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Diabetes mellitus and the risk of ovarian cancer: a systematic review and meta-analysis of cohort and case–control studies

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ABSTRACT

Objective Emerging evidence from observational studies (cohort and case–control studies) suggests that a history of diabetes mellitus (DM) has been linked to increased risk of ovarian cancer (OC), but the association between them remains inconclusive. The aim of this systematic review and meta-analysis of observational studies was to clarify this association.

Design Systematic review and meta-analysis.

Methods We searched PubMed, Embase and the Cochrane library databases published from the inception through 9 April 2020 without language restriction. Observational studies that evaluated the correlation between DM and the incidence of OC were included in our study. Relative risk (RR) with 95% CI was pooled by use of a random-effects model.

Results A total of 36 epidemiological articles, including 9 case–control and 27 cohort studies, were finally enrolled, consisting of 14 496 incident cases of OC. Synthesised RRs of developing OC by history of DM were 1.20 (95% CI=1.10 to 1.31) for all eligible studies, 1.08 (95% CI=0.77 to 1.53) for case–control studies and 1.22 (95% CI=1.11 to 1.33) for cohort studies. The above-mentioned positive association persisted across most of subgroup analyses, whereas it was not significant among studies from North American and European countries, level of unadjusted, and patients with low-quality and gestational DM group. The cumulative meta-analysis and sensitivity analysis showed pooled effect was stable and reliable, and no apparent publication bias was identified in this study.

Conclusions Our study found weaker but still association between DM and OC risk. However, further well-designed prospective studies that control for potential confounders are warranted.

Strengths and limitations of this study

- ► Largest systematic review and meta-analysis examining diabetes mellitus (DM) and the risk of ovarian cancer (OC).
- ► We also investigated the link between type 1 DM, type 2 DM or gestational DM and OC risk, respectively, which might be more generalisable than previous published meta-analyses.
- ► The sensitivity analysis and cumulative meta-analysis showed pooled effect was stable and reliable, and no apparent publication bias was identified in our study.
- ► Substantial heterogeneity was observed among these studies.

INTRODUCTION

Diabetes mellitus (DM), characterised as hyperglycaemia, is a rock-ribbed and costly chronic ailment metabolic disease,[1] divided into four different subtypes—type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM) and other specific categories of diabetes.[2] The International Diabetes Federation report of 2017 has estimated that the number of DM will reach approximately 693 million (9.9%) by 2045, up over 1.5-fold from 451 million (8.4%) in 2017 among adults aged 18–99 years worldwide.[3] That is, the number of DM will continue to rise due to the increasing ageing population and prevalence of rising obesity, recognised as a global public health issue challenge of the 21st century across the world.[4 5]

Ovarian cancer (OC), as a leading cause of death in women with gynaecological malignancy, is the fifth leading cause of carcinoma-related death in women, with a 5-year survival rate varying from 30% to 40%.[6 7] The Global Cancer Observatory predicted that in 2018 there are 295 414 people with OC and the incidence of this disease worldwide increased by 47% in 2040 estimates (434 184).[8] Furthermore, in the last 30 years, the cure rate for OC has barely budged.[9]

Too well known, the ovarian disease, which is located deep in the pelvic cavity, lacks early identifiable clinical symptoms, specific laboratory indicators as well as effective screening strategies, making early lesions difficult to detect.[10] Therefore, the majority

of patients are already diagnosed in an advanced stage owing to the insidious onset of OC.[11 12] Early identification and intervention is of vital significance in controlling cancer, especially for OC; unfortunately, few modifiable risk factors for this cancer are well documented such as smoking, hormonal replacement therapy and dietary factors.[13 14] Besides, other immutable risk factors included age of menarche, age of natural menopause, endometriosis and so on.[13]

In recent years, the causal relationship between DM and cancer risk has been widely concerned in cancer prevention research. Accumulating lines of evidence have demonstrated that DM is associated with greater risk of certain types of cancer at multiple sites, such as pancreatic, liver and endometrium cancer.[15–20] Nonetheless, the relationship between DM and the observed excess risk of cancer may be a result of confounding factors such as age, obesity, physical activity and exogenous insulin therapy.[15 21 22]

In recent decades, there are several epidemiological observational studies in this area since the first study investigating the association between DM and subsequent risk of OC in women was published. Several cohort [23–26] and case–control[27] studies have been reported that a history of DM is associated with an augmented risk of OC, however, other relevant studies found a negative significant association.[28–31] Because obesity or high body mass index (BMI) has been regarded as a risk factor for both DM and OC, it remains unclear as to whether or not DM is associated with an increased OC risk on account of confounding by this factor. Studies in recent years have shown that DM may be closely related to OC, but epidemiological findings between them remain open to discussion.

In view of these conflicting results, we decided to update a meta-analysis of case–control and cohort studies to clarify whether there is an association between DM and OC risk in women.

METHODS

This meta-analysis was performed and reported based on the Meta-analysis Of Observational Studies in Epidemiology protocol checklist[32] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[33] (online supplemental file 1).

Patient and public involvement

Since our meta-analysis is based on previous published researches, patient and public involvement is not required.

Search strategy and selection criteria

Online databases, such as PubMed, Embase and the Cochrane library databases, were searched from the inception to 9 April 2020 for observational studies. The inclusion criteria were as follows: (1) original observational studies (cohort and case–control studies), (2) evaluating the association between DM and OC risk, (3) the risk estimates were reported, (4) human population, (5) without language restriction. The Medical Subject Headings keywords were as follows: “diabetes mellitus”, “diabetes mellitus, type 1”, “diabetes mellitus, type 2”, “diabetes, gestational”, “ovarian neoplasms”, “ovarian cancer”, “cohort studies”, “case-control studies”. A comprehensive search strategy was provided in online supplemental file 2. In addition, we searched the potentially eligible bibliographies of relevant articles for the purpose of completeness. The exclusion criteria in this meta-analysis were: randomised controlled trial, case reports, letters, reviews or animals studies. Eligibility assessment was performed by two authors (LW and LZ).

First, these two authors excluded duplicates via a reference manager. Second, the two authors read the title and abstract to further screen the eligible studies. Finally, we included the studies by reviewing the full text. Any disagreements were solved by means of discussion.

Data extraction

Data were extracted by one author (LW), and then checked by a second investigator (LZ). The main extracted information is described in tables 1 and 2. The association between DM and OC was the primary outcome of interest of our study.

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) score was employed to evaluate the study quality of observational studies (cohort and case–control studies), with a maximum score of 9, of which 0–3, 4–6 and 7–9 scores were considered as low, fair and high quality, respectively.[34]

Assessment of risk of bias

All selected literature was subjected to a sensitivity analysis to explore the robustness of the pooled effects.[35]

Statistical analysis

The effect estimates of original studies were five measures of association, including relative risk (RR), standardised incidence ratio, incidence rate ratio, HR and OR. Given that the frequency of OC is relatively low, the last four measures were considered to yield approximately equal estimates to that of the RR. Therefore, we reported all pooled results as RR with 95% CI.[36]

The statistical heterogeneity was measured by χ^2 (threshold p=0.10) and quantified by the I^2 statistic. The publication bias was also appraised using the funnel plot, Begg’s and Egger’s test. We prefer to choose the random-effects model to analyse all data due to the conservativeness of the analysed results.[37] The statistical analyses were performed with the Stata V.12.0 software (StataCorp, College Station, Texas, USA). All statistical analyses were two-sided with an α level of 0.05.

Prespecified subgroup analyses were carried out to identify the sources of heterogeneity between studies in accordance with the study design (case–control vs cohort studies), DM types (T1DM vs T2DM vs GDM), duration of follow-up (<10 years vs ≥10 years), level of adjustment (unadjusted vs adjusted and BMI adjusted vs BMI unadjusted), study quality (NOS ≥7 vs <7 points) and geographical areas (North America vs Europe vs Asia vs Oceania). Subsequently, a cumulative

Table 1 Baseline characteristics of the cohort studies

Study ID	Country or region	Study period	Follow-up duration (years)	Population	Age (years)	No of subjects	No of OC cases	Population setting	NOS score
Weiderpass *et al*[55]	Sweden	1965–1994	5.7	Type 2 DM	66.4	141 627	337	PBR	8
Zendehdel *et al*[56]	Sweden	1965–1999	15.0	Type 1 DM	17.3	14 323	9	PBR	7
Swerdlow *et al*[57]	UK	1972–2003	18.0	Type 1 DM	<30	11 047	16	PBR	7
Swerdlow *et al*[57]	UK	1972–2003	18.0	Type 2 DM	30–49	2122	6	PBR	7
Inoue *et al*[58]	Japan	1990–2003	10.7	Type 2 DM	51.8	51 223	74	PBR	8
Khan *et al*[59]	Japan	1988–1997	7.6	Type 2 DM	40–79	33 503	29	PBR and HBR	7
Hemminki *et al*[60]	Sweden	1964–2007	15.0	Type 2 DM	39–75	24 827	192	PBR and HBR	7
Chodick *et al*[61]	Israel	2000–2008	8.0	Type 2 DM	62	47 682	88	PBR	7
Shu *et al*[38]	Sweden	1964–2006	17.0	Type 1 DM	12.3	11 290	9	PBR and HBR	8
Wotton *et al*[62]	Southern England	1963–1998	—	Type 2 DM	>30	132 271	37	PBR and HBR	7
Wotton *et al*[62]	Southern England	1999–2008	—	Type 2 DM	>30	90 427	8	PBR and HBR	7
Johnson *et al*[63]	Canada	1994–2006	4.4	Type 2 DM	60.7	169 012	295	PBR	7
Lambe *et al*[64]	Sweden	1985–1996	11.7	Type 2 DM	46.6	230 737	536	PBR	8
Gapstur *et al*[31]	USA	1992–2007	—	Type 2 DM	62.28	63 440	524	PBR	7
Lo *et al*[65]	Taiwan	1996–2009	3.5	Type 2 DM	60.45	912 447	948	PBR	7
Chen *et al*[30]	Taiwan	2000–2008	>9.0	Type 2 DM	61.09	638 618	935	PBR	9
Hsu *et al*[66]	Taiwan	2000–2008	6.2	Type 1 DM	49.2	7752	7	PBR	7
Harding *et al*[25]	Australia	1997–2008	12.0	Type 1 DM	27.4	38 644	38	PBR	7
Harding *et al*[25]	Australia	1997–2008	5.8	Type 2 DM	60.4	408 426	792	PBR	7
Dankner *et al*[24]	Israel	2002–2012	11.0	Type 2 DM	46.63	1 152 122	1495	PBR	8
Carstensen *et al*[21]	Multicountries	1972–2014	—	Type 1 DM	<40	—	252	PBR	7
Fuchs *et al*[23]	Israel	1988–2013	12.0	GDM	28.45	104 715	56	PB	7
Ballotari *et al*[26]	Italy	2010–2013	4.0	Type 2 DM	47	195 930	160	PBR	6
Han *et al*[28]	Korean	2002–2015	10.0	GDM	27.33	102 900	1148	PB	8
He *et al*[29]	China	2003–2014	—	Type 2 DM	63.7	14 193	24	PB	7
Bao *et al*[67]	Swedish	1998–2014	—	Type 2 DM	62.57	25 154	57	Twin	6
Saarela *et al*[68]	Finland	1988–2014	10.5	Type 2 DM	—	223 602	977	PBR	6
Linkeviciute-Ulinskiene *et al*[15]	Lithuania	2000–2012	6.8	Type 2 DM	64.0	78 823	249	PBR	7
Peng *et al*[69]	Taiwan	2000–2013	6.8	GDM	28.97	990 572	1196	PB	7
Pace *et al*[70]	Canada	1990–2007	13.1	GDM	—	68 588	56	PB	7

DM, diabetes mellitus; GDM, gestational DM; HBR, hospital-based registry; NOS, Newcastle–Ottawa Scale; OC, ovarian cancer; PB, population-based; PBR, population-based registry.

Table 2 Baseline characteristics of the case–control studies

Study ID	Country or region	Study period	Population	Age (years)	No of cases/controls	Population setting	NOS score
O'Mara *et al*[71]	USA	1957–1965	Type 2 DM	30–89	328/2342	HB	5
Adler *et al*[72]	USA	1975–1987	Type 2 DM	51.98	595/1587	PBR	5
Parazzini *et al*[73]	Italy	1983–1991	Type 2 DM	52.52	971/2758	HB	5
Mori *et al*[74]	Japan	1994–1996	Type 2 DM	54.24	89/323	PB	7
Kuriki *et al*[75]	Japan	1988–2000	Type 2 DM	57.57	218/33 569	PBR and HBR	6
Reis and Kizilkaya Beji[27]	Turkey	2002–2003	Type 2 DM	51.0	217/1050	HB	6
Attner *et al*[76]	Sweden	1998–2007	Type 2 DM	—	289/2207	PBR	7
Bosetti *et al*[77]	Italy	1991–2009	Type 2 DM	56.70	1031/2411	HB	5
Ruiz *et al*[78]	USA	2003–2008	Type 2 DM	57.5	208/224	HB	5

DM, diabetes mellitus; HB, hospital-based; HBR, hospital-based registry; NOS, Newcastle–Ottawa Scale; PB, population-based; PBR, population-based registry.

meta-analysis for the association between DM and the risk of OC was performed to detect the accumulated effects of DM on OC risk based on the publication year.

RESULTS

Search results and study characteristics

The details on the study-selection procedure are shown in figure 1. As of 9 April 2020, our search strategy initially identified 543 records and 36 citations met criteria for final inclusion after screening. These 36 publications published between 1985 and 2020, which included 9 case–control and 27 cohort studies, were eligible for final analysis, with 14 496 incident cases of OC in this meta-analysis.

Among these included studies, 6 studies evaluated the relation between T1DM and risk of OC, 28 studies investigated the relationship between T2DM and OC risk, and the remaining 4 studies assessed this association between GDM and OC risk as well. With regard to geographical location, 1 study originated from Oceania, 1 in Europe and Oceania, 6 in North America, 14 in Europe and 14 studies from Asia. The follow-up period of cohort studies

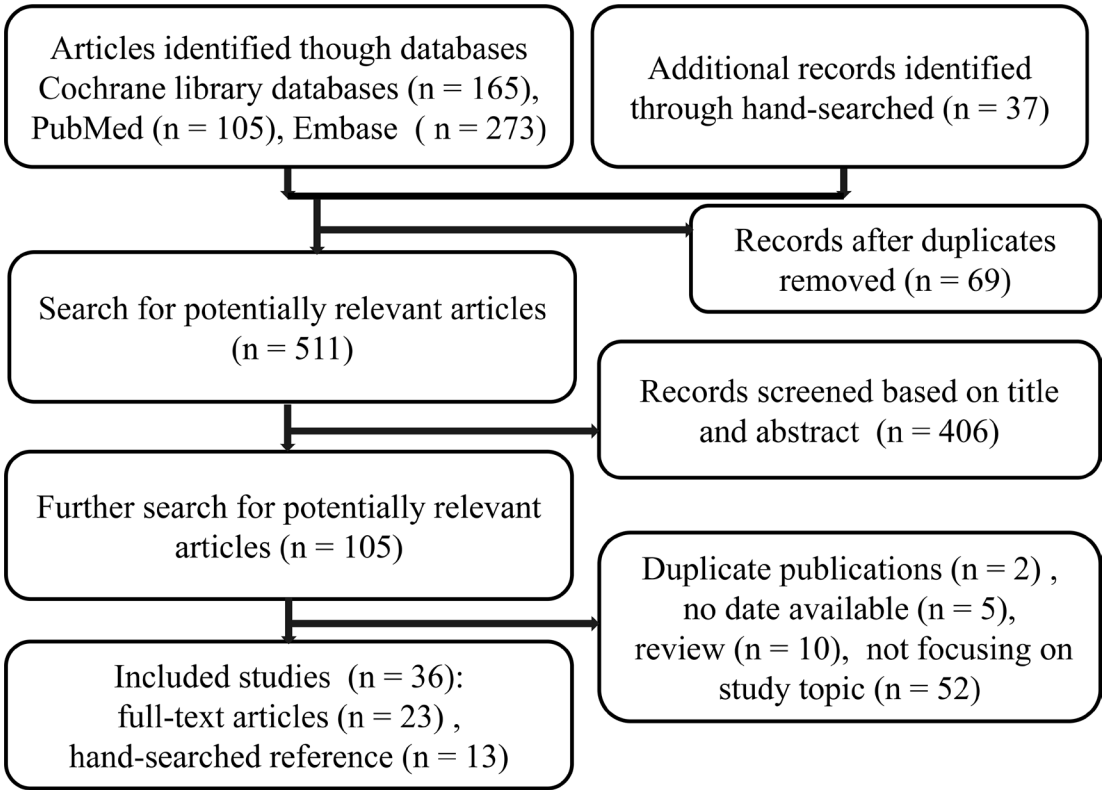

Figure 1 Article screening flow diagram.

varied, ranging from 3.5 to 18.0 years. Studies were heterogeneous regarding age, ranging from 12.3 to 89 years. The case–control studies comprised 3946 OC cases and 46 471 controls.

The main characteristics of included studies are given in tables 1 and 2.

Assessment of study quality

The NOS quality stars ranged between 5 and 9, and the average score was 6.3 for case–control and 7.19 for cohort studies (online supplemental file 3). Two (22.22%) case–control and 24 (88.89%) cohort studies were regarded as high quality (NOS ≥7 points).

The sensitivity analysis suggested no single study had significant influence on the summarised RR, which revealed the stability of pooled estimate (online supplemental file 4). No obvious evidence of publication bias was detected by inspection of the funnel plot and statistical tests (Begg's test, p=0.246; Egger's test, p=0.132; online supplemental file 4).

Synthesis of primary outcome

All 36 studies reported the association between DM and OC risk, and the combined RR was 1.20 (95% CI=1.10 to 1.31), with substantial statistical heterogeneity among these studies (X^2=152.43, p=0.000; I^2=75.1%; figure 2).

The results of subgroup analysis

When stratified by study design subtypes, a statistically significant effect of DM on OC risk was observed in cohort studies (RR, 1.22; 95% CI=1.11 to 1.33), however, the case–control studies found no relationship between

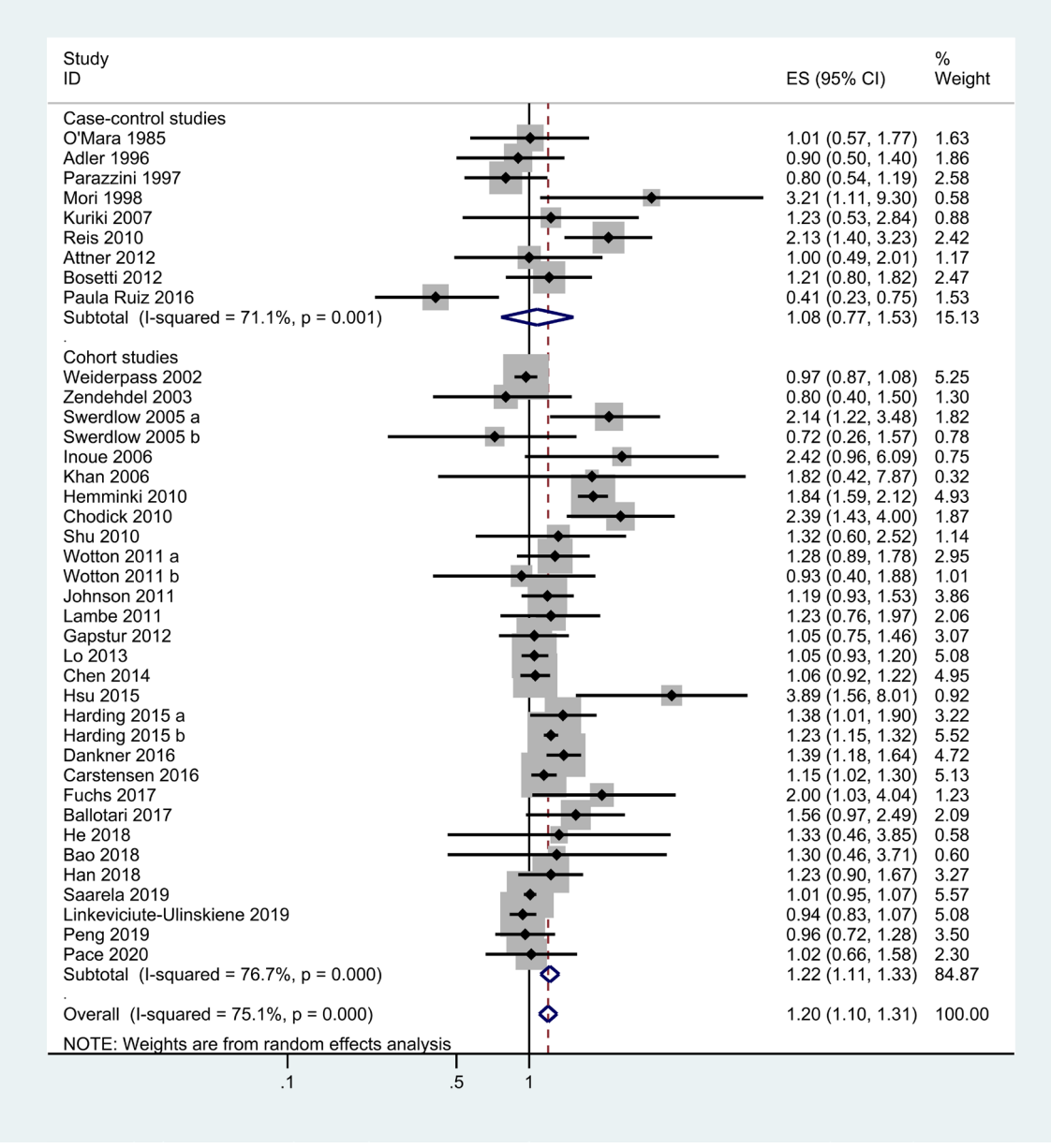

Figure 2 Meta-analysis of the association between DM and the risk of OC. DM, diabetes mellitus; ES, effect size; OC, ovarian cancer.

DM and the incidence of OC in spite of a positive trend (RR, 1.08; 95% CI=0.77 to 1.53). In the analysis stratified according to DM types, a positive significant association was noted in both T1DM (RR, 1.44; 95% CI=1.06 to 1.95) and T2DM group (RR, 1.17; 95% CI=1.06 to 1.30), but not in GDM group (RR, 1.14; 95% CI=0.90 to 1.43).

A subgroup analysis was conducted considering the level of adjustment, the summary of RR in adjusted studies (RR, 1.23; 95% CI=1.10 to 1.37) was more marked than in unadjusted studies (RR, 1.13; 95% CI=0.98 to 1.31). Both BMI-adjusted (RR, 1.37; 95% CI=1.16 to 1.62) and BMI-unadjusted (RR, 1.12; 95% CI=1.03 to 1.22) analyses were associated with an augmented risk of OC. In further analysis by the length of follow-up, women who experienced a long period of follow-up, that is, ≥10 years (RR, 1.33; 95% CI=1.09 to 1.63) were more likely to have a higher risk of OC than those who had less than 10 years (RR, 1.14; 95% CI=1.01 to 1.29).

In a subgroup analysis by continent, DM was significantly positively correlated with increased OC risk among studies conducted in Asia (RR, 1.43; 95% CI=1.20 to 1.71) and Oceania (RR, 1.24; 95% CI=1.16 to 1.32) except for European (RR, 1.15; 95% CI=0.99 to 1.35) and North American (RR, 0.94; 95% CI=0.73 to 1.21) studies. The RR was 1.24 (95% CI=1.12 to 1.36) for high-quality studies with significant difference and 1.07 (95% CI=0.85 to 1.35) for non-high-quality studies without statistical significance (online supplemental file 4).

The results of subgroup analyses are shown in table 3.

Table 3 Summary risk estimates of the subgroup analysis results of DM and OC risk

Subgroup	Studies (n)	RR (95% CI)	I^2 (%)	P value
Total	36	1.20 (1.10 to 1.31)	75.1	0.000
Study design				
Case–control	9	1.08 (0.77 to 1.53)	71.1	0.001
Cohort	27	1.22 (1.11 to 1.33)	76.7	0.000
DM types				
Type 1 DM	6	1.44 (1.06 to 1.95)	67.2	0.009
Type 2 DM	28	1.17 (1.06 to 1.30)	78.5	0.000
GDM	4	1.14 (0.90 to 1.43)	31.5	0.224
Geographical location				
North America	6	0.94 (0.73 to 1.21)	53.9	0.054
Europe	14	1.15 (0.99 to 1.35)	81.3	0.000
Asia	14	1.43 (1.20 to 1.71)	69.5	0.000
Oceania	1	1.24 (1.16 to 1.32)	0.00	0.486
Follow-up				
<10 years	11	1.14 (1.01 to 1.29)	77.0	0.000
≥10 years	12	1.33 (1.09 to 1.63)	84.8	0.000
Level of adjustment				
No	8	1.13 (0.98 to 1.31)	85.0	0.000
Yes	28	1.23 (1.10 to 1.37)	63.9	0.000
BMI				
Yes	13	1.37 (1.16 to 1.62)	53.5	0.011
No	23	1.12 (1.03 to 1.22)	69.9	0.000
Study quality				
NOS <7	10	1.07 (0.85 to 1.35)	66.7	0.001
NOS ≥7	26	1.24 (1.12 to 1.36)	74.2	0.000

BMI, body mass index; DM, diabetes mellitus; GDM, gestational DM; NOS, Newcastle–Ottawa Scale; OC, ovarian cancer; RR, relative risk.

Cumulative meta-analysis

Although there is no association between DM and the risk of OC before Shu *et al*[38] (cumulative RR, 1.32; 95% CI=1.00 to 1.74), subsequent studies after this study show a consistently positive association (cumulative RR, 1.32; 95% CI=1.01 to 1.71; figure 3).

DISCUSSION

Our systematic review and meta-analysis of 27 cohort and 9 case–control studies evaluated the association between DM and the incidence of OC, and suggested that women with DM had a 20% elevated risk of OC as compared with those without a history of DM. Similar positive finding was observed when we analysed by cohort studies, however, no meaningful difference was noted when pooled by the case–control studies. Since there is inherent nature of recall and select bias in case–control study, certain biases might lead to inaccurate reporting of causal relationship.[39]

A subgroup meta-analysis based on DM types indicated that the risk of OC in T1DM group (44%) is higher than in T2DM group (17%), while no significant association is found in GDM group. That may explain the excess risk in populations with T1DM that persons with T1DM usually require exogenous insulin treatment for the purpose of regulating blood glucose level,[40] and those who are treated with insulin appear to be at higher risk to develop cancer.[41] On the other hand, due to the limited numbers of eligible studies and sample sizes, the result obtained from GDM group should be interpreted with caution. In addition, owing to an increased risk of cancer with age, the length of follow-up for patients with GDM might be too short to detect cancers in young women.[42]

The positive link was even more prominent arresting in studies that adjusted for covariates (ie, age, obesity, hypertension, reproductive history, smoking or alcohol) than these for unadjusted covariates analysis. Similarly, compared with subjects without BMI adjusted, the significant relationship between DM and OC also still existed and became stronger in BMI-adjustment studies. These two suggested DM is a potential independent risk factor for the development of OC.

In keeping with finding, women with DM had a less risk of OC during the early follow-up period (<10 years) than during the late follow-up duration (≥10 years). Owing that OC occurs mostly in middle-aged and elderly women, therefore, women who enjoyed a long-term follow-up are more susceptible to OC compared with those who had a short follow-up period.[26] Subgroup analysis on geographical areas, the Asian and Oceania studies, yielded similar positive results as the aforementioned analyses apart from European and North American studies, which is consistent with a previous

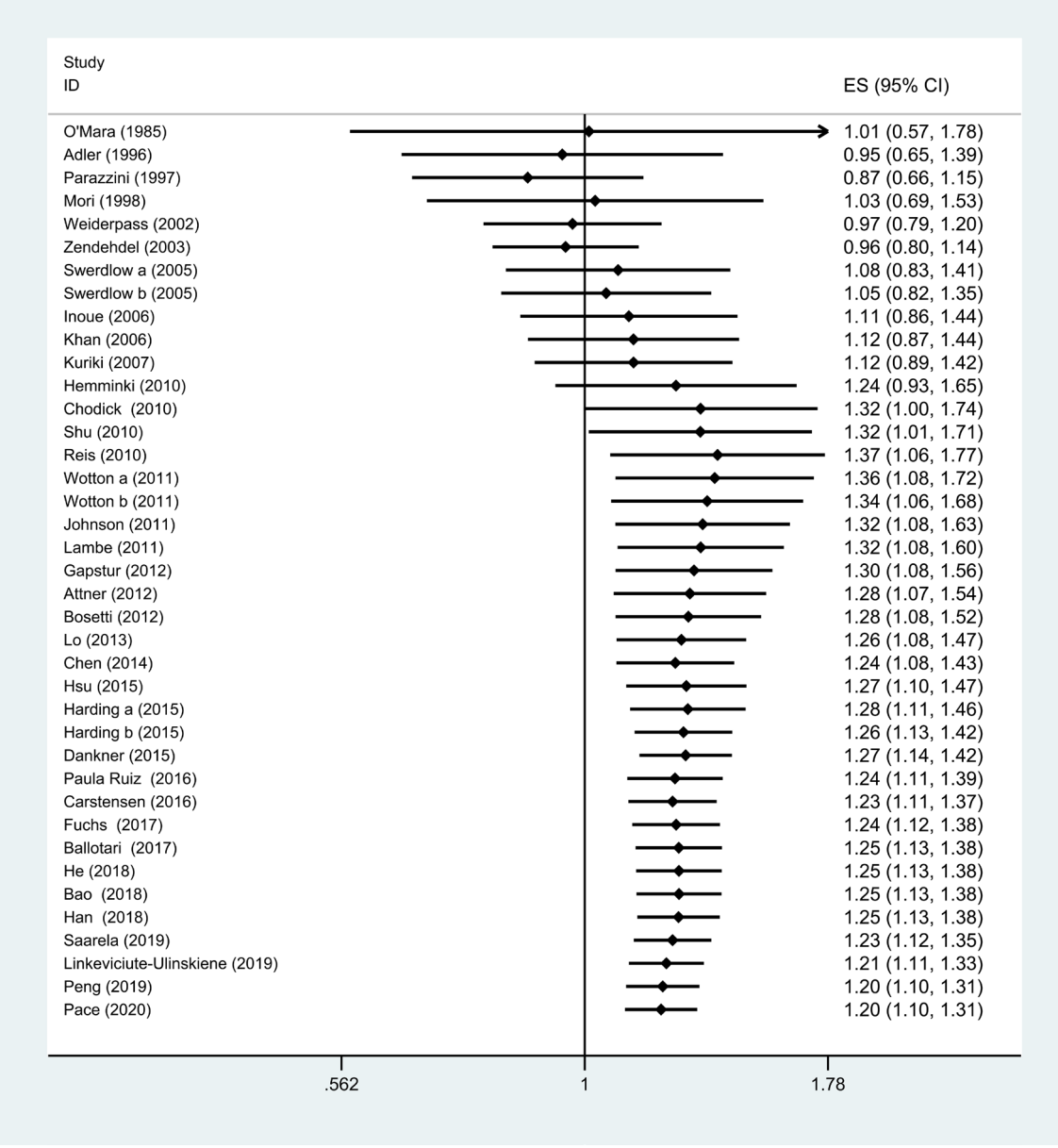

Figure 3 Cumulative meta-analysis of the association between DM and risk of OC. DM, diabetes mellitus; ES, effect size; OC, ovarian cancer.

meta-analysis described by Zhang *et al*.[43] Geographical variation in the incidence of OC in women worldwide might explain such heterogeneity. The significant association was consistent in high-quality studies (NOS ≥7 points) except for non-high-quality studies (NOS <7 points).

To our knowledge, only three previous meta-analyses were published in this field. In 2013, Lee *et al*[44] performed a first meta-analysis with 7 case–control and 11 cohort studies, and supported that patients with DM have a 17% increased risk of OC compared with patients without DM. A subsequent meta-analysis carried out by Wang *et al* in 2017 with 14 cohort studies exposed that DM is associated with a 19% raised risk of OC,[45] which was further confirmed by a meta-analysis with 15 cohort studies (32%) later the same year.[43] Our results, in accordance with these relevant studies, suggested that DM is correlated with a 20% increased risk of OC, and a significant positive association between them was observed in cohort studies (22%) but not in case–control studies (8%). Furthermore, the result of cumulative meta-analysis showed that it is not until in Shu *et al*[38] that aforementioned positive result first appeared and the association tended to be stable thereafter.

The underlying carcinogenesis effect of DM to ovary was not completely uncovered at present, but several plausible mechanisms have been postulated to explain the links between them. Previous studies have shown that the neoplastic process has been considered to influenced by DM through these mechanisms, mainly including hyperglycaemia, hyperinsulinaemia and chronic inflammation.[46 47] Because of a prolonged exposure to inflammation and hyperglycaemic condition, the reiterant lesion and repair cycles which are associated with incessant ovulation process could be slowed down, thus, resulting in an underlying risk of

OC.[48] Studies have shown that the hyperglycaemic state of patients with DM produces many of inflammatory cytokines, such as tumour necrosis factor-α, interleukin-1β (IL-1β) and IL-6, thereby facilitating a tumour-favourable microenvironment and potentially causing immune hyperactivation and tumour cell growth.[49 50] Moreover, previous research confirmed that higher concentration of glucose is associated with an elevated expression level of vascular endothelial growth factor, and the latter has been known as a potent proangiogenic factor,[51] indicating a tumour-promotion effect of DM. Biologically, an excess of insulin, as a growth factor, may stimulate the growth of tumour, whether endogenous or exogenous.[52] Besides, several oral antihyperglycaemic therapies (sulfonylureas) have been shown to increase risk of cancer development.[53] However, metformin, as an insulin sensitiser, may reduce this risk mediated by stimulation of AMP-activated protein kinase and inhibition of gluconeogenesis in the liver.[54]

Various strengths of our meta-analysis should be mentioned. First, this update study included a comprehensive search strategy, a great number of participants, a detailed subgroup and sensitivity analysis, which provided a more reliable estimate of the association between DM and OC risk. Second, we investigated the link between T1DM, T2DM or GDM and the risk of OC, respectively, which might be more generalisable than the previous three meta-analyses. Third, most of the included observational studies have controlled at least one potential confounder, such as age, BMI, obesity, drinking and smoking habits, as well as regular physical exercise, suggesting the reliability of the outcomes. Finally, in a cumulative meta-analysis by publication date, the 95% CIs became progressively narrower as the number of sample size increases, indicating increased estimation accuracy of risk estimates.

However, the present study has several limitations. First, the aggregated data of our study were originated from observational studies, thus, the causality between DM and the prevalence of OC remains speculative. Second, the heterogeneity among the individual studies was substantial, so does in subgroup analysis. Finally, although the majority of eligible studies adjusted for many potential confounders, we could not determine the influence of other various factors such as different treatment modalities (eg, sulfonylureas, insulin-sensitising agents and insulin) of DM, oral contraceptive use and hormone replacement therapy. Therefore, further trials are warranted to clarify the association.

CONCLUSIONS

Accumulated evidence from cohort and case–control studies suggested that women with a history of DM have a higher risk of OC than those without, despite significant heterogeneity among individual studies. However, further high-quality studies with prospective design that are adequately controlled for potential confounding factors should be conducted to identify our results.

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Contributors HH, LW and LZ conceived the study idea and designed the study. LW and LZ collected literature, reviewed the articles, collected the data and performed all data analyses. LW, LZ, HH, BX and MC were responsible for drafting of the manuscript. All the authors approved the final version of this manuscript.

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