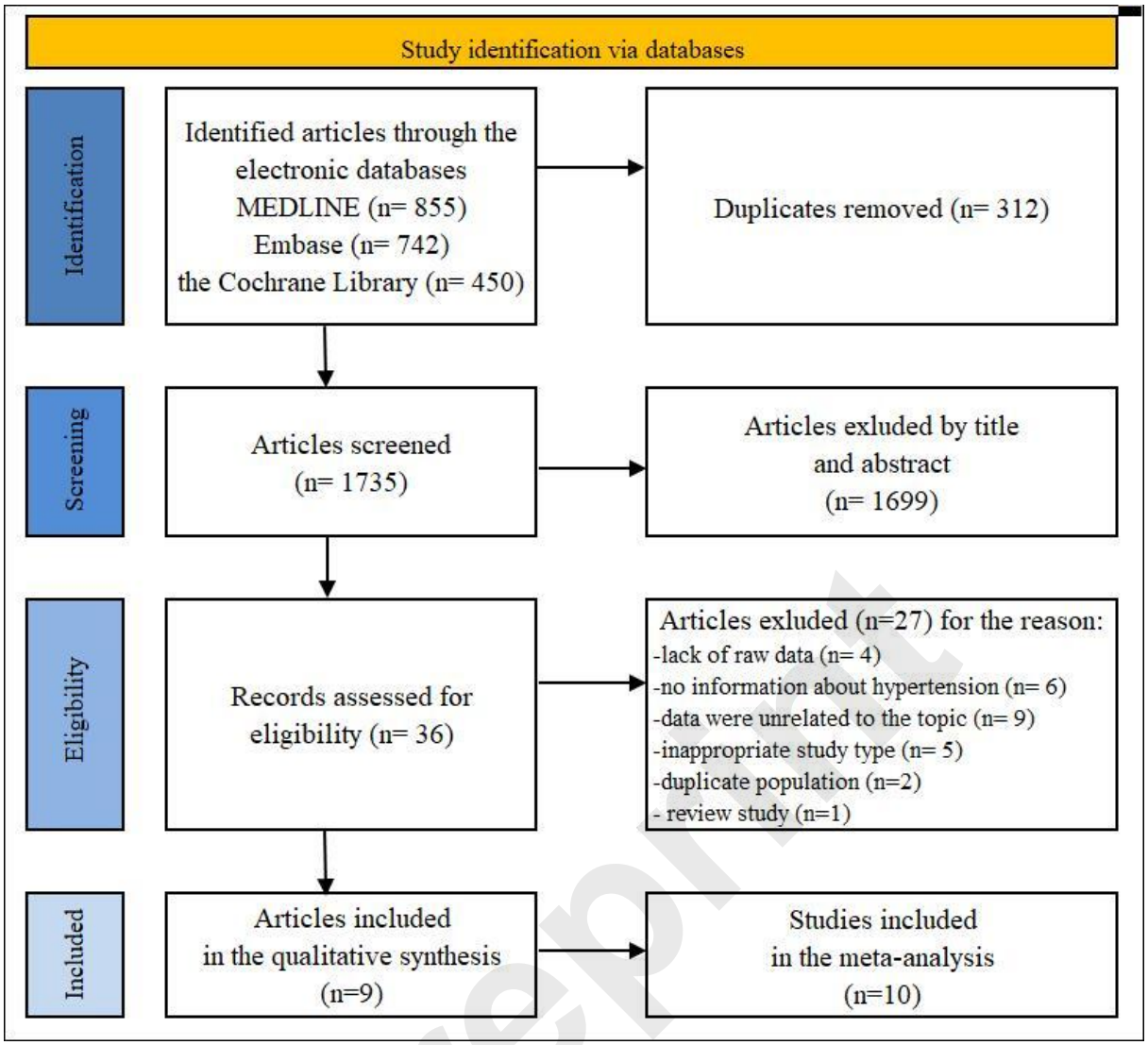
Study ID	Location	Study design	Years of study	Age (years)	Ovarian cancer vs. controls	Definition of Hypertension	NOS
Parazzini et al. 1997 [40]	Italy	Case–control	1983–1991	22–74	971 / 2758	Not available	7
Soler et al. 1999 [41]	Italy	Case–control	1983–1996	Median: 54	970 / 3054	Not available	6
Brinton et al. 2007 [42]	Denmark	Cohort	1978–1998	Mean: 44	2491 / 99,421	Not available	7
Chia et al. 2013 [43]	United States	Cohort	1998–2002	>=66	5087 / 5087	Not available	8
Huang et al. 2016 [44]	United States	Cohort	NHS* 1988–2012	30–50	687 / 1,479,857	BP ≥140/90 mm Hg	7
Huang et al. 2016 [44]	United States	Cohort	NHS* II 1989-2011	25–42	261 / 2,210,479	BP ≥140/90 mm Hg	7
Chen et al. 2017 [45]	China	Case–control	2010–2015	Mean: 52	573 / 1146	BP ≥140/90 mm Hg	8
Michels et al. 2019 [46]	United States** SEER-Medicare	Case–control	1994–2013	68–89	16,850 / 281,878	Not available	7
Staples et al. 2020 [47]	Multicenter*** AACES	Case–control	2010–2015	20–79	593 / 732	Not available	8
Alrobaiq et al. 2023 [48]	Saudi Arabia	Case–control	2016–2019	Mean: 57	133 / 137	SBP >130–mm Hg, and/or DBP >80mm Hg	6

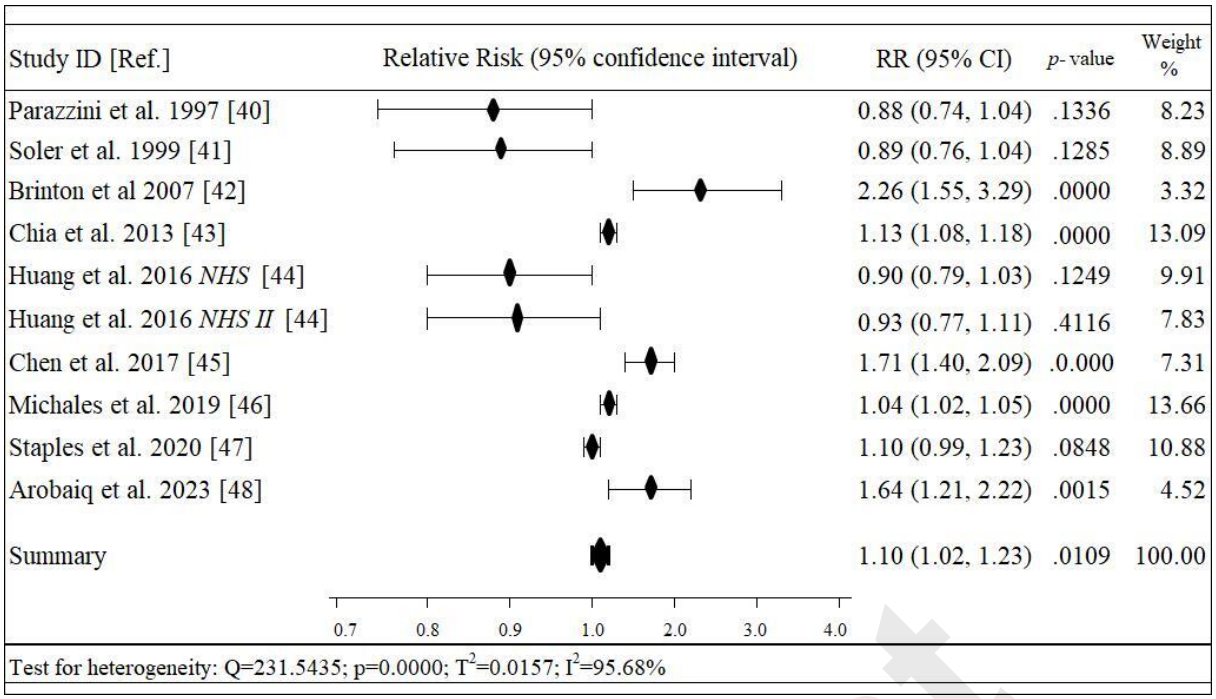
Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; NOS, Newcastle-Ottawa Quality Assessment Scale;
* NHS, Nurses' Health Study; AACES;
** SEER-Medicare, Surveillance, Epidemiology and End Results database;
***African American Cancer Epidemiology Study;

Table 2. Subgroup analysis.

SUBGROUP		No. of studies	RR	95% CI	$p<$	I^2 (%)
Study design	case–control	6	1.11	0.94, 1.31	.2047	90.71
	cohort	5	1.11	0.98, 1.27	.1075	86.82
Newcastle-Ottawa	< 7	2	1.19	0.65, 2.17	.5768	91.95
Scale	≥ 7	9	1.10	0.99, 1.23	.0618	83.63
Parity	gave birth	5	1.43	1.05, 1.96	.0025	86.91
	nulliparous	5				
Diabetes	yes	4	1.27	0.94, 1.72	.1155	97.99
	no	4				
Menopausal status	postmenopausal	4	1.20	0.89, 1.61	.2242	94.75
	premenopausal	4				
Body mass index	≥ 25	4	1.12	1.07, 1.18	.0001	00.00
	< 25	4				
Cigarette smoking	yes	2	2.20	0.53, 9.16	.2791	99.17
	no	2				

Abbreviations: No., number; RR, relative risk; CI, confidence interval, p<, p value for heterogeneity


Study identification via databases
Identification
Identified articles through the electronic databases MEDLINE (n= 855) Embase (n= 742) the Cochrane Library (n= 450)
Duplicates removed (n= 312)
Screening
Articles screened (n= 1735)
Articles exluded by title and abstract (n= 1699)
Eligibility
Records assessed for eligibility (n= 36)
Articles exluded (n=27) for the reason:
-lack of raw data (n= 4)
-no information about hypertension (n= 6)
-data were unrelated to the topic (n= 9)
-inappropriate study type (n= 5)
-duplicate population (n=2)
- review study (n=1)
Included
Articles included in the qualitative synthesis (n=9)
Studies included in the meta-analysis (n=10)


Study ID [Ref.]
Relative Risk (95% confidence interval)
RR (95% CI)
p- value
Weight %
Parazzini et al. 1997 [40]
0.88 (0.74, 1.04)
.1336
8.23
Soler et al. 1999 [41]
0.89 (0.76, 1.04)
.1285
8.89
Brinton et al 2007 [42]
2.26 (1.55, 3.29)
.0000
3.32
Chia et al. 2013 [43]
1.13 (1.08, 1.18)
.0000
13.09
Huang et al. 2016 NHS [44]
0.90 (0.79, 1.03)
.1249
9.91
Huang et al. 2016 NHS II [44]
0.93 (0.77, 1.11)
.4116
7.83
Chen et al. 2017 [45]
1.71 (1.40, 2.09)
.0.000
7.31
Michales et al. 2019 [46]
1.04 (1.02, 1.05)
.0000
13.66
Staples et al. 2020 [47]
1.10 (0.99, 1.23)
.0848
10.88
Arobaiq et al. 2023 [48]
1.64 (1.21, 2.22)
.0015
4.52
Summary
1.10 (1.02, 1.23)
.0109
100.00
0.7
0.8
0.9
1.0
2.0
3.0
4.0
Test for heterogeneity: Q=231.5435; p=0.0000; T2=0.0157; I2=95.68%