BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040137
Article Type:	Original research
Date Submitted by the Author:	06-May-2020
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Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, Gynaecological oncology < GYNAECOLOGY, Adult oncology < ONCOLOGY

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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 in women were included in our study. Relative risk (RR) with 95% confidence interval (CI) were 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. Synthesized RR of developing OC by history of DM was 1.20 (1.10,1.31) for all

eligible studies, 1.08 (0.77,1.53) for case-control studies and 1.22 (1.11,1.33) for cohort studies. The above-mentioned positive association persisted across most of subgroup analyses, whereas was not significant among studies from North America and Europe countries, level of unadjusted, low-quality study and gestational DM patients. 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 significant association between DM and OC risk. However, further well-designed prospective studies that control for potential confounders and confirm the association with subtypes of OC 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 GDM and OC risk, respectively, which might be more generalizable 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.

►No data on the histologic subtypes of OC.

INTRODUCTION

Diabetes mellitus (DM), characterized as hyperglycemia, is a rock-ribbed and costly chronic ailment metabolic disease,[1] dividing into four different subtypes—type 1 DM (T1DM), type 2 DM (T2DM), gestational diabetes mellitus (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 in worldwide.[3] That is, the number of DM will continue to rise due to population ageing and rising obesity, recognized 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 gynecological 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 predicts that in 2018 there are 295,414 people with OC and the incidence of this disease in the worldwide increased by 47% in 2040 estimates (434,184).[8] In the last 30 years, the cure rate for OC has barely budged.[9]

Too well known, the ovary disease, located deep in the pelvic cavity, lacks early identifiable clinical symptoms, specific laboratory indicators as well as effective screening strategies, making early lesions are 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 etc.[13,14]

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 are associated with greater risk of certain types of cancer at multiple sites, such as pancreatic, liver, endometrium cancer, etc.[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, exogenous insulin therapy, etc.[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 studies[23-26] and case-control[27] have been reported that a history of DM is significantly associated with an augmented risk of OC, however, other relevant studies found a negative significant association.[28-31] Because obesity or high 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 are remains open to discussion or absent.

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 (MOOSE) protocol checklist [32] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [33] (Additional file 1).

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, without language restriction, for observational studies (cohort and case-control studies) which investigated the association between DM and the risk of OC in women. The MeSH 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”, etc. A comprehensive search strategy was provided in the additional 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: randomized controlled trial, case reports, letters, reviews or animals studies. Eligibility assessment was performed by two authors (WHL and ZL).

Data extraction

Data were extracted by one author (WHL), and then checked by a second investigator (ZL). The main extracted information are described in Table 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 to 3, 4 to 6, 7 to 9 score were considered as low, fair, and high quality, respectively.[34]

Assessment of risk of bias

All selected literatures were subjected to a sensitivity analysis to explore the robustness of the pooled effects. The publication bias was also appraised using the funnel plot, Begg’s and Egger’s Test.[35]

Statistical analysis

The effect estimates of original studies were 5 measures of association, including relative risk (RR), standardized incidence ratio (SIR), incidence rate ratio (IRR), hazard ratio (HR) and odds ratio (OR). Given that the frequency of OC is relatively low, the latter four measures were considered to yield approximately equal estimates to that of the RR. Therefore, we reported all pooled results as RR with 95% confidence interval (CI).[36]

The statistical heterogeneity was measured by χ^2 (threshold p=0·10) and

quantified by the I^2 statistic. We prefer to choose the random-effects model to analyze all data due to the conservativeness of the analyze results.[37]The statistical analysis were performed with the Stata 12.0 software (StataCorp, College Station, TX, 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 (type 1 DM vs. type 2 DM vs. GDM), duration of follow-up (<10 year vs. ⩾10 year), level of adjustment (unadjusted vs. adjusted and BMI-adjusted vs. BMI-unadjusted), study quality (NOS ⩾7 vs. <7 points) and geographic areas (North America vs. Europe vs. Asian vs. Oceania). Subsequently, a cumulative 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 type 1 DM and risk of OC, 28 studies investigated the relationship between type 2 DM and OC risk, and the remaining 4 studies assessed this association between GDM and OC risk as well. With regard to geographic location, 1 studies 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 varied, ranging from 3.5 years to 18.01 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 Table 1 and Table 2.

Table 1 Baseline characteristics of the cohort studies

Study ID	Country or region	Study period	Follow-Up Duration, y	Population	age (years)	No. of Subjects	No. of OC Cases	Population setting	NOS score
Weiderpass 2002 [38]	Sweden	1965–1994	5.7	Type 2 DM	66.4	141,627	337	PBR	8
Zendehdel 2003 [39]	Sweden	1965-1999	15.0	Type 1 DM	17.3	14,323	9	PBR	7
Swerdlow 2005[a] [40]	UK	1972–2003	18.0	Type 1 DM	<30	11,047	16	PBR	7
Swerdlow 2005[b] [40]	UK	1972–2003	18.01	Type 2 DM	30–49	2122	6	PBR	7
Inoue 2006 [41]	Japan	1990-2003	10.7	Type 2 DM	51.8	51,223	74	PBR	8
Khan 2006 [42]	Japan	1988-1997	7.6	Type 2 DM	40-79	33503	29	PBR and HBR	7
Hemminki 2010 [43]	Sweden	1964-2007	15	Type 2 DM	39-75	24,827	192	PBR and HBR	7
Chodick 2010 [44]	Israel	2000-2008	8	Type 2 DM	62	47,682	88	PBR	7
Shu 2010 [45]	Sweden	1964-2006	17	Type 1 DM	12.3	11,290	9	PBR and HBR	8
Wotton 2011[a] [46]	Southern England	1963–1998	…	Type 2 DM	>30	132271	37	PBR and HBR	7
Wotton 2011[b] [46]	southern England	1999–2008	…	Type 2 DM	>30	90427	8	PBR and HBR	7
Johnson 2011 [47]	Canada	1994-2006	4.35	Type 2 DM	60.7	169,012	295	PBR	7
Lambe 2011 [48]	Sweden	1985-1996	11.7	Type 2 DM	46.6	230,737	536	PBR	8
Gapstur 2012 [31]	USA	1992-2007	…	Type 2 DM	62.28	63,440	524	PBR	7
Lo 2013 [49]	Taiwan	1996-2009	3.5	Type 2 DM	60.45	912,447	948	PBR	7
Chen 2014 [30]	Taiwan	2000–2008	>9	Type 2 DM	61.09	638,618	935	PBR	9
Hsu 2015 [50]	Taiwan	2000–2008	6.16	Type 1 DM	49.2	7752	7	PBR	7
Harding 2015 [25]	Australia	1997–2008	12.0	Type 1 DM	27.4	38,644	38	PBR	7
Harding 2015 [25]	Australia	1997–2008	5.8	Type 2 DM	60.4	408426	792	PBR	7

Dankner 2016 [24]	Israel	2002-2012	11	Type 2 DM	46.63	1,152,122	1,495	PBR	8
Carstensen 2016 [21]	Multi-countries	1972-2014	…	Type 1 DM	<40	…	252	PBR	7
Fuchs 2017 [23]	Israel	1988–2013	12	GDM	28.45	104,715	56	PB	7
Ballotari 2017 [26]	Italy	2010–2013	4	Type 2 DM	47	195,930	160	PBR	6
Han 2018 [28]	Korean	2002–2015	10	GDM	27.33	102,900	1,148	PB	8
He 2018 [29]	China	2003-2014	…	Type 2 DM	63.7	14,193	24	PB	7
Bao 2018 [51]	Swedish	1998–2014	…	Type 2 DM	62.57	25,154	57	Twin	6
Saarela 2019 [52]	Finland	1988–2014	10.5	Type 2 DM	…	223,602	977	PBR	6
Linkeviciute-Ulinskiene 2019 [15]	Lithuania	2000–2012	6.8	Type 2 DM	64.0	78,823	249	PBR	7
Peng 2019 [53]	Taiwan	2000-2013	6.84	GDM	28.97	990,572	1196	PB	7
Pace 2020 [54]	Canada	1990-2007	13.1	GDM	…	68,588	56	PB	7

T1DM type 1 diabetes mellitus, T2DM type 2 DM, GDM gestational DM, HB hospital-based, HB hospital-based registry, PBR population-based registry. PB population-based

Table 2 Baseline characteristics of the case-control studies

Study ID	Country or region	Study period	Population	age (years)	No. Cases/ Controls	Population setting	NOS score
O'Mara 1985 [55]	USA	1957-1965	Type 2 DM	30-89	328/2,342	HB	5
Adler 1996 [56]	USA	1975-1987	Type 2 DM	51.98	595/1,587	PBR	5
Parazzini 1997 [57]	Italy	1983-1991	Type 2 DM	52.52	971/2,758	HB	5
Mori 1998 [58]	Japan	1994-1996	Type 2 DM	54.24	89/323	PB	7
Kuriki 2007 [59]	Japan	1988-2000	Type 2 DM	57.57	218/33,569	PBR and HBR	6
Reis 2010 [27]	Turkey	2002-2003	Type 2 DM	51.0	217/1,050	HB	6
Attner 2012 [60]	Sweden	1998–2007	Type 2 DM	…	289/2,207	PBR	7
Bosetti 2012 [61]	Italy	1991-2009	Type 2 DM	56.70	1,031/2,411	HB	5
Ruiz 2016 [62]	USA	2003-2008	Type 2 DM	57.5	208/224	HB	5

T1DM type 1 diabetes mellitus, T2DM type 2 DM, GDM gestational DM, HB hospital-based, HB hospital-based registry, PBR population-based registry. PB population-based

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 (Additional file 3). Two (22.22%) case-control and twenty-four (88.89%) cohort studies were regarded as high-quality (NOS⩾7 points).

Assessment of reporting biases

The sensitivity analysis suggested no single study had significant influence on the summarized RR, which revealed the stability of pooled estimate (Additional file 4).

No obvious evidence of publication bias was detected by inspection of the funnel plot and statistical tests (Begg test, *P*=0.246; Egger test, *P*=0.132; Additional 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; *P* =0.000), 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; *P* =0.00), however, the case-control studies found no relationship between DM and the incidence of OC in spite of a positive trend (RR, 1.08; 95% CI = 0.77 to 1.53; *P* =0.659). In the analysis stratified according to DM types, a positive significant association was noted in both type 1 DM (RR, 1.44; 95% CI = 1.06 to 1.95; *P* =0.019) and type 2 DM group (RR, 1.17; 95% CI = 1.06 to 1.30; *P* =0.002), but not in GDM group (RR, 1.14; 95% CI = 0.90 to 1.43; *P* =0.277).

A subgroup analysis was conducted considering the level of adjustment, the summary RR in adjusted studies (RR, 1.23; 95% CI =1.10 to 1.37; *P* =0.000) was more marked than in unadjusted studies (RR, 1.13; 95% CI =0.98 to 1.31; *P* =0.083). Both BMI-adjusted (RR, 1.37; 95% CI =1.16 to 1.62; *P* =0.00) and BMI-unadjusted (RR, 1.12; 95% CI =1.03 to 1.22; *P* =0.008) 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 i.e. ⩾10 years (RR, 1.33; 95% CI =1.09 to 1.63; *P* =0.005) 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; *P* =0.030).

Subgroup analysis by continent, DM was significantly positively correlated with increased the OC risk among studies conducted in Asia (RR, 1.43; 95% CI =1.20 to 1.71; *P* =0.00) and Oceania (RR, 1.24; 95% CI =1.16 to 1.32; P =0.000) except for Europe (RR, 1.15; 95% CI = 0.99 to 1.35; *P* =0.064) and North America (RR, 0.94; 95% CI = 0.73 to 1.21; *P* =0.635) studies. The RR was 1.24 (95% CI =1.12 to 1.36; *P* =0.00) for high study quality studies with significant difference and 1.07 (95% CI =0.85 to 1.35; P =0.557) for non-high study quality studies without statistical

significance (Additional 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*
Total	36	1.20 (1.10,1.31)	75.1	0.000
Study design				
Case-control	9	1.08 (0.77,1.53)	71.1	0.001
Cohort	27	1.22 (1.11,1.33)	76.7	0.000
DM types				
type 1 DM	6	1.44 (1.06,1.95)	67.2	0.009
type 2 DM	28	1.17 (1.06,1.30)	78.5	0.000
GDM	4	1.14 (0.90,1.43)	31.5	0.224
Geographic location				
North America	6	0.94 (0.73,1.21)	53.9	0.054
Europe	14	1.15 (0.99,1.35)	81.3	0.000
Asian	14	1.43 (1.20,1.71)	69.5	0.000
Oceania	1	1.24 (1.16,1.32)	0.00	0.486
Follow-up				
<10 year	11	1.14 (1.01,1.29)	77	0.000
≥10 year	12	1.33 (1.09,1.63)	84.8	0.000
Level of adjustment				
No	8	1.13(0.98,1.31)	85	0.000
Yes	28	1.23 (1.10,1.37)	63.9	0.000
BMI				
Yes	13	1.37 (1.16,1.62)	53.5	0.011
No	23	1.12 (1.03,1.22)	69.9	0.000
Study quality				
NOS <7	10	1.07 (0.85,1.35)	66.7	0.001
NOS≥7	26	1.24 (1.12,1.36)	74.2	0.000

RR relative risk, CI confidence interval, NOS Newcastle–Ottawa Quality Assessment Scale, BMI body mass index, P for heterogeneity within each subgroup.

Cumulative meta-analysis

Although there is no association between DM and the risk of OC before Shu 2010 [45] (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 suggests that women with DM had a 20% elevated risk of OC, as compared to those without history of DM. Similar positive finding was observed when we analyzed by cohort studies, however, no meaningful difference was noted when pooled by the case-control studies. Since the inherent nature of recall and select bias in case-control study, certain biases might lead to inaccurate reporting of causal relationship. [63]

A subgroup meta-analysis based on DM types indicated that the risk of OC in type 1 DM group (44%) is higher than in type 2 DM group (17%), while no significant association is found in GDM group. That may explain the excess risk in type 1 DM populations that, persons with type 1 DM usually require exogenous insulin treatment for the purpose of regulating blood glucose level,[64] and those who treated with insulin appear to be at higher risk to develop cancer.[65] 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 increase risk of cancer with age, the length of follow-up for GDM patients might be too short to detect cancers in young women. [66]

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

In keeping with finding, women with DM had less risk of OC during the early follow-up period (<10 years) than during the late follow-up duration ($\geqslant$ 10 years). Owing that OC occurs mostly in middle and elderly women, therefore, women who enjoyed a long-term follow up are more susceptible to OC compared to those who had a short follow-up period.[26] Subgroup analysis on geographic areas, the Asian and Oceania studies yielded similar positive results as the aforementioned analyses apart from Europe and North America studies, which is consistent with a previous meta-analysis described by Zhang.[67] Geographic variation in the incidence of OC in women worldwide might explain such heterogeneity. The significant association was consistent in high study studies (NOS $\geqslant$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. [68] performed a first meta-analysis with 7 case-control and 11 cohort studies and supported that DM patients have a 17% increased risk of OC, compared with non-DM patients. 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, [69] which was further confirmed by a meta-analysis with 15 cohort studies (32%) later the same year.[67] Our results, in accordance with these relevant studies, suggest 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 2010 [45] 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 hyperglycemia, hyperinsulinemia and chronic inflammation.[70,71] Because of a prolonged exposure to inflammation and hyperglycemic condition, the reiterant lesion and repair cycles which is associated with incessant ovulation process could be slow down, thus, resulting in an underlying risk of OC.[72] 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 know as a potent proangiogenic factor,[73] indicating a tumor-promotion effect of DM. Biologically, an excess of insulin, as a growth factor, may stimulate the growth of tumor, whether for endogenous or exogenous [74]. Besides, several oral anti-hyperglycemic therapies have been shown to increase risk of cancer development. [75]

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 type 1 DM, type 2 DM or GDM and the risk of OC, respectively, which might be more generalizable than previous three meta-analyses. Third, most of included observational studies has controlled at least one potential confounder, such as age, BMI, obesity, drinking and smoking habits, as well as regular physical exercise, etc. 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 increasing the 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, there are variety of histologic subtypes in OC with distinct clinical characteristics, thus, the relation between DM and the different of OC subtypes risk is being explored in the future. Third, 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 of DM, oral contraceptive use, hormone replacement therapy, etc.

CONLUSIONS

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

confounding factors and verified the association with subtypes of OC should be conducted to identify our results.

Acknowledgements The authors would like to thank all the anonymous reviewers for their valuable comments and suggestions on improving quality of this study.

Contributors HXH, WHL and ZL conceived the study idea and designed the study. WHL and ZL collected literatures, reviewed the articles, collected the data and performed all data analyses. W-HL, ZL, HXH, XB and CM were responsible for drafting of the manuscript. All the authors approved the final version of this manuscript.

Funding This research received no specific grant from any funding agency.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Ethical Approval Not applicable.

Data availability statement All data are fully available without restriction.

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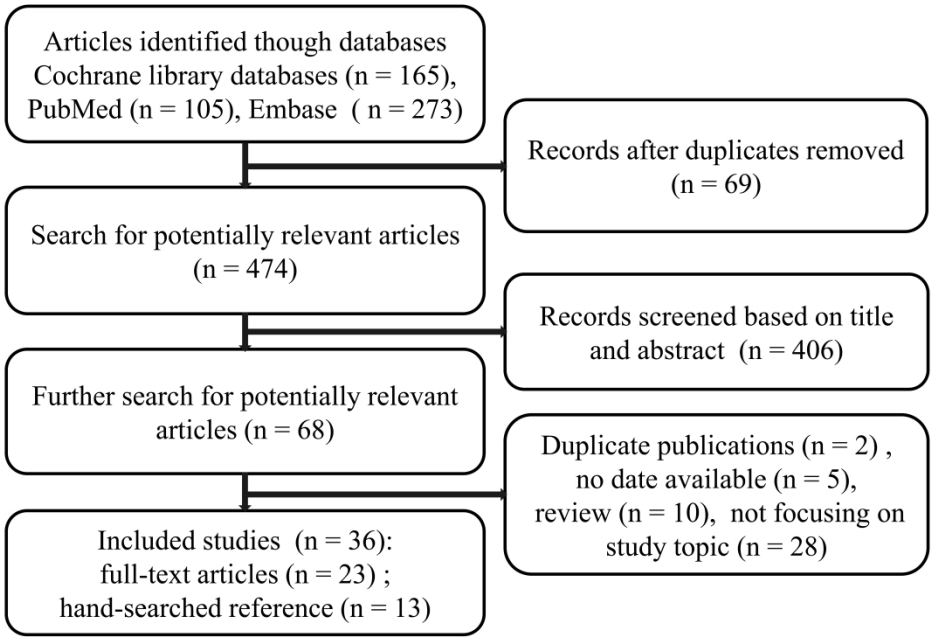
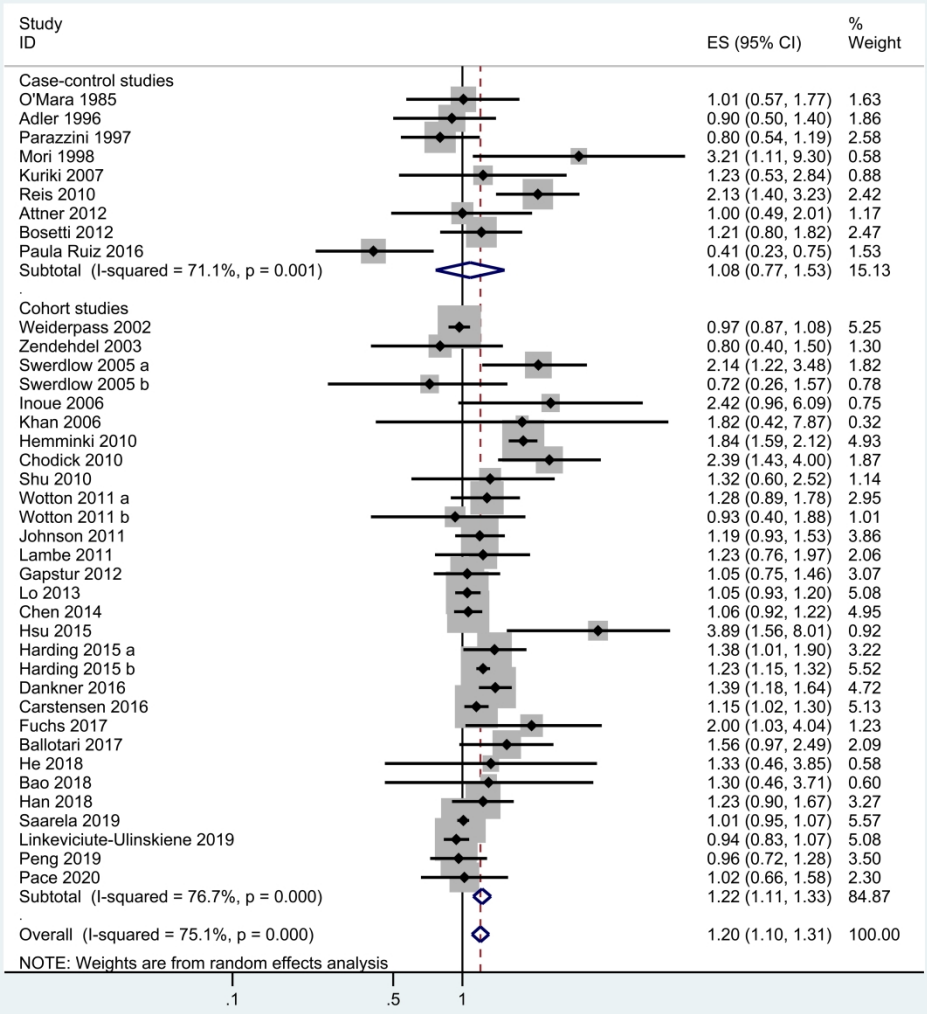
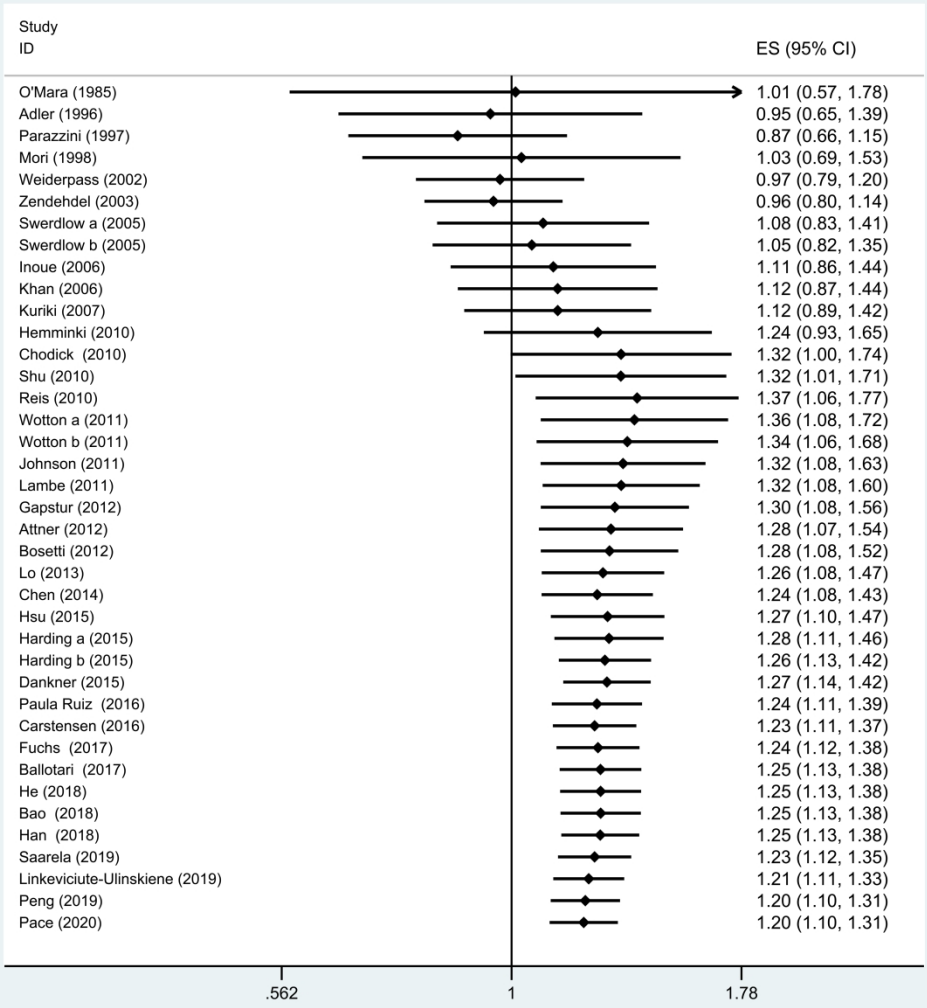

Articles identified though databases
Cochrane library databases (n = 165),
PubMed (n = 105), Embase (n = 273)
Records after duplicates removed
(n = 69)
Search for potentially relevant articles
(n = 474)
Records screened based on title
and abstract (n = 406)
Further search for potentially relevant
articles (n = 68)
Duplicate publications (n = 2) ,
no date available (n = 5),
review (n = 10), not focusing on
study topic (n = 28)
Included studies (n = 36):
full-text articles (n = 23) ;
hand-searched reference (n = 13)


Study ID
ES (95% CI)
% Weight
Case-control studies
O'Mara 1985 1.01 (0.57, 1.77) 1.63
Adler 1996 0.90 (0.50, 1.40) 1.86
Parazzini 1997 0.80 (0.54, 1.19) 2.58
Mori 1998 3.21 (1.11, 9.30) 0.58
Kuriki 2007 1.23 (0.53, 2.84) 0.88
Reis 2010 2.13 (1.40, 3.23) 2.42
Attner 2012 1.00 (0.49, 2.01) 1.17
Bosetti 2012 1.21 (0.80, 1.82) 2.47
Paula Ruiz 2016 0.41 (0.23, 0.75) 1.53
Subtotal (I-squared = 71.1%, p = 0.001) 1.08 (0.77, 1.53) 15.13
Cohort studies
Weiderpass 2002 0.97 (0.87, 1.08) 5.25
Zendehdel 2003 0.80 (0.40, 1.50) 1.30
Swerdlow 2005 a 2.14 (1.22, 3.48) 1.82
Swerdlow 2005 b 0.72 (0.26, 1.57) 0.78
Inoue 2006 2.42 (0.96, 6.09) 0.75
Khan 2006 1.82 (0.42, 7.87) 0.32
Hemminki 2010 1.84 (1.59, 2.12) 4.93
Chodick 2010 2.39 (1.43, 4.00) 1.87
Shu 2010 1.32 (0.60, 2.52) 1.14
Wotton 2011 a 1.28 (0.89, 1.78) 2.95
Wotton 2011 b 0.93 (0.40, 1.88) 1.01
Johnson 2011 1.19 (0.93, 1.53) 3.86
Lambe 2011 1.23 (0.76, 1.97) 2.06
Gapstur 2012 1.05 (0.75, 1.46) 3.07
Lo 2013 1.05 (0.93, 1.20) 5.08
Chen 2014 1.06 (0.92, 1.22) 4.95
Hsu 2015 3.89 (1.56, 8.01) 0.92
Harding 2015 a 1.38 (1.01, 1.90) 3.22
Harding 2015 b 1.23 (1.15, 1.32) 5.52
Dankner 2016 1.39 (1.18, 1.64) 4.72
Carstensen 2016 1.15 (1.02, 1.30) 5.13
Fuchs 2017 2.00 (1.03, 4.04) 1.23
Ballotari 2017 1.56 (0.97, 2.49) 2.09
He 2018 1.33 (0.46, 3.85) 0.58
Bao 2018 1.30 (0.46, 3.71) 0.60
Han 2018 1.23 (0.90, 1.67) 3.27
Saarela 2019 1.01 (0.95, 1.07) 5.57
Linkeviciute-Ulinskiene 2019 0.94 (0.83, 1.07) 5.08
Peng 2019 0.96 (0.72, 1.28) 3.50
Pace 2020 1.02 (0.66, 1.58) 2.30
Subtotal (I-squared = 76.7%, p = 0.000) 1.22 (1.11, 1.33) 84.87
Overall (I-squared = 75.1%, p = 0.000) 1.20 (1.10, 1.31) 100.00
NOTE: Weights are from random effects analysis
.1
.5
1


Study
ID
ES (95% CI)
O'Mara (1985) 1.01 (0.57, 1.78)
Adler (1996) 0.95 (0.65, 1.39)
Parazzini (1997) 0.87 (0.66, 1.15)
Mori (1998) 1.03 (0.69, 1.53)
Weiderpass (2002) 0.97 (0.79, 1.20)
Zendehdel (2003) 0.96 (0.80, 1.14)
Swerdlow a (2005) 1.08 (0.83, 1.41)
Swerdlow b (2005) 1.05 (0.82, 1.35)
Inoue (2006) 1.11 (0.86, 1.44)
Khan (2006) 1.12 (0.87, 1.44)
Kuriki (2007) 1.12 (0.89, 1.42)
Hemminki (2010) 1.24 (0.93, 1.65)
Chodick (2010) 1.32 (1.00, 1.74)
Shu (2010) 1.32 (1.01, 1.71)
Reis (2010) 1.37 (1.06, 1.77)
Wotton a (2011) 1.36 (1.08, 1.72)
Wotton b (2011) 1.34 (1.06, 1.68)
Johnson (2011) 1.32 (1.08, 1.63)
Lambe (2011) 1.32 (1.08, 1.60)
Gapstur (2012) 1.30 (1.08, 1.56)
Attner (2012) 1.28 (1.07, 1.54)
Bosetti (2012) 1.28 (1.08, 1.52)
Lo (2013) 1.26 (1.08, 1.47)
Chen (2014) 1.24 (1.08, 1.43)
Hsu (2015) 1.27 (1.10, 1.47)
Harding a (2015) 1.28 (1.11, 1.46)
Harding b (2015) 1.26 (1.13, 1.42)
Dankner (2015) 1.27 (1.14, 1.42)
Paula Ruiz (2016) 1.24 (1.11, 1.39)
Carstensen (2016) 1.23 (1.11, 1.37)
Fuchs (2017) 1.24 (1.12, 1.38)
Ballotari (2017) 1.25 (1.13, 1.38)
He (2018) 1.25 (1.13, 1.38)
Bao (2018) 1.25 (1.13, 1.38)
Han (2018) 1.25 (1.13, 1.38)
Saarela (2019) 1.23 (1.12, 1.35)
Linkeviciute-Ulinskiene (2019) 1.21 (1.11, 1.33)
Peng (2019) 1.20 (1.10, 1.31)
Pace (2020) 1.20 (1.10, 1.31)
.562
1
1.78

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	A history of diabetes mellitus (DM) has been linked to increased risk of ovarian cancer (OC), but the results have not been consistent. The aim of this study was to clarify this association.
√	Hypothesis statement	DM increases the risk of OC.
√	Description of study outcomes	OC
√	Type of exposure or intervention used	DM
√	Type of study designs used	Observational studies: cohort and case-control studies.
√	Study population	No restriction.
Reporting of search strategy should include		
√	Qualifications of searchers	ZL (first author) and WHL have published a meta-analysis in Critical care in 2017 (with experience of literature search).
√	Search strategy, including time period included in the synthesis and keywords	PubMed from 1965 –April 2020 EMBASE from 1974 –April 2020 Cochrane library databases 1974 –April 2020 See additional file 2 the search strategy and search results.
√	Databases and registries searched	PubMed, Embase and the Cochrane library databases
√	Search software used, name and version, including special features	No search software is being used. The process of retrieving citations and eliminating the duplications was used by EndNote software.
√	Use of hand searching	The potentially eligible bibliographies of relevant articles were manually examined to identify any additional publications relevant to our study.
√	List of citations located and those excluded, including justifications	The literature search process is given in flow diagram.
√	Method of addressing articles published in languages other than English	Through a translation app or consult professionals.
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	Not applicable

Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were also given in our study.
√	Rationale for the selection and coding of data	The PICO framework
√	Assessment of confounding	Sensitivity analyses
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The Newcastle-Ottawa Scale (NOS) score
√	Assessment of heterogeneity	The statistical heterogeneity was measured by χ^2 (threshold p=0·10) and quantified by the I^2 statistic.
√	Description of statistical methods in sufficient detail to be replicated	The details refer to the "Statistical analysis" in our study.
√	Provision of appropriate tables and graphics	We included 1 box detailing the terms used for database search, 1 flow chart,1 summary table, 1 forest plot of all studies, 1 forest plot to examine effect modification by age, 1 table of sensitivity analyses.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Additional file 4
√	Indication of statistical uncertainty of findings	For more details refer to the The pooled effects were analyzed by relative risk (RR) with 95% confidence interval, and the statistical heterogeneity was measured by χ^2 (threshold p=0·10) and quantified by the I^2 statistic.
Reporting of discussion should include		
√	Quantitative assessment of bias	The cumulative meta-analysis and sensitivity analysis showed pooled effect was stable and reliable.
√	Justification for exclusion	The exclusion criteria in this meta-analysis were: randomized controlled trial, case reports, letters, reviews or animals studies.
√	Assessment of quality of	No apparent publication bias was identified in this

	included studies	meta-analysis.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Significant heterogeneity between these studies was observed.
√	Generalization of the conclusions	Women with history of DM have a higher risk of OC than those who without.
√	Guidelines for future research	Further high-quality studies with prospective design that are adequately controlled for potential confounding factors and verified the association with subtypes of OC should be conducted to identify our results.
√	Disclosure of funding source	This research received no specific grant from any funding agency.

Systematic reviews and meta-analyses (PRISMA) guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Methods
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Additional file 2：The search strategy and search results

PubMed (n=105), the Cochrane library databases(n=165) and Embase (n=273)

PubMed:

#1 ((((((((((((((("Ovarian Neoplasms"[Mesh]) OR "Ovarian Neoplasms"[Title/Abstract]) OR "Neoplasm, Ovarian"[Title/Abstract]) OR "Ovarian Neoplasm"[Title/Abstract]) OR "Ovary Neoplasms"[Title/Abstract]) OR "Neoplasm, Ovary"[Title/Abstract]) OR "Ovary Neoplasm"[Title/Abstract]) OR "Neoplasms, Ovarian"[Title/Abstract]) OR "Ovary Cancer"[Title/Abstract]) OR "Cancer, Ovary"[Title/Abstract]) OR "Ovary Cancers"[Title/Abstract]) OR "Ovarian Cancer"[Title/Abstract]) OR "Cancer, Ovarian"[Title/Abstract]) OR "Ovarian Cancers"[Title/Abstract]) OR "Cancer of Ovary"[Title/Abstract]) OR "Cancer of the Ovary"[Title/Abstract])) OR ((((((((((("Carcinoma, Ovarian Epithelial"[Mesh]) OR "Ovarian Epithelial Carcinomas"[Title/Abstract]) OR "Epithelial Ovarian Cancer"[Title/Abstract]) OR "Ovarian Epithelial Cancers"[Title/Abstract]) OR "Ovarian Epithelial Cancer"[Title/Abstract]) OR "Epithelial Ovarian Cancers"[Title/Abstract]) OR "Ovarian Epithelial Carcinoma"[Title/Abstract]) OR "Epithelial Ovarian Carcinoma"[Title/Abstract]) OR "Epithelial Ovarian Carcinomas"[Title/Abstract]) OR "ovarian carcinoma"[Title/Abstract])) 101778

#2 ((((("diabete*"[Title/Abstract]) OR ((((((((((((((((("Diabetes Mellitus, Type 1"[Title/Abstract]) OR "Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Juvenile-Onset Diabetes Mellitus"[Title/Abstract]) OR "IDDM"[Title/Abstract]) OR "Juvenile-Onset Diabetes"[Title/Abstract]) OR "Juvenile Onset Diabetes"[Title/Abstract]) OR "Sudden-Onset Diabetes Mellitus"[Title/Abstract]) OR "Type 1 Diabetes Mellitus"[Title/Abstract]) OR "Insulin-Dependent Diabetes Mellitus 1"[Title/Abstract]) OR "Insulin Dependent Diabetes Mellitus 1"[Title/Abstract]) OR "Type 1 Diabetes"[Title/Abstract]) OR "Diabetes, Type 1"[Title/Abstract]) OR "Autoimmune Diabetes"[Title/Abstract]) OR "Brittle Diabetes Mellitus"[Title/Abstract]) OR "Ketosis-Prone Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Type 1"[Mesh])) OR ((((((((((((((((("Diabetes Mellitus, Type 2"[Title/Abstract]) OR "Ketosis-Resistant Diabetes Mellitus"[Title/Abstract]) OR "Non-Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Stable Diabetes Mellitus"[Title/Abstract]) OR "NIDDM"[Title/Abstract]) OR "Maturity-Onset Diabetes Mellitus"[Title/Abstract]) OR "Maturity Onset Diabetes Mellitus"[Title/Abstract]) OR "MODY"[Title/Abstract]) OR "Type 2 Diabetes Mellitus"[Title/Abstract]) OR "Noninsulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Noninsulin Dependent Diabetes Mellitus"[Title/Abstract]) OR "Maturity-Onset Diabetes"[Title/Abstract]) OR "Maturity Onset Diabetes"[Title/Abstract]) OR "Type 2 Diabetes"[Title/Abstract]) OR "Adult-Onset Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Type 2"[Mesh])) OR (("Diabetes Mellitus"[Mesh]) OR "Diabetes Mellitus"[Title/Abstract])))))) OR ((((((("Gestational Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Gestational"[Title/Abstract]) OR

"Gestational Diabetes"[Title/Abstract]) OR "Pregnancy-Induced Diabetes"[Title/Abstract]) OR "Diabetes, Gestational"[Mesh])) 523490

#3 ((((("Observational Studies as Topic"[Mesh]) OR "Observational Study"[Publication Type])))) OR ((((((((((((((((((((("Case-Control Studies"[Mesh]) OR "Case-Control Studies"[Title/Abstract]) OR "Case-Control Study"[Title/Abstract]) OR "Case-Comparison Studies"[Title/Abstract]) OR "Case Comparison Studies"[Title/Abstract]) OR "Case-Comparison Study"[Title/Abstract]) OR "Case-Compeer Studies"[Title/Abstract]) OR "Case-Referent Studies"[Title/Abstract]) OR "Case Referent Studies"[Title/Abstract]) OR "Case-Referent Study"[Title/Abstract]) OR "Case-Base Studies"[Title/Abstract]) OR "Case Base Studies"[Title/Abstract]) OR "Case Control Studies"[Title/Abstract]) OR "Case Control Study"[Title/Abstract]) OR "Nested Case-Control Studies"[Title/Abstract]) OR "Case-Control Studies, Nested"[Title/Abstract]) OR "Nested Case Control Studies"[Title/Abstract]) OR "Nested Case-Control Study"[Title/Abstract]) OR "Matched Case-Control Studies"[Title/Abstract]) OR "Matched Case Control Studies"[Title/Abstract]) OR "Matched Case-Control Study"[Title/Abstract]))) OR ((((((((((((("Cohort Studies"[Mesh]) OR "Cohort Studies"[Title/Abstract]) OR "Cohort Study"[Title/Abstract]) OR "Concurrent Studies"[Title/Abstract]) OR "Concurrent Study"[Title/Abstract]) OR "Closed Cohort Studies"[Title/Abstract]) OR "Closed Cohort Study"[Title/Abstract]) OR "Cohort Analysis"[Title/Abstract]) OR "Cohort Analyses"[Title/Abstract]) OR "Historical Cohort Studies"[Title/Abstract]) OR "Historical Cohort Study"[Title/Abstract]) OR "Incidence Studies"[Title/Abstract]) OR "Incidence Study"[Title/Abstract]) OR "Cohort*"[Title/Abstract]))) 2451208

#4 #1 and #2 and #3 105 **(search results)**

Cochrane library:

ID Search

#1 (Ovarian Neoplasms):ti,ab,kw OR (Neoplasm, Ovarian):ti,ab,kw OR (Ovarian Neoplasm):ti,ab,kw OR (Ovary Neoplasms):ti,ab,kw OR (Neoplasm, Ovary):ti,ab,kw (Word variations have been searched)

#2 (Neoplasms, Ovary):ti,ab,kw OR (Ovary Neoplasm):ti,ab,kw OR (Neoplasms, Ovarian):ti,ab,kw OR (Ovary Cancer):ti,ab,kw OR (Cancer, Ovary):ti,ab,kw (Word variations have been searched)

#3 (Cancers, Ovary):ti,ab,kw OR (Ovary Cancers):ti,ab,kw OR (Ovarian Cancer):ti,ab,kw OR (Cancer, Ovarian):ti,ab,kw OR (Cancers, Ovarian):ti,ab,kw (Word variations have been searched)

#4 (Ovarian Cancers):ti,ab,kw OR (Cancer of Ovary):ti,ab,kw OR (Cancer of the Ovary):ti,ab,kw OR (Carcinoma, Ovarian Epithelial):ti,ab,kw OR (Carcinomas, Ovarian Epithelial):ti,ab,kw (Word variations have been searched)

#5 (Epithelial Carcinoma, Ovarian):ti,ab,kw OR (Epithelial Carcinomas, Ovarian):ti,ab,kw OR (Ovarian Epithelial Carcinomas):ti,ab,kw OR (Epithelial Ovarian Cancer):ti,ab,kw OR (Ovarian Epithelial Cancer):ti,ab,kw (Word variations have been searched)

#6 (Cancer, Ovarian Epithelial):ti,ab,kw OR (Cancers, Ovarian Epithelial):ti,ab,kw OR (Epithelial Cancer, Ovarian):ti,ab,kw OR (Epithelial Cancers, Ovarian):ti,ab,kw OR (Ovarian Epithelial Cancers):ti,ab,kw (Word variations have been searched)

#7 (Ovarian Cancer, Epithelial):ti,ab,kw OR (Cancer, Epithelial Ovarian):ti,ab,kw OR (Cancers, Epithelial Ovarian):ti,ab,kw OR (Epithelial Ovarian Cancers):ti,ab,kw OR (Ovarian Cancers, Epithelial):ti,ab,kw (Word variations have been searched)

#8 (Ovarian Epithelial Carcinoma):ti,ab,kw OR (Epithelial Ovarian Carcinoma):ti,ab,kw OR (Carcinoma, Epithelial Ovarian):ti,ab,kw OR (Carcinomas, Epithelial Ovarian):ti,ab,kw OR (Epithelial Ovarian Carcinomas):ti,ab,kw (Word variations have been searched)

#9 (Ovarian Carcinoma, Epithelial):ti,ab,kw OR (Ovarian Carcinomas, Epithelial):ti,ab,kw OR (ovarian carcinoma):ti,ab,kw OR (Ovar*):ti,ab,kw (Word variations have been searched)

#10 MeSH descriptor: [Ovarian Neoplasms] explode all trees

#11 MeSH descriptor: [Carcinoma, Ovarian Epithelial] explode all trees

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 17934

#13 (Diabetes mellitus):ti,ab,kw OR (Diabetes Mellitus, Type 2):ti,ab,kw OR (Diabetes Mellitus, Noninsulin-Dependent):ti,ab,kw OR (Diabetes Mellitus, Ketosis-Resistant):ti,ab,kw OR (Diabetes Mellitus, Ketosis Resistant):ti,ab,kw (Word variations have been searched)

#14 (Ketosis-Resistant Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Non Insulin Dependent):ti,ab,kw OR (Diabetes Mellitus, Non-Insulin-Dependent):ti,ab,kw OR (Non-Insulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Stable):ti,ab,kw (Word variations have been searched)

#15 (Stable Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR

(NIDDM):ti,ab,kw OR (Diabetes Mellitus, Noninsulin Dependent):ti,ab,kw OR (Diabetes Mellitus, Maturity-Onset):ti,ab,kw (Word variations have been searched)
#16 (Diabetes Mellitus, Maturity Onset):ti,ab,kw OR (Maturity-Onset Diabetes Mellitus):ti,ab,kw OR (Maturity Onset Diabetes Mellitus):ti,ab,kw OR (MODY):ti,ab,kw OR (Diabetes Mellitus, Slow-Onset):ti,ab,kw (Word variations have been searched)
#17 (Diabetes Mellitus, Slow Onset):ti,ab,kw OR (Slow-Onset Diabetes Mellitus):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Noninsulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Noninsulin Dependent Diabetes Mellitus):ti,ab,kw (Word variations have been searched)
#18 (Maturity-Onset Diabetes):ti,ab,kw OR (Diabetes, Maturity-Onset):ti,ab,kw OR (Maturity Onset Diabetes):ti,ab,kw OR (Type 2 Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw (Word variations have been searched)
#19 (Diabetes Mellitus, Adult-Onset):ti,ab,kw OR (Adult-Onset Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Adult Onset):ti,ab,kw OR (Diabetes Mellitus, Type 1):ti,ab,kw OR (Diabetes Mellitus, Insulin-Dependent):ti,ab,kw (Word variations have been searched)
#20 (Diabetes Mellitus, Insulin Dependent):ti,ab,kw OR (Insulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Juvenile-Onset):ti,ab,kw OR (Diabetes Mellitus, Juvenile Onset):ti,ab,kw OR (Juvenile-Onset Diabetes Mellitus):ti,ab,kw (Word variations have been searched)
#21 (IDDM):ti,ab,kw OR (Juvenile-Onset Diabetes):ti,ab,kw OR (Diabetes, Juvenile-Onset):ti,ab,kw OR (Juvenile Onset Diabetes):ti,ab,kw OR (Diabetes Mellitus, Sudden-Onset):ti,ab,kw (Word variations have been searched)
#22 (Diabetes Mellitus, Sudden Onset):ti,ab,kw OR (Sudden-Onset Diabetes Mellitus):ti,ab,kw OR (Type 1 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Insulin-Dependent, 1):ti,ab,kw OR (Insulin-Dependent Diabetes Mellitus 1):ti,ab,kw (Word variations have been searched)
#23 (Insulin Dependent Diabetes Mellitus 1):ti,ab,kw OR (Type 1 Diabetes):ti,ab,kw OR (Diabetes, Type 1):ti,ab,kw OR (Diabetes Mellitus, Type I):ti,ab,kw OR (Diabetes, Autoimmune):ti,ab,kw (Word variations have been searched)
#24 (Autoimmune Diabetes):ti,ab,kw OR (Diabetes Mellitus, Brittle):ti,ab,kw OR (Brittle Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Ketosis-Prone):ti,ab,kw OR (Diabetes Mellitus, Ketosis Prone):ti,ab,kw (Word variations have been searched)
#25 (Ketosis-Prone Diabetes Mellitus):ti,ab,kw OR (Diabetes, Gestational):ti,ab,kw OR (Diabetes, Pregnancy-Induced):ti,ab,kw OR (Diabetes, Pregnancy Induced):ti,ab,kw OR (Pregnancy-Induced Diabetes):ti,ab,kw (Word variations have been searched)
#26 (Gestational Diabetes):ti,ab,kw OR (Diabetes Mellitus, Gestational):ti,ab,kw OR (Gestational Diabetes Mellitus):ti,ab,kw OR (diabete):ti,ab,kw OR (diabet*):ti,ab,kw (Word variations have been searched)
#27 MeSH descriptor: [Diabetes Mellitus] explode all trees
#28 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#29 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees

#30 MeSH descriptor: [Diabetes, Gestational] explode all trees
#31 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 **89079**

#32 (Cohort Studies):ti,ab,kw OR (Cohort Study):ti,ab,kw OR (Studies, Cohort):ti,ab,kw OR (Study, Cohort):ti,ab,kw OR (Concurrent Studies):ti,ab,kw (Word variations have been searched)
#33 (Studies, Concurrent):ti,ab,kw OR (Concurrent Study):ti,ab,kw OR (Study, Concurrent):ti,ab,kw OR (Closed Cohort Studies):ti,ab,kw OR (Cohort Studies, Closed):ti,ab,kw (Word variations have been searched)
#34 (Closed Cohort Study):ti,ab,kw OR (Cohort Study, Closed):ti,ab,kw OR (Study, Closed Cohort):ti,ab,kw OR (Studies, Closed Cohort):ti,ab,kw OR (Analysis, Cohort):ti,ab,kw (Word variations have been searched)
#35 (Cohort Analysis):ti,ab,kw OR (Analyses, Cohort):ti,ab,kw OR (Cohort Analyses):ti,ab,kw OR (Historical Cohort Studies):ti,ab,kw OR (Cohort Study, Historical):ti,ab,kw (Word variations have been searched)
#36 (Historical Cohort Study):ti,ab,kw OR (Study, Historical Cohort):ti,ab,kw OR (Cohort Studies, Historical):ti,ab,kw OR (Studies, Historical Cohort):ti,ab,kw OR (Incidence Studies):ti,ab,kw (Word variations have been searched)
#37 (Incidence Study):ti,ab,kw OR (Studies, Incidence):ti,ab,kw OR (Study, Incidence):ti,ab,kw AND (Cohort*):ti,ab,kw (Word variations have been searched)
#38 MeSH descriptor: [Cohort Studies] explode all trees
#39 #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 (Case-Control Studies):ti,ab,kw OR (Case-Control Study):ti,ab,kw OR (Studies, Case-Control):ti,ab,kw OR (Study, Case-Control):ti,ab,kw OR (Case-Comparison Studies):ti,ab,kw (Word variations have been searched)
#41 (Case Comparison Studies):ti,ab,kw OR (Case-Comparison Study):ti,ab,kw OR (Studies, Case-Comparison):ti,ab,kw OR (Study, Case-Comparison):ti,ab,kw OR (Case-Compeer Studies):ti,ab,kw (Word variations have been searched)
#42 (Studies, Case-Compeer):ti,ab,kw OR (Case-Referrent Studies):ti,ab,kw OR (Case Referrent Studies):ti,ab,kw OR (Case-Referrent Study):ti,ab,kw OR (Studies, Case-Referrent):ti,ab,kw (Word variations have been searched)
#43 (Study, Case-Referrent):ti,ab,kw OR (Case-Referent Studies):ti,ab,kw OR (Case Referent Studies):ti,ab,kw OR (Case-Referent Study):ti,ab,kw OR (Studies, Case-Referent):ti,ab,kw (Word variations have been searched)
#44 (Study, Case-Referent):ti,ab,kw OR (Case-Base Studies):ti,ab,kw OR (Case Base Studies):ti,ab,kw OR (Studies, Case-Base):ti,ab,kw OR (Case Control Studies):ti,ab,kw (Word variations have been searched)
#45 (Case Control Study):ti,ab,kw OR (Studies, Case Control):ti,ab,kw OR (Study, Case Control):ti,ab,kw OR (Nested Case-Control Studies):ti,ab,kw OR (Case-Control Studies, Nested):ti,ab,kw (Word variations have been searched)
#46 (Case-Control Study, Nested):ti,ab,kw OR (Nested Case Control Studies):ti,ab,kw OR (Nested Case-Control Study):ti,ab,kw OR (Studies, Nested Case-Control):ti,ab,kw OR (Study, Nested Case-Control):ti,ab,kw (Word variations

have been searched)
#47 (Matched Case-Control Studies):ti,ab,kw OR (Case-Control Studies, Matched):ti,ab,kw OR (Case-Control Study, Matched):ti,ab,kw OR (Matched Case Control Studies):ti,ab,kw OR (Matched Case-Control Study):ti,ab,kw (Word variations have been searched)
#48 (Study, Matched Case-Control):ti,ab,kw OR (Studies, Matched Case-Control):ti,ab,kw OR (Case-Control):ti,ab,kw OR (Case Control):ti,ab,kw (Word variations have been searched)
#49 MeSH descriptor: [Case-Control Studies] explode all trees
#50 #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 104520
#51 MeSH descriptor: [Observational Study] explode all trees
#52 (Observational Study):ti,ab,kw OR (observation*):ti,ab,kw (Word variations have been searched)
#53 #51 or #52 224361
#54 #39 or #50 or #53 487408
#55 #12 and #31 and #54 **165** **(search results)**

Embase Session Results (9 Apr 2020) （search results: 273）

No.	Query	Results	Date
#196.	#48 AND #120 AND #195	273	9 Apr 2020
#195.	#121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #178 OR #179 OR #180 OR #181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194	1,012,386	9 Apr 2020
#194.	'cohort analysis'/exp	563,360	9 Apr 2020
#193.	'case control study'/exp	170,234	9 Apr 2020
#192.	'observational study'/exp	192,953	9 Apr 2020
#191.	'observational study':ab,ti	124,700	9 Apr 2020
#190.	'study, matched case-control':ab,ti	6	9 Apr 2020
#189.	'studies, matched case-control':ab,ti	2	9 Apr 2020
#188.	'matched case-control study':ab,ti	4,504	9 Apr 2020
#187.	'matched case control studies':ab,ti	242	9 Apr 2020
#186.	'case-control study, matched':ab,ti	115	9 Apr 2020
#185.	'case-control studies, matched':ab,ti	7	9 Apr 2020
#184.	'matched case-control studies':ab,ti	242	9 Apr 2020
#183.	'study, nested case-control':ab,ti	13	9 Apr 2020
#182.	'studies, nested case-control':ab,ti	15	9 Apr 2020
#181.	'nested case-control study':ab,ti	8,227	9 Apr 2020
#180.	'nested case control studies':ab,ti	668	9 Apr 2020
#179.	'case-control study, nested':ab,ti	1,239	9 Apr 2020
#178.	'case-control studies, nested':ab,ti	80	9 Apr 2020
#177.	'nested case-control studies':ab,ti	668	9 Apr 2020
#176.	'study, case control':ab,ti	212	9 Apr 2020
#175.	'studies, case control':ab,ti	513	9 Apr 2020
#174.	'case control study':ab,ti	107,936	9 Apr 2020
#173.	'case control studies':ab,ti	19,908	9 Apr 2020
#172.	'studies, case-base':ab,ti	1	9 Apr 2020
#171.	'case base studies':ab,ti	8	9 Apr 2020
#170.	'case-base studies':ab,ti	8	9 Apr 2020
#169.	'study, case-referent':ab,ti	1	9 Apr 2020

#168.'studies, case-referent':ab,ti	1	9 Apr 2020
#167.'case-referent study':ab,ti	523	9 Apr 2020
#166.'case referent studies':ab,ti	84	9 Apr 2020
#165.'case-referent studies':ab,ti	84	9 Apr 2020
#164.'study, case-referrent':ab,ti		9 Apr 2020
#163.'studies, case-referrent':ab,ti		9 Apr 2020
#162.'case-referrent study':ab,ti	1	9 Apr 2020
#161.'case referrent studies':ab,ti		9 Apr 2020
#160.'case-referrent studies':ab,ti		9 Apr 2020
#159.'studies, case-compeer':ab,ti	1	9 Apr 2020
#158.'case-compeer studies':ab,ti	1	9 Apr 2020
#157.'study, case-comparison':ab,ti		9 Apr 2020
#156.'studies, case-comparison':ab,ti		9 Apr 2020
#155.'case-comparison study':ab,ti	215	9 Apr 2020
#154.'case comparison studies':ab,ti	9	9 Apr 2020
#153.'case-comparison studies':ab,ti	9	9 Apr 2020
#152.'study, case-control':ab,ti	212	9 Apr 2020
#151.'studies, case-control':ab,ti	513	9 Apr 2020
#150.'case-control study':ab,ti	107,936	9 Apr 2020
#149.'case-control studies':ab,ti	19,908	9 Apr 2020
#148.'study, incidence':ab,ti	662	9 Apr 2020
#147.'studies, incidence':ab,ti	140	9 Apr 2020
#146.'incidence study':ab,ti	1,373	9 Apr 2020
#145.'incidence studies':ab,ti	750	9 Apr 2020
#144.'studies, historical cohort':ab,ti	2	9 Apr 2020
#143.'cohort studies, historical':ab,ti		9 Apr 2020
#142.'study, historical cohort':ab,ti	20	9 Apr 2020
#141.'historical cohort study':ab,ti	2,683	9 Apr 2020
#140.'cohort study, historical':ab,ti	5	9 Apr 2020
#139.'historical cohort studies':ab,ti	70	9 Apr 2020
#138.'cohort analyses':ab,ti	809	9 Apr 2020
#137.'analyses, cohort':ab,ti	30	9 Apr 2020
#136.'cohort analysis':ab,ti	11,330	9 Apr 2020
#135.'analysis, cohort':ab,ti	473	9 Apr 2020
#134.'studies, closed cohort':ab,ti		9 Apr 2020
#133.'study, closed cohort':ab,ti	1	9 Apr 2020
#132.'cohort study, closed':ab,ti		9 Apr 2020
#131.'closed cohort study':ab,ti	41	9 Apr 2020
#130.'cohort studies, closed':ab,ti		9 Apr 2020
#129.'closed cohort studies':ab,ti	2	9 Apr 2020
#128.'study, concurrent':ab,ti	148	9 Apr 2020
#127.'concurrent study':ab,ti	239	9 Apr 2020
#126.'studies, concurrent':ab,ti	46	9 Apr 2020
#125.'concurrent studies':ab,ti	198	9 Apr 2020

#124.'study, cohort':ab,ti	21,934	9 Apr 2020
#123.'studies, cohort':ab,ti	490	9 Apr 2020
#122.'cohort study':ab,ti	260,094	9 Apr 2020
#121.'cohort studies':ab,ti	31,752	9 Apr 2020
#120.#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119	1,047,969	9 Apr 2020
#119.'pregnancy diabetes mellitus'/exp	36,590	9 Apr 2020
#118.'non insulin dependent diabetes mellitus'/exp	253,232	9 Apr 2020
#117.'insulin dependent diabetes mellitus'/exp	117,492	9 Apr 2020
#116.'diabetes mellitus'/exp	1,001,964	9 Apr 2020
#115.'gestational diabetes mellitus':ab,ti	11,376	9 Apr 2020
#114.'diabetes mellitus, gestational':ab,ti	91	9 Apr 2020
#113.'gestational diabetes':ab,ti	22,863	9 Apr 2020
#112.'pregnancy-induced diabetes':ab,ti	14	9 Apr 2020
#111.'diabetes, pregnancy induced':ab,ti	57	9 Apr 2020
#110.'diabetes, pregnancy-induced':ab,ti	57	9 Apr 2020
#109.'diabetes, gestational':ab,ti	313	9 Apr 2020
#108.'ketosis-prone diabetes mellitus':ab,ti	16	9 Apr 2020
#107.'diabetes mellitus, ketosis prone':ab,ti		9 Apr 2020
#106.'diabetes mellitus, ketosis-prone':ab,ti		9 Apr 2020
#105.'brittle diabetes mellitus':ab,ti	26	9 Apr 2020
#104.'diabetes mellitus, brittle':ab,ti	3	9 Apr 2020
#103.'autoimmune diabetes':ab,ti	4,106	9 Apr 2020
#102.'diabetes, autoimmune':ab,ti	213	9 Apr 2020
#101.'diabetes, type 1':ab,ti	1,452	9 Apr 2020
#100.'type 1 diabetes':ab,ti	60,696	9 Apr 2020
#99. 'insulin dependent diabetes mellitus 1':ab,ti	31	9 Apr 2020
#98. 'insulin-dependent diabetes mellitus 1':ab,ti	31	9 Apr 2020
#97. 'diabetes mellitus, insulin-dependent, 1':ab,ti		9 Apr 2020
#96. 'type 1 diabetes mellitus':ab,ti	14,962	9 Apr 2020
#95. 'sudden-onset diabetes mellitus':ab,ti	1	9 Apr 2020
#94. 'diabetes mellitus, sudden onset':ab,ti	1	9 Apr 2020
#93. 'diabetes mellitus, sudden-onset':ab,ti	1	9 Apr 2020
#92. 'juvenile onset diabetes':ab,ti	494	9 Apr 2020

#91. 'diabetes, juvenile-onset':ab,ti	4	9 Apr 2020
#90. 'juvenile-onset diabetes':ab,ti	494	9 Apr 2020
#89. 'iddm':ab,ti	7,833	9 Apr 2020
#88. 'juvenile-onset diabetes mellitus':ab,ti	232	9 Apr 2020
#87. 'diabetes mellitus, juvenile onset':ab,ti	3	9 Apr 2020
#86. 'diabetes mellitus, juvenile-onset':ab,ti	3	9 Apr 2020
#85. 'insulin-dependent diabetes mellitus':ab,ti	17,759	9 Apr 2020
#84. 'diabetes mellitus, insulin dependent':ab,ti	47	9 Apr 2020
#83. 'diabetes mellitus, insulin-dependent':ab,ti	47	9 Apr 2020
#82. 'diabetes mellitus, type 1':ab,ti	1,786	9 Apr 2020
#81. 'diabetes mellitus, adult onset':ab,ti	3	9 Apr 2020
#80. 'adult-onset diabetes mellitus':ab,ti	193	9 Apr 2020
#79. 'diabetes mellitus, adult-onset':ab,ti	3	9 Apr 2020
#78. 'diabetes, type 2':ab,ti	2,279	9 Apr 2020
#77. 'type 2 diabetes':ab,ti	185,187	9 Apr 2020
#76. 'maturity onset diabetes':ab,ti	2,618	9 Apr 2020
#75. 'diabetes, maturity-onset':ab,ti	43	9 Apr 2020
#74. 'maturity-onset diabetes':ab,ti	2,618	9 Apr 2020
#73. 'noninsulin dependent diabetes mellitus':ab,ti	1,037	9 Apr 2020
#72. 'noninsulin-dependent diabetes mellitus':ab,ti	1,037	9 Apr 2020
#71. 'type 2 diabetes mellitus':ab,ti	61,709	9 Apr 2020
#70. 'slow-onset diabetes mellitus':ab,ti		9 Apr 2020
#69. 'diabetes mellitus, slow onset':ab,ti	1	9 Apr 2020
#68. 'diabetes mellitus, slow-onset':ab,ti	1	9 Apr 2020
#67. 'mody':ab,ti	2,136	9 Apr 2020
#66. 'maturity onset diabetes mellitus':ab,ti	183	9 Apr 2020
#65. 'maturity-onset diabetes mellitus':ab,ti	183	9 Apr 2020
#64. 'diabetes mellitus, maturity onset':ab,ti	14	9 Apr 2020
#63. 'diabetes mellitus, maturity-onset':ab,ti	14	9 Apr 2020
#62. 'diabetes mellitus, noninsulin dependent':ab,ti	4	9 Apr 2020
#61. 'niddm':ab,ti	7,991	9 Apr 2020
#60. 'diabetes mellitus, type ii':ab,ti	1,081	9 Apr 2020
#59. 'stable diabetes mellitus':ab,ti	28	9 Apr 2020
#58. 'diabetes mellitus, stable':ab,ti	16	9 Apr 2020
#57. 'non-insulin-dependent diabetes mellitus':ab,ti	7,743	9 Apr 2020
#56. 'diabetes mellitus, non-insulin-dependent':ab,ti	40	9 Apr 2020
#55. 'diabetes mellitus, non insulin dependent':ab,ti	40	9 Apr 2020
#54. 'ketosis-resistant diabetes mellitus':ab,ti	2	9 Apr 2020
#53. 'diabetes mellitus, ketosis resistant':ab,ti		9 Apr 2020
#52. 'diabetes mellitus, ketosis-resistant':ab,ti		9 Apr 2020
#51. 'diabetes mellitus, noninsulin-dependent':ab,ti	4	9 Apr 2020
#50. 'diabetes mellitus, type 2':ab,ti	4,600	9 Apr 2020
#49. 'diabetes mellitus':ab,ti	278,869	9 Apr 2020
#48. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR	161,803	9 Apr 2020

#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47		
#47. 'ovary cancer'/exp	120,100	9 Apr 2020
#46. 'ovary tumor'/exp	150,462	9 Apr 2020
#45. 'ovary tumor':ab,ti	129	9 Apr 2020
#44. 'ovarian tumor':ab,ti	7,638	9 Apr 2020
#43. 'ovarian carcinoma':ab,ti	17,377	9 Apr 2020
#42. 'ovarian carcinomas, epithelial':ab,ti	1	9 Apr 2020
#41. 'ovarian carcinoma, epithelial':ab,ti	6	9 Apr 2020
#40. 'epithelial ovarian carcinomas':ab,ti	459	9 Apr 2020
#39. 'carcinomas, epithelial ovarian':ab,ti	2	9 Apr 2020
#38. 'carcinoma, epithelial ovarian':ab,ti	6	9 Apr 2020
#37. 'epithelial ovarian carcinoma':ab,ti	2,143	9 Apr 2020
#36. 'ovarian epithelial carcinoma':ab,ti	290	9 Apr 2020
#35. 'ovarian cancers, epithelial':ab,ti	1	9 Apr 2020
#34. 'epithelial ovarian cancers':ab,ti	1,189	9 Apr 2020
#33. 'cancers, epithelial ovarian':ab,ti	7	9 Apr 2020
#32. 'cancer, epithelial ovarian':ab,ti	21	9 Apr 2020
#31. 'ovarian cancer, epithelial':ab,ti	43	9 Apr 2020
#30. 'ovarian epithelial cancers':ab,ti	100	9 Apr 2020
#29. 'epithelial cancers, ovarian':ab,ti	1	9 Apr 2020
#28. 'epithelial cancer, ovarian':ab,ti	4	9 Apr 2020
#27. 'cancers, ovarian epithelial':ab,ti		9 Apr 2020
#26. 'cancer, ovarian epithelial':ab,ti	3	9 Apr 2020
#25. 'ovarian epithelial cancer':ab,ti	414	9 Apr 2020
#24. 'epithelial ovarian cancer':ab,ti	13,087	9 Apr 2020
#23. 'ovarian epithelial carcinomas':ab,ti	84	9 Apr 2020
#22. 'epithelial carcinomas, ovarian':ab,ti		9 Apr 2020
#21. 'epithelial carcinoma, ovarian':ab,ti	1	9 Apr 2020
#20. 'carcinomas, ovarian epithelial':ab,ti	1	9 Apr 2020
#19. 'carcinoma, ovarian epithelial':ab,ti	2	9 Apr 2020
#18. 'cancer of the ovary':ab,ti	735	9 Apr 2020
#17. 'cancer of ovary':ab,ti	32	9 Apr 2020
#16. 'ovarian cancers':ab,ti	8,913	9 Apr 2020
#15. 'cancers, ovarian':ab,ti	139	9 Apr 2020
#14. 'cancer, ovarian':ab,ti	1,121	9 Apr 2020
#13. 'ovarian cancer':ab,ti	76,611	9 Apr 2020
#12. 'ovary cancers':ab,ti	89	9 Apr 2020
#11. 'cancers, ovary':ab,ti	12	9 Apr 2020
#10. 'cancer, ovary':ab,ti	65	9 Apr 2020

#9.	'ovary cancer':ab,ti	595	9 Apr 2020
#8.	'neoplasms, ovarian':ab,ti	23	9 Apr 2020
#7.	'ovary neoplasm':ab,ti	7	9 Apr 2020
#6.	'neoplasms, ovary':ab,ti	5	9 Apr 2020
#5.	'neoplasm, ovary':ab,ti	2	9 Apr 2020
#4.	'ovarian neoplasm':ab,ti	760	9 Apr 2020
#3.	'ovary neoplasms':ab,ti	14	9 Apr 2020
#2.	'neoplasm, ovarian':ab,ti	13	9 Apr 2020
#1.	'ovarian neoplasms':ab,ti	1,859	9 Apr 2020

Quality assessment of included studies based on the Newcastle-Ottawa Scale score

Cohort studies

Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis∞	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total stars
Weiderpass 2002	★	★	★	★	★	★	★	★	8
Zendehdel 2003	★	★	★	★	★	★	★	…	7
Swerdlow 2005	★	★	★	…	★	★	★	★	7
Inoue 2006	★	★	★	★	★	★	★	★	8
Khan 2006	★	★	★	★	★	★	…	★	7
Hemminki 2010	★	★	★	★	★	★	★	…	7
Chodick 2010	★	★	★	★	★	★	…	★	7
Shu 2010	★	★	★	★	★	★	★	★	8
Wotton 2011	…	★	★	★	★	★	★	★	7
Johnson 2011	★	★	★	★	★	★	…	★	7
Lambe 2011	★	★	★	★	★	★	★	★	8
Gapstur 2012	★	★	★	★	★	★	…	★	7
Lo 2013	★	★	★	★	★	★	…	★	7
Chen 2014	★	★	★	★	★★	★	★	★	9
Hsu 2015	★	★	★	★	★	★	…	★	7

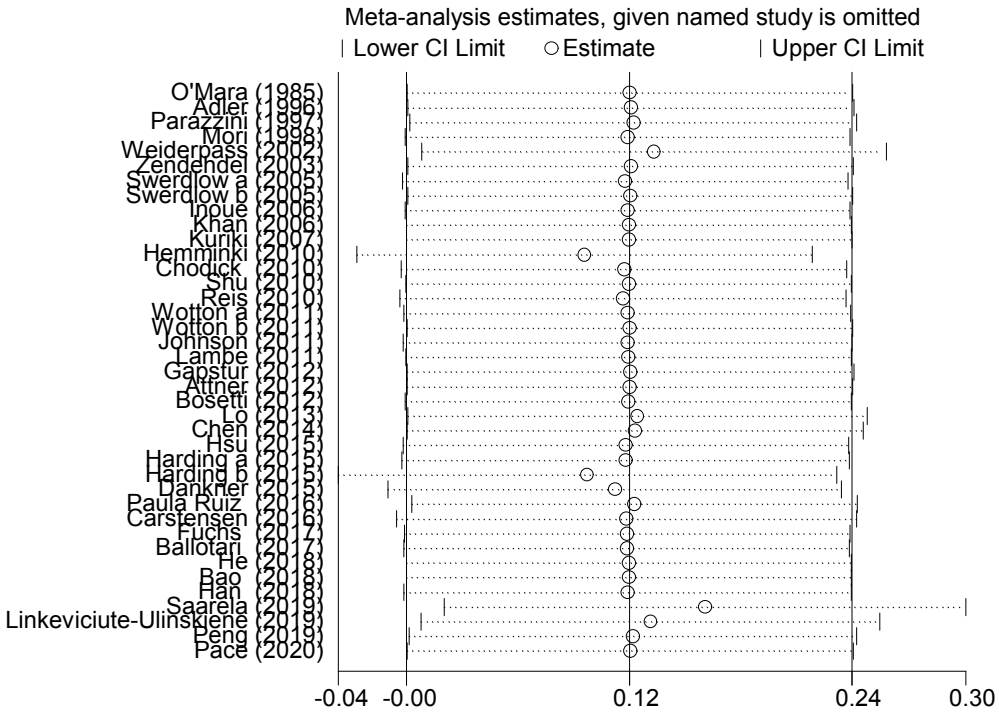
Harding 2015	★	★	★	★	…	★	★	★	7
Dankner 2016	★	★	★	★	★	★	★	★	8
Carstensen 2016	★	★	★	★	★	★	★	…	7
Fuchs 2017	★	★	★	★	…	★	★	★	7
Ballotari 2017	★	★	★	…	★	★	★	…	6
He 2018	★	★	★	★	★	★	…	★	7
Han 2018	★	★	★	★	★	★	★	★	8
Bao 2018	…	★	★	★	★	★	…	★	6
Saarela 2019	★	★	★	★	…	★	★	…	6
Linkeviciute-Ulinskiene 2019	★	★	★	★	…	★	★	★	7
Peng 2019	★	★	★	★	★	★	…	★	7
Pace 2020	★	★	★	★	★	★	★	…	7

Case-control studies

Study ID	Is the case definition adequate	Representativeness of the cases	Selection of the controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total stars
O'Mara 1985	★	★	…	★	★	…	★	…	5
Adler 1996	★	★	★	…	…	★	★	…	5
Parazzini 1997	★	★	…	★	★	…	★	…	5
Mori 1998	★	★	★	★	★	…	★	★	7
Kuriki 2007	★	★	★	…	…	★	★	★	6
Reis 2010	★	★	…	★	…	★	★	★	6
Attner 2012	★	★	★	★	★	★	★	…	7
Bosetti 2012	★	★	…	★	★	…	★	…	5
Ruiz 2016	★	★	…	★	★	…	★	…	5

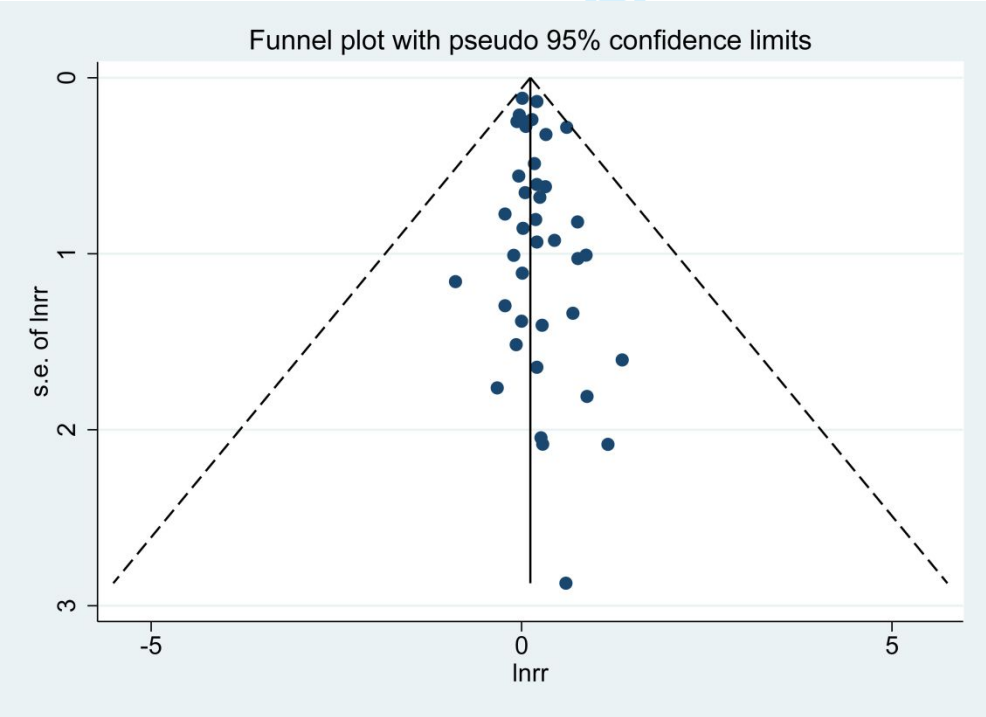
One star is awarded if matched on, or adjusted for maternal age; another star is awarded if other confounders are taken into account.

Sensitivity analysis



Assessment of reporting biases

Funnel plot



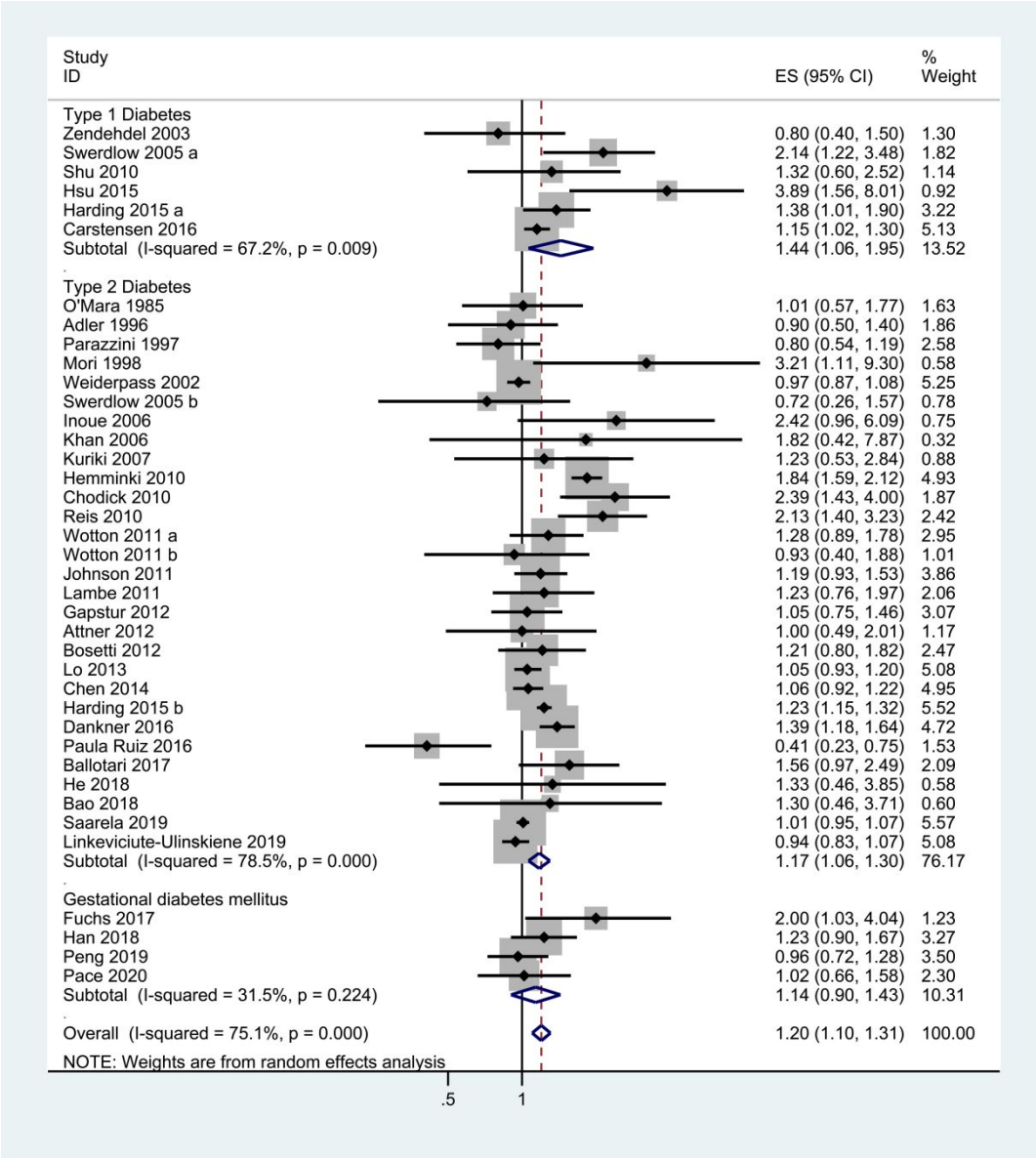
Begg's Test

Begg's Test

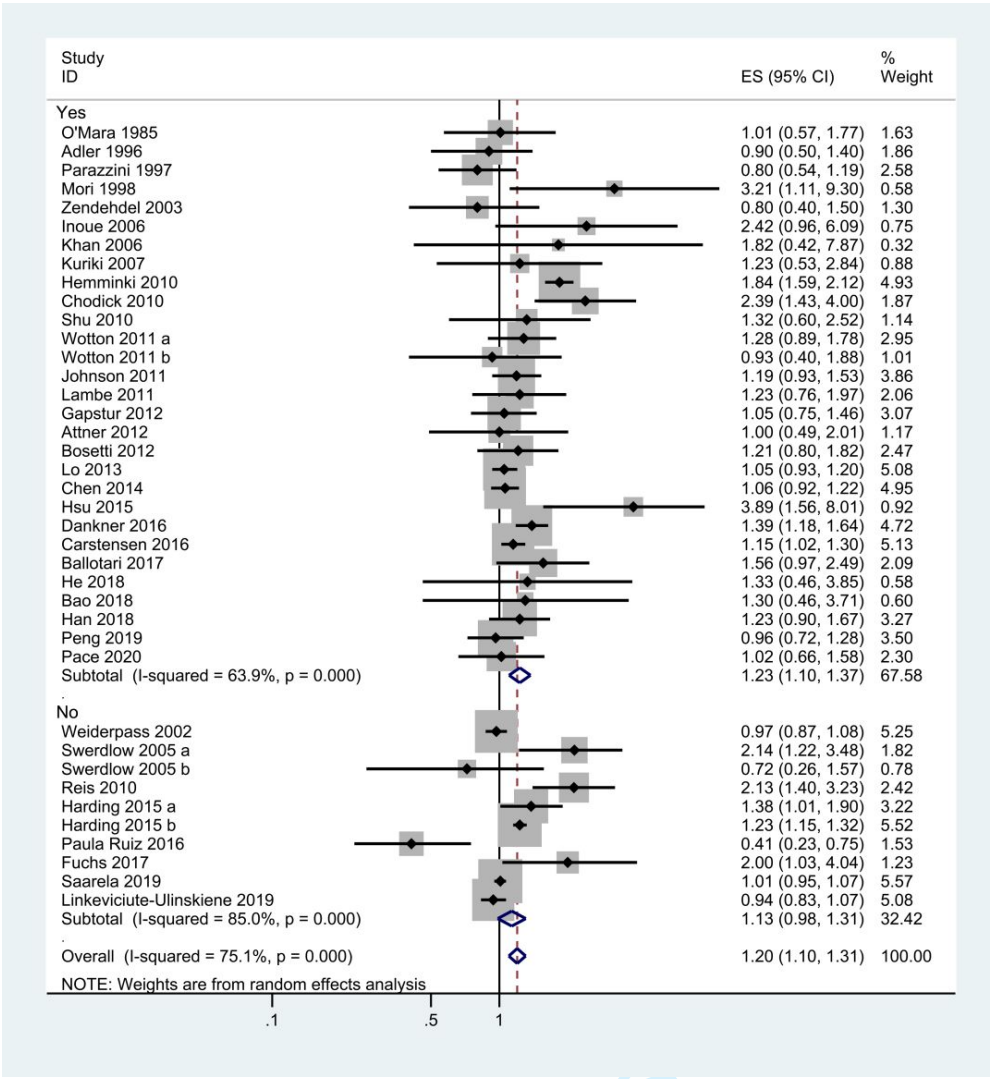
adj. Kendall's Score (P-Q) = 97
Std. Dev. of Score = 82.67
Number of Studies = 39
z = 1.17
Pr > |z| = 0.241
z = 1.16 (continuity corrected)
Pr > |z| = 0.246 (continuity corrected)

Egger's test

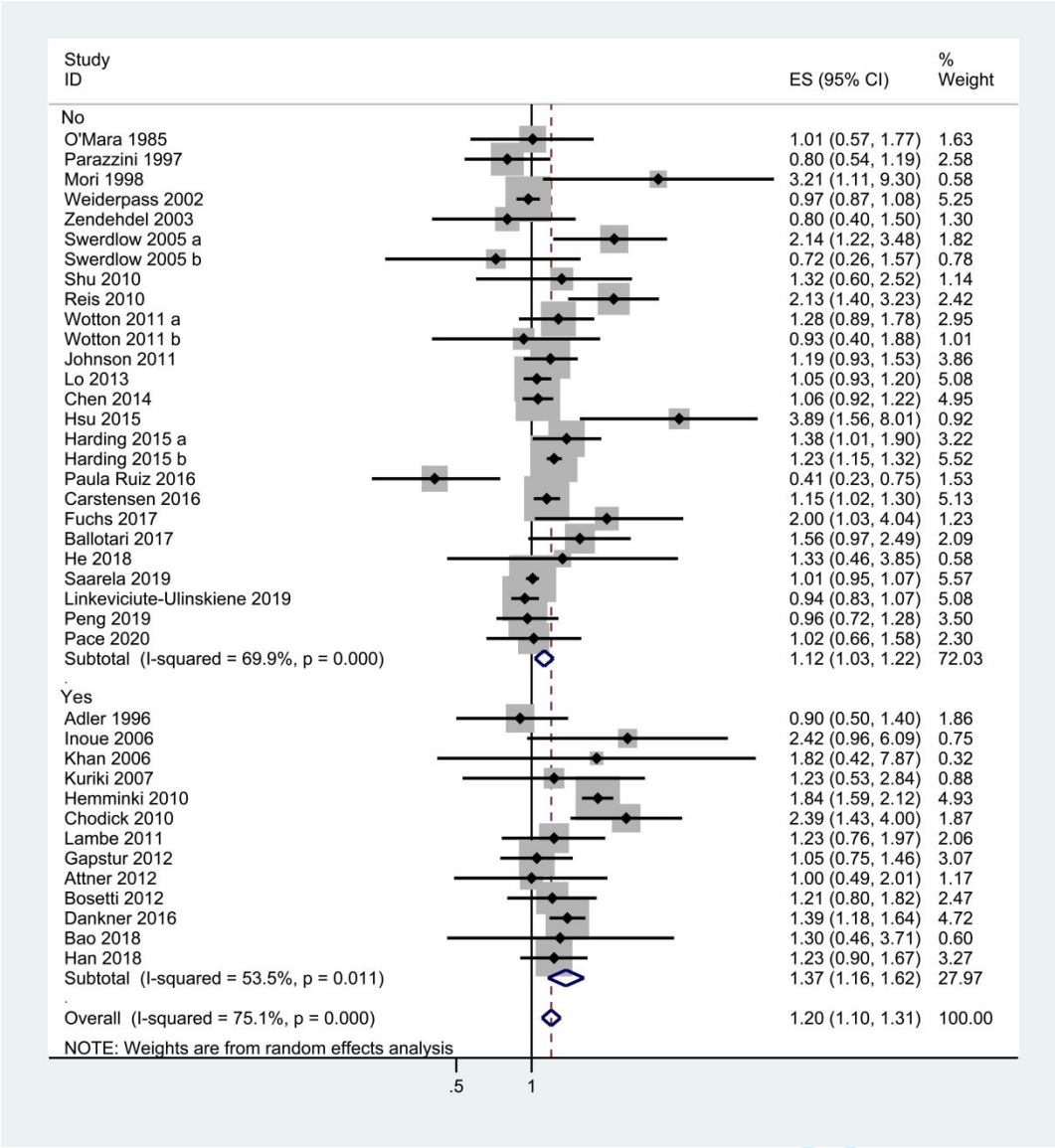
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0705791	.0441485	1.60	0.118	-.0188741	.1600324
bias	.6885655	.4468107	1.54	0.132	-.2167589	1.59389



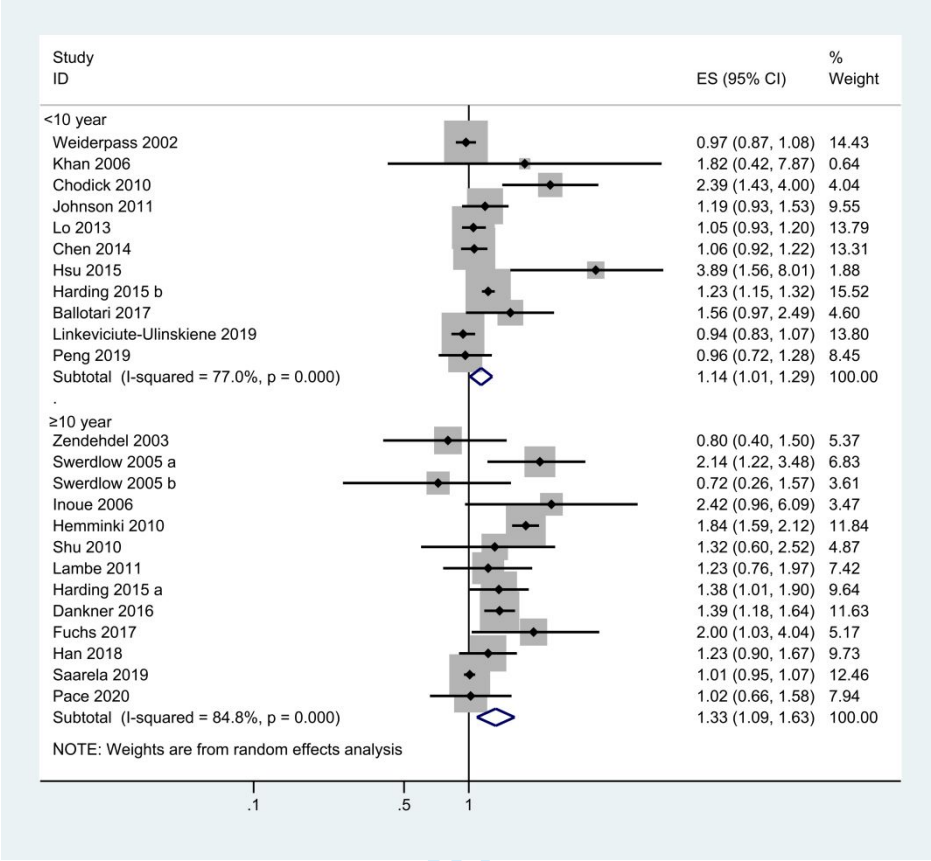
a. Subgroup analysis based on the DM types (type 1 DM vs. type 2 DM vs. GDM). RR relative risk, CI confidence interval, DM diabetes mellitus, GDM gestational DM.



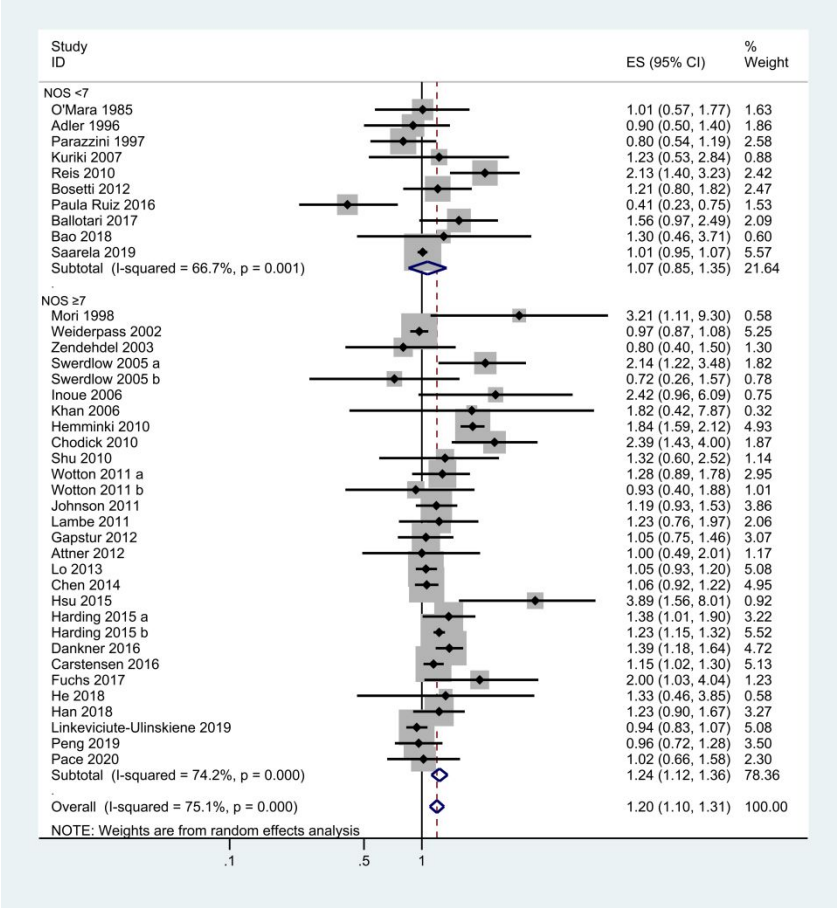
b. Subgroup analysis based on the level of adjustment (unadjusted vs. adjusted). RR relative risk, CI confidence interval.



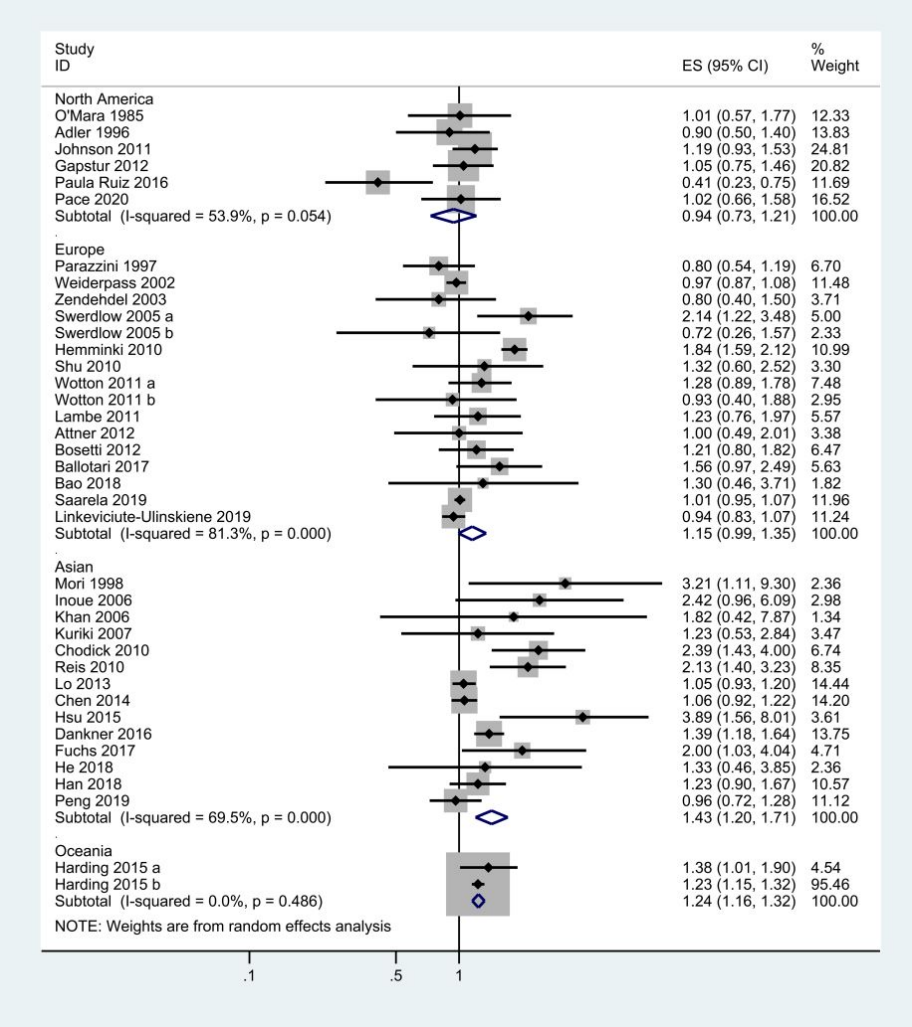
c. Subgroup analysis based on whether the study adjusted for BMI (yes vs. no). RR relative risk, CI confidence interval, BMI body mass index.



d. Subgroup analysis based on the duration of follow-up (<10 year vs. ⩾10 year). RR relative risk, CI confidence interval.



e. Subgroup analysis based on the study quality (NOS <7 vs. ⩾7 points). RR relative risk, CI confidence interval, NOS the Newcastle-Ottawa Scale score.



f. Subgroup analysis based on the geographic areas (North America vs. Europe vs. Asian vs. Oceania). RR relative risk, CI confidence interval.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040137.R1
Article Type:	Original research
Date Submitted by the Author:	05-Oct-2020
Complete List of Authors:	Wang, Li; Huzhou Central Hospital, Obstetrics and Gynecology Zhong, Lei; Huzhou Central Hospital, Intensive Care Unit Xu, Bin; Huzhou Central Hospital, Obstetrics and Gynecology Chen, Min; Huzhou Central Hospital, Obstetrics and Gynecology Huang, Hong; Huzhou Central Hospital, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Diabetes and endocrinology, Evidence based practice
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, Gynaecological oncology < GYNAECOLOGY, Adult oncology < ONCOLOGY

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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% confidence interval (CI) were 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. Synthesized RR of developing OC by history of DM was 1.20 (1.10,1.31) for all

eligible studies, 1.08 (0.77,1.53) for case-control studies and 1.22 (1.11,1.33) for cohort studies. The above-mentioned positive association persisted across most of subgroup analyses, whereas it was not significant among studies from North America and Europe countries, level of unadjusted, low-quality and gestational DM patients 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 GDM and OC risk, respectively, which might be more generalizable than previous published meta-analys es.

►The sensitivity analysis and cumulative meta-analysis showed pooled effect was sta ble and reliable, and no apparent publication bias was identified in our study.

►Substantial heterogeneity was observed among these studies.

INTRODUCTION

Diabetes mellitus (DM), characterized as hyperglycemia, is a rock-ribbed and costly chronic ailment metabolic disease,[1] dividing into four different subtypes—type 1 DM (T1DM), type 2 DM (T2DM), gestational diabetes mellitus (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 in worldwide.[3] That is, the number of DM will continue to rise due to the increasing population ageing and prevalence of rising obesity, recognized 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 gynecological 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 in the 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 ovary 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 etc.[13 14] Besides, other immutable risk factors included age of menarche、age of natural menopausea and endometriosis ,etc.[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 are associated with greater risk of certain types of cancer at multiple sites, such as pancreatic, liver, endometrium cancer, etc.[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, exogenous insulin therapy, etc.[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 studies[23-26] and case-control[27] 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 are remains 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 (MOOSE) protocol checklist [32] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [33] (Additional file 1).

Patient and public involvement

Since our meta-analysis is based on previous published researches, patient and public involvement are 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 MeSH 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”, etc. A comprehensive search strategy was provided in the additional 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: randomized controlled trial, case reports, letters, reviews or animals studies. Eligibility assessment was performed by two authors (WHL and ZL).

First, this 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 (WHL), and then checked by a second investigator (ZL). The main extracted information are described in Table 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 to 3, 4 to 6, 7 to 9 score were considered as low, fair, and high quality, respectively.[34]

Assessment of risk of bias

All selected literatures were subjected to a sensitivity analysis to explore the

robustness of the pooled effects.[35]

Statistical analysis

The effect estimates of original studies were 5 measures of association, including relative risk (RR), standardized incidence ratio (SIR), incidence rate ratio (IRR), hazard ratio (HR) and odds ratio (OR). Given that the frequency of OC is relatively low, the latter four measures were considered to yield approximately equal estimates to that of the RR. Therefore, we reported all pooled results as RR with 95% confidence interval (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 analyze all data due to the conservativeness of the analyze results.[37]The statistical analysis were performed with the Stata 12.0 software (StataCorp, College Station, TX, 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 (type 1 DM vs. type 2 DM vs. GDM), duration of follow-up (<10 year vs. ≥10 year), level of adjustment (unadjusted vs. adjusted and BMI-adjusted vs. BMI-unadjusted), study quality (NOS ≥ 7 vs. <7 points) and geographic areas (North America vs. Europe vs. Asian vs. Oceania). Subsequently, a cumulative 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 type 1 DM and risk of OC, 28 studies investigated the relationship between type 2 DM and OC risk, and the remaining 4 studies assessed this association between GDM and OC risk as well. With regard to geographic location, 1 studies 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 varied, ranging from 3.5 years 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 Table 1 and Table 2.

Table 1 Baseline characteristics of the cohort studies

Study ID	Country or region	Study period	Follow-Up Duration, y	Population	age (years)	No. of Subjects	No. of OC Cases	Population setting	NOS score
Weiderpass 2002 [38]	Sweden	1965–1994	5.7	Type 2 DM	66.4	141,627	337	PBR	8
Zendehdel 2003 [39]	Sweden	1965-1999	15.0	Type 1 DM	17.3	14,323	9	PBR	7
Swerdlow 2005[a] [40]	UK	1972–2003	18.0	Type 1 DM	<30	11,047	16	PBR	7
Swerdlow 2005[b] [40]	UK	1972–2003	18.0	Type 2 DM	30–49	2122	6	PBR	7
Inoue 2006 [41]	Japan	1990-2003	10.7	Type 2 DM	51.8	51,223	74	PBR	8
Khan 2006 [42]	Japan	1988-1997	7.6	Type 2 DM	40-79	33503	29	PBR and HBR	7
Hemminki 2010 [43]	Sweden	1964-2007	15.0	Type 2 DM	39-75	24,827	192	PBR and HBR	7
Chodick 2010 [44]	Israel	2000-2008	8.0	Type 2 DM	62	47,682	88	PBR	7
Shu 2010 [45]	Sweden	1964-2006	17.0	Type 1 DM	12.3	11,290	9	PBR and HBR	8
Wotton 2011[a] [46]	Southern England	1963–1998	…	Type 2 DM	>30	132271	37	PBR and HBR	7
Wotton 2011[b] [46]	southern England	1999–2008	…	Type 2 DM	>30	90427	8	PBR and HBR	7
Johnson 2011 [47]	Canada	1994-2006	4.4	Type 2 DM	60.7	169,012	295	PBR	7
Lambe 2011 [48]	Sweden	1985-1996	11.7	Type 2 DM	46.6	230,737	536	PBR	8
Gapstur 2012 [31]	USA	1992-2007	…	Type 2 DM	62.28	63,440	524	PBR	7
Lo 2013 [49]	Taiwan	1996-2009	3.5	Type 2 DM	60.45	912,447	948	PBR	7
Chen 2014 [30]	Taiwan	2000–2008	>9.0	Type 2 DM	61.09	638,618	935	PBR	9
Hsu 2015 [50]	Taiwan	2000–2008	6.2	Type 1 DM	49.2	7752	7	PBR	7
Harding 2015 [25]	Australia	1997–2008	12.0	Type 1 DM	27.4	38,644	38	PBR	7
Harding 2015 [25]	Australia	1997–2008	5.8	Type 2 DM	60.4	408426	792	PBR	7

Dankner 2016 [24]	Israel	2002-2012	11.0	Type 2 DM	46.63	1,152,122	1,495	PBR	8
Carstensen 2016 [21]	Multi-countries	1972-2014	…	Type 1 DM	<40	…	252	PBR	7
Fuchs 2017 [23]	Israel	1988–2013	12.0	GDM	28.45	104,715	56	PB	7
Ballotari 2017 [26]	Italy	2010–2013	4.0	Type 2 DM	47	195,930	160	PBR	6
Han 2018 [28]	Korean	2002–2015	10.0	GDM	27.33	102,900	1,148	PB	8
He 2018 [29]	China	2003-2014	…	Type 2 DM	63.7	14,193	24	PB	7
Bao 2018 [51]	Swedish	1998–2014	…	Type 2 DM	62.57	25,154	57	Twin	6
Saarela 2019 [52]	Finland	1988–2014	10.5	Type 2 DM	…	223,602	977	PBR	6
Linkeviciute-Ulinskiene 2019 [15]	Lithuania	2000–2012	6.8	Type 2 DM	64.0	78,823	249	PBR	7
Peng 2019 [53]	Taiwan	2000-2013	6.8	GDM	28.97	990,572	1196	PB	7
Pace 2020 [54]	Canada	1990-2007	13.1	GDM	…	68,588	56	PB	7

T1DM type 1 diabetes mellitus, T2DM type 2 DM, GDM gestational DM, HB hospital-based, HB hospital-based registry, PBR population-based registry. PB population-based

Table 2 Baseline characteristics of the case-control studies

Study ID	Country or region	Study period	Population	age (years)	No. Cases/ Controls	Population setting	NOS score
O'Mara 1985 [55]	USA	1957-1965	Type 2 DM	30-89	328/2,342	HB	5
Adler 1996 [56]	USA	1975-1987	Type 2 DM	51.98	595/1,587	PBR	5
Parazzini 1997 [57]	Italy	1983-1991	Type 2 DM	52.52	971/2,758	HB	5
Mori 1998 [58]	Japan	1994-1996	Type 2 DM	54.24	89/323	PB	7
Kuriki 2007 [59]	Japan	1988-2000	Type 2 DM	57.57	218/33,569	PBR and HBR	6
Reis 2010 [27]	Turkey	2002-2003	Type 2 DM	51.0	217/1,050	HB	6
Attner 2012 [60]	Sweden	1998–2007	Type 2 DM	…	289/2,207	PBR	7
Bosetti 2012 [61]	Italy	1991-2009	Type 2 DM	56.70	1,031/2,411	HB	5
Ruiz 2016 [62]	USA	2003-2008	Type 2 DM	57.5	208/224	HB	5

T1DM type 1 diabetes mellitus, T2DM type 2 DM, GDM gestational DM, HB hospital-based, HB hospital-based registry, PBR population-based registry. PB population-based

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 (Additional file 3). Two (22.22%) case-control and twenty-four (88.89%) cohort studies were regarded as high-quality (NOS⩾7 points).

The sensitivity analysis suggested no single study had significant influence on the summarized RR, which revealed the stability of pooled estimate (Additional file 4). No obvious evidence of publication bias was detected by inspection of the funnel plot and statistical tests (Begg test, P=0.246; Egger test, P=0.132; Additional 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 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 type 1 DM (RR, 1.44; 95% CI = 1.06 to 1.95) and type 2 DM 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 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 i.e. ⩾ 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).

Subgroup analysis by continent, DM was significantly positively correlated with increased the 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 Europe (RR, 1.15; 95% CI = 0.99 to 1.35) and North America (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 study quality studies with significant difference and 1.07 (95% CI =0.85 to 1.35) for non-high study quality studies without statistical significance (Additional 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*
Total	36	1.20 (1.10,1.31)	75.1	0.000
Study design				
Case-control	9	1.08 (0.77,1.53)	71.1	0.001
Cohort	27	1.22 (1.11,1.33)	76.7	0.000
DM types				
type 1 DM	6	1.44 (1.06,1.95)	67.2	0.009
type 2 DM	28	1.17 (1.06,1.30)	78.5	0.000
GDM	4	1.14 (0.90,1.43)	31.5	0.224
Geographic location				
North America	6	0.94 (0.73,1.21)	53.9	0.054
Europe	14	1.15 (0.99,1.35)	81.3	0.000
Asian	14	1.43 (1.20,1.71)	69.5	0.000
Oceania	1	1.24 (1.16,1.32)	0.00	0.486
Follow-up				
<10 year	11	1.14 (1.01,1.29)	77.0	0.000
⩾10 year	12	1.33 (1.09,1.63)	84.8	0.000
Level of adjustment				
No	8	1.13(0.98,1.31)	85.0	0.000
Yes	28	1.23 (1.10,1.37)	63.9	0.000
BMI				
Yes	13	1.37 (1.16,1.62)	53.5	0.011
No	23	1.12 (1.03,1.22)	69.9	0.000
Study quality				
NOS <7	10	1.07 (0.85,1.35)	66.7	0.001
NOS⩾7	26	1.24 (1.12,1.36)	74.2	0.000

RR relative risk, CI confidence interval, NOS Newcastle–Ottawa Quality Assessment Scale, BMI body mass index, P for heterogeneity within each subgroup.

Cumulative meta-analysis

Although there is no association between DM and the risk of OC before Shu 2010 [45] (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 to those without history of DM. Similar positive finding was observed when we analyzed by cohort studies, however, no meaningful difference was noted when pooled by the case-control studies.

Since the inherent nature of recall and select bias in case-control study, certain biases might lead to inaccurate reporting of causal relationship. [63]

A subgroup meta-analysis based on DM types indicated that the risk of OC in type 1 DM group (44%) is higher than in type 2 DM group (17%), while no significant association is found in GDM group. That may explain the excess risk in type 1 DM populations that, persons with type 1 DM usually require exogenous insulin treatment for the purpose of regulating blood glucose level,[64] and those who treated with insulin appear to be at higher risk to develop cancer.[65] 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 increase risk of cancer with age, the length of follow-up for GDM patients might be too short to detect cancers in young women. [66]

The positive link was even more prominent arresting in studies that adjusted for covariates (ie, age, obesity, hypertension, reproductive history, smoking or alcohol, etc.) than these for unadjusted covariates analysis. Similarly, compared to 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 ($\geqslant$ 10 years). Owing that OC occurs mostly in middle and elderly women, therefore, women who enjoyed a long-term follow up are more susceptible to OC compared to those who had a short follow-up period.[26] Subgroup analysis on geographic areas, the Asian and Oceania studies yielded similar positive results as the aforementioned analyses apart from Europe and North America studies, which is consistent with a previous meta-analysis described by Zhang.[67] Geographic variation in the incidence of OC in women worldwide might explain such heterogeneity. The significant association was consistent in high study studies (NOS $\geqslant$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. [68] performed a first meta-analysis with 7 case-control and 11 cohort studies and supported that DM patients have a 17% increased risk of OC, compared with non-DM patients. 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, [69] which was further confirmed by a meta-analysis with 15 cohort studies (32%) later the same year.[67] 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 2010 [45] 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 hyperglycemia, hyperinsulinemia and chronic inflammation.[70 71] Because of a prolonged exposure to inflammation and hyperglycemic condition, the reiterant lesion and repair cycles which is associated with incessant ovulation process could be slow down, thus, resulting in an underlying risk of OC.[72] Studies have shown that the hyperglycemic state of patients with DM produces many of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β and IL-6, thereby facilitating a tumor-favorable microenvironment and potentially causing immune hyperactivation and tumor cells growth.[73 74] 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 know as a potent proangiogenic factor,[75] indicating a tumor-promotion effect of DM. Biologically, an excess of insulin, as a growth factor, may stimulate the growth of tumor, whether for endogenous or exogenous [76]. Besides, several oral anti-hyperglycemic therapies (sulfonylureas) have been shown to increase risk of cancer development. [77] However, metformin, as a insulin sensitizer, may reduce this risk via mediated by stimulation of AMP-activated protein kinase and inhibition of gluconeogenesis in the liver.[78]

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 type 1 DM, type 2 DM or GDM and the risk of OC, respectively, which might be more generalizable than the previous three meta-analyses. Third, most of included observational studies has controlled at least one potential confounder, such as age, BMI, obesity, drinking and smoking habits, as well as regular physical exercise, etc. 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 the 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 sensitizing agents and insulin) of DM, oral contraceptive use, hormone replacement therapy, etc. Therefore, further trials are warranted to clarify the association.

CONLUSIONS

Accumulated evidence from cohort and case–control studies suggested that women with history of DM have a higher risk of OC than those who 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.

Acknowledgements The authors would like to thank all the anonymous reviewers for their valuable comments and suggestions on improving quality of this study.

Contributors HXH, WHL and ZL conceived the study idea and designed the study. WHL and ZL collected literatures, reviewed the articles, collected the data and performed all data analyses. W-HL, ZL, HXH, XB and CM were responsible for drafting of the manuscript. All the authors approved the final version of this manuscript.

Funding This research received no specific grant from any funding agency.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Ethical Approval Not applicable.

Data availability statement All data are fully available without restriction.

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Figure 1 Article screening flow diagram.
Figure 2 Meta-analysis of the association between DM and the risk of OC. DM diabetes mellitus, OC ovarian cancer.

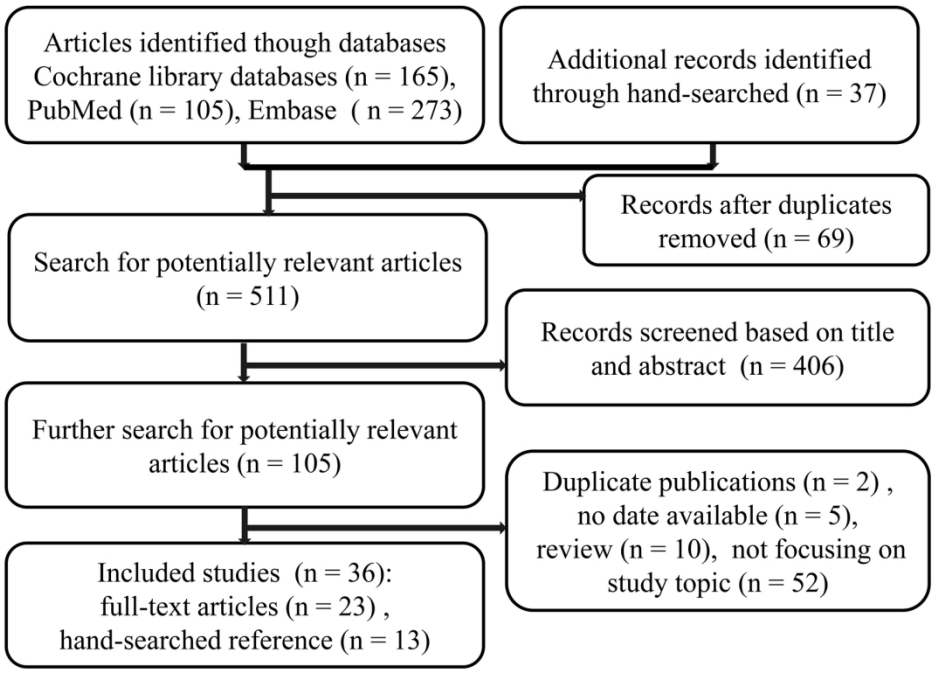
Figure 3 Cumulative meta-analysis of the association between DM and risk of OC. DM diabetes mellitus, OC ovarian cancer.

Additional file 1 The PRISMA checklist and MOOSE checklist.

Additional file 2 The search strategy and search results.

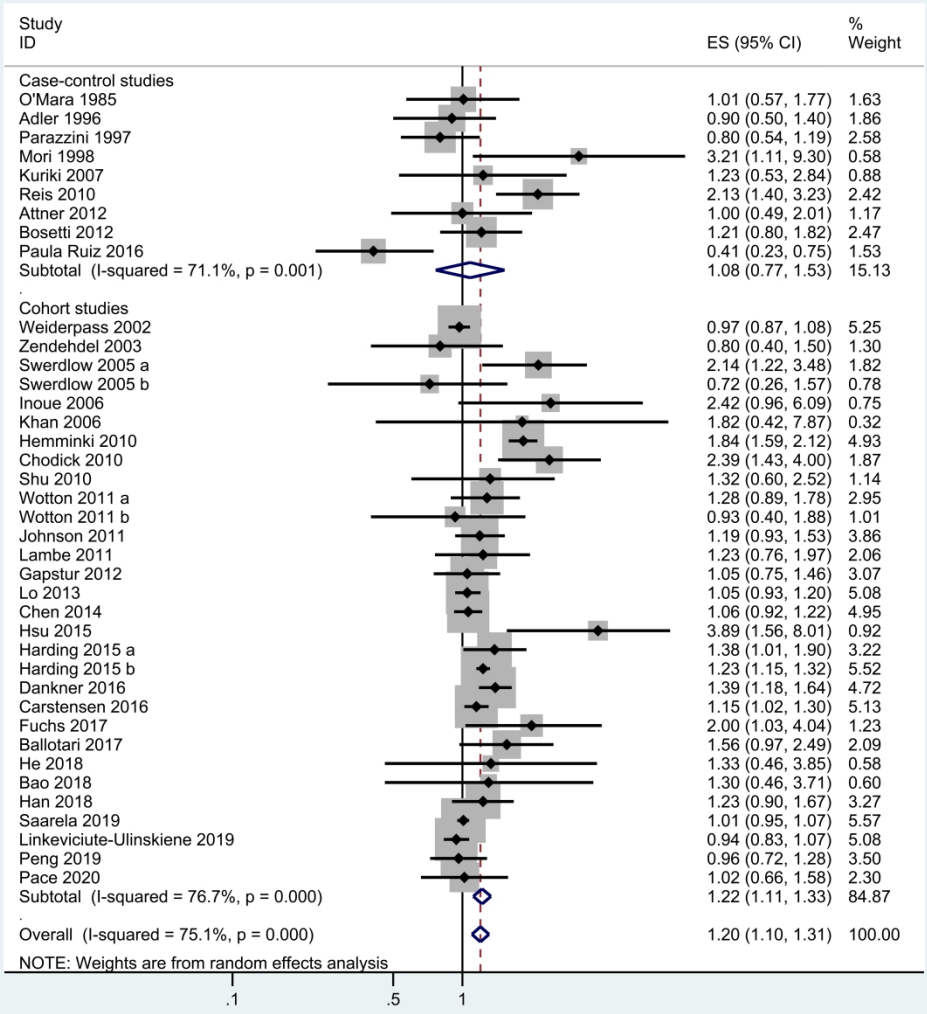
Additional file 3 Quality assessment of included studies based on the Newcastle-Ottawa Scale score.

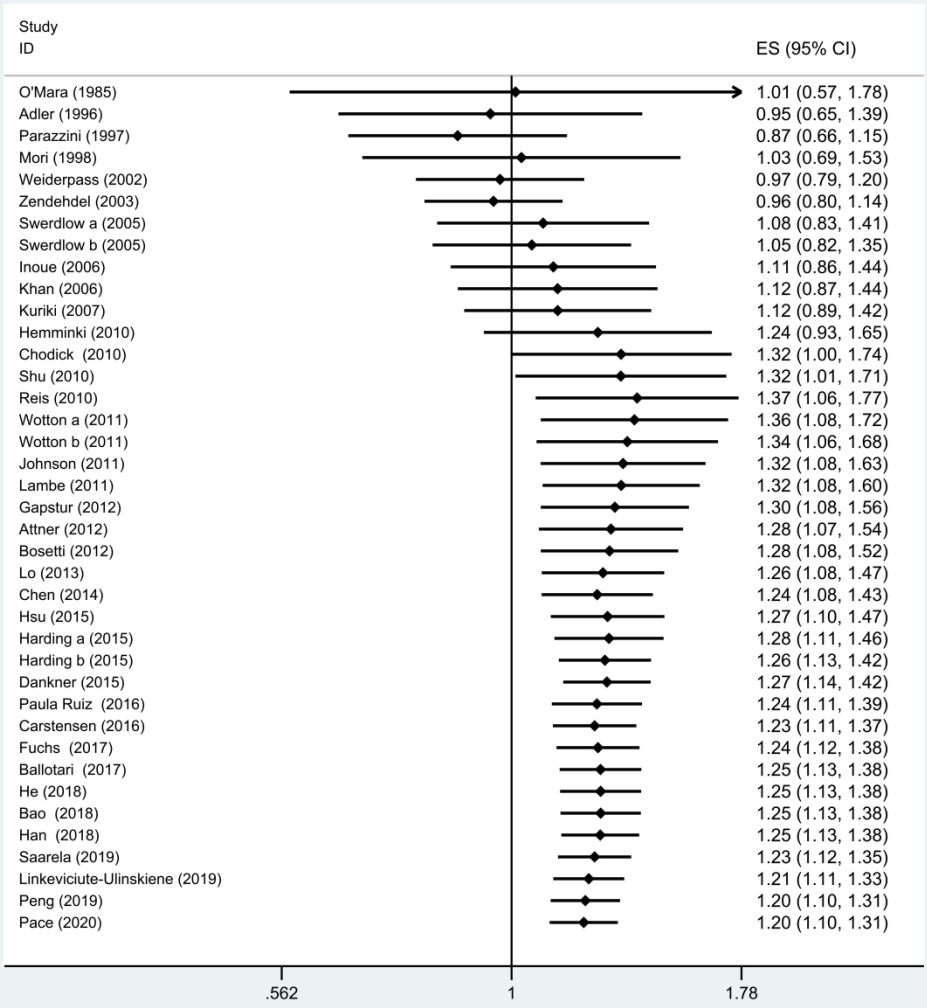
Additional file 4 Sensitivity analysis and assessment of reporting biases & Forest plots for the subgroup analyses of DM and subsequent risk of OC. DM diabetes mellitus, OC ovarian cancer.



709 KB

80x56mm (600 x 600 DPI)


Study ID
ES (95% CI)
% Weight
Case-control studies
O'Mara 1985 1.01 (0.57, 1.77) 1.63
Adler 1996 0.90 (0.50, 1.40) 1.86
Parazzini 1997 0.80 (0.54, 1.19) 2.58
Mori 1998 3.21 (1.11, 9.30) 0.58
Kuriki 2007 1.23 (0.53, 2.84) 0.88
Reis 2010 2.13 (1.40, 3.23) 2.42
Attner 2012 1.00 (0.49, 2.01) 1.17
Bosetti 2012 1.21 (0.80, 1.82) 2.47
Paula Ruiz 2016 0.41 (0.23, 0.75) 1.53
Subtotal (I-squared = 71.1%, p = 0.001) 1.08 (0.77, 1.53) 15.13
Cohort studies
Weiderpass 2002 0.97 (0.87, 1.08) 5.25
Zendehdel 2003 0.80 (0.40, 1.50) 1.30
Swerdlow 2005 a 2.14 (1.22, 3.48) 1.82
Swerdlow 2005 b 0.72 (0.26, 1.57) 0.78
Inoue 2006 2.42 (0.96, 6.09) 0.75
Khan 2006 1.82 (0.42, 7.87) 0.32
Hemminki 2010 1.84 (1.59, 2.12) 4.93
Chodick 2010 2.39 (1.43, 4.00) 1.87
Shu 2010 1.32 (0.60, 2.52) 1.14
Wotton 2011 a 1.28 (0.89, 1.78) 2.95
Wotton 2011 b 0.93 (0.40, 1.88) 1.01
Johnson 2011 1.19 (0.93, 1.53) 3.86
Lambe 2011 1.23 (0.76, 1.97) 2.06
Gapstur 2012 1.05 (0.75, 1.46) 3.07
Lo 2013 1.05 (0.93, 1.20) 5.08
Chen 2014 1.06 (0.92, 1.22) 4.95
Hsu 2015 3.89 (1.56, 8.01) 0.92
Harding 2015 a 1.38 (1.01, 1.90) 3.22
Harding 2015 b 1.23 (1.15, 1.32) 5.52
Dankner 2016 1.39 (1.18, 1.64) 4.72
Carstensen 2016 1.15 (1.02, 1.30) 5.13
Fuchs 2017 2.00 (1.03, 4.04) 1.23
Ballotari 2017 1.56 (0.97, 2.49) 2.09
He 2018 1.33 (0.46, 3.85) 0.58
Bao 2018 1.30 (0.46, 3.71) 0.60
Han 2018 1.23 (0.90, 1.67) 3.27
Saarela 2019 1.01 (0.95, 1.07) 5.57
Linkeviciute-Ulinskiene 2019 0.94 (0.83, 1.07) 5.08
Peng 2019 0.96 (0.72, 1.28) 3.50
Pace 2020 1.02 (0.66, 1.58) 2.30
Subtotal (I-squared = 76.7%, p = 0.000) 1.22 (1.11, 1.33) 84.87
Overall (I-squared = 75.1%, p = 0.000) 1.20 (1.10, 1.31) 100.00
NOTE: Weights are from random effects analysis
.1
.5
1


Study
ID
ES (95% CI)
O'Mara (1985) 1.01 (0.57, 1.78)
Adler (1996) 0.95 (0.65, 1.39)
Parazzini (1997) 0.87 (0.66, 1.15)
Mori (1998) 1.03 (0.69, 1.53)
Weiderpass (2002) 0.97 (0.79, 1.20)
Zendehdel (2003) 0.96 (0.80, 1.14)
Swerdlow a (2005) 1.08 (0.83, 1.41)
Swerdlow b (2005) 1.05 (0.82, 1.35)
Inoue (2006) 1.11 (0.86, 1.44)
Khan (2006) 1.12 (0.87, 1.44)
Kuriki (2007) 1.12 (0.89, 1.42)
Hemminki (2010) 1.24 (0.93, 1.65)
Chodick (2010) 1.32 (1.00, 1.74)
Shu (2010) 1.32 (1.01, 1.71)
Reis (2010) 1.37 (1.06, 1.77)
Wotton a (2011) 1.36 (1.08, 1.72)
Wotton b (2011) 1.34 (1.06, 1.68)
Johnson (2011) 1.32 (1.08, 1.63)
Lambe (2011) 1.32 (1.08, 1.60)
Gapstur (2012) 1.30 (1.08, 1.56)
Attner (2012) 1.28 (1.07, 1.54)
Bosetti (2012) 1.28 (1.08, 1.52)
Lo (2013) 1.26 (1.08, 1.47)
Chen (2014) 1.24 (1.08, 1.43)
Hsu (2015) 1.27 (1.10, 1.47)
Harding a (2015) 1.28 (1.11, 1.46)
Harding b (2015) 1.26 (1.13, 1.42)
Dankner (2015) 1.27 (1.14, 1.42)
Paula Ruiz (2016) 1.24 (1.11, 1.39)
Carstensen (2016) 1.23 (1.11, 1.37)
Fuchs (2017) 1.24 (1.12, 1.38)
Ballotari (2017) 1.25 (1.13, 1.38)
He (2018) 1.25 (1.13, 1.38)
Bao (2018) 1.25 (1.13, 1.38)
Han (2018) 1.25 (1.13, 1.38)
Saarela (2019) 1.23 (1.12, 1.35)
Linkeviciute-Ulinskiene (2019) 1.21 (1.11, 1.33)
Peng (2019) 1.20 (1.10, 1.31)
Pace (2020) 1.20 (1.10, 1.31)
.562
1
1.78

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) protocol checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	A history of diabetes mellitus (DM) has been linked to increased risk of ovarian cancer (OC), but the results have not been consistent. The aim of this study was to clarify this association.
√	Hypothesis statement	DM increases the risk of OC.
√	Description of study outcomes	OC
√	Type of exposure or intervention used	DM
√	Type of study designs used	Observational studies: cohort and case-control studies.
√	Study population	No restriction.
Reporting of search strategy should include		
√	Qualifications of searchers	ZL (first author) and WHL have published a meta-analysis in Critical care in 2017 (with experience of literature search).
√	Search strategy, including time period included in the synthesis and keywords	PubMed from 1965 –April 2020 EMBASE from 1974 –April 2020 Cochrane library databases 1974 –April 2020 See additional file 2 the search strategy and search results.
√	Databases and registries searched	PubMed, Embase and the Cochrane library databases
√	Search software used, name and version, including special features	No search software is being used. The process of retrieving citations and eliminating the duplications was used by EndNote software.
√	Use of hand searching	The potentially eligible bibliographies of relevant articles were manually examined to identify any additional publications relevant to our study.
√	List of citations located and those excluded, including justifications	The literature search process is given in flow diagram.
√	Method of addressing articles published in languages other than English	Through a translation app or consult professionals.
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	Not applicable

Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were also given in our study.
√	Rationale for the selection and coding of data	The PICO framework
√	Assessment of confounding	Sensitivity analyses
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The Newcastle-Ottawa Scale (NOS) score
√	Assessment of heterogeneity	The statistical heterogeneity was measured by χ^2 (threshold p=0 ·10) and quantified by the I ²statistic.
√	Description of statistical methods in sufficient detail to be replicated	The details refer to the "Statistical analysis" in our study.
√	Provision of appropriate tables and graphics	We included 1 box detailing the terms used for database search, 1 flow chart,1 summary table, 1 forest plot of all studies, 1 forest plot to examine effect modification by age, 1 table of sensitivity analyses.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Additional file 4
√	Indication of statistical uncertainty of findings	For more details refer to the The pooled effects were analyzed by relative risk (RR) with 95% confidence interval, and the statistical heterogeneity was measured by χ^2 (threshold p=0·10) and quantified by the *I* ²statistic.
Reporting of discussion should include		
√	Quantitative assessment of bias	The cumulative meta-analysis and sensitivity analysis showed pooled effect was stable and reliable.
√	Justification for exclusion	The exclusion criteria in this meta-analysis were: randomized controlled trial, case reports, letters, reviews or animals studies.
√	Assessment of quality of	No apparent publication bias was identified in this

	included studies	meta-analysis.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Significant heterogeneity between these studies was observed.
√	Generalization of the conclusions	Women with history of DM have a higher risk of OC than those who without.
√	Guidelines for future research	Further high-quality studies with prospective design that are adequately controlled for potential confounding factors and verified the association with subtypes of OC should be conducted to identify our results.
√	Disclosure of funding source	This research received no specific grant from any funding agency.

Systematic reviews and meta-analyses (PRISMA) guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Methods
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Additional file 2：The search strategy and search results

PubMed (n=105), the Cochrane library databases(n=165) and Embase (n=273)

PubMed:

#1 ((((((((((((((("Ovarian Neoplasms"[Mesh]) OR "Ovarian Neoplasms"[Title/Abstract]) OR "Neoplasm, Ovarian"[Title/Abstract]) OR "Ovarian Neoplasm"[Title/Abstract]) OR "Ovary Neoplasms"[Title/Abstract]) OR "Neoplasm, Ovary"[Title/Abstract]) OR "Ovary Neoplasm"[Title/Abstract]) OR "Neoplasms, Ovarian"[Title/Abstract]) OR "Ovary Cancer"[Title/Abstract]) OR "Cancer, Ovary"[Title/Abstract]) OR "Ovary Cancers"[Title/Abstract]) OR "Ovarian Cancer"[Title/Abstract]) OR "Cancer, Ovarian"[Title/Abstract]) OR "Ovarian Cancers"[Title/Abstract]) OR "Cancer of Ovary"[Title/Abstract]) OR "Cancer of the Ovary"[Title/Abstract])) OR ((((((((((("Carcinoma, Ovarian Epithelial"[Mesh]) OR "Ovarian Epithelial Carcinomas"[Title/Abstract]) OR "Epithelial Ovarian Cancer"[Title/Abstract]) OR "Ovarian Epithelial Cancers"[Title/Abstract]) OR "Ovarian Epithelial Cancer"[Title/Abstract]) OR "Epithelial Ovarian Cancers"[Title/Abstract]) OR "Ovarian Epithelial Carcinoma"[Title/Abstract]) OR "Epithelial Ovarian Carcinoma"[Title/Abstract]) OR "Epithelial Ovarian Carcinomas"[Title/Abstract]) OR "ovarian carcinoma"[Title/Abstract])) 101778

#2 ((((("diabete*"[Title/Abstract]) OR ((((((((((((((((("Diabetes Mellitus, Type 1"[Title/Abstract]) OR "Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Juvenile-Onset Diabetes Mellitus"[Title/Abstract]) OR "IDDM"[Title/Abstract]) OR "Juvenile-Onset Diabetes"[Title/Abstract]) OR "Juvenile Onset Diabetes"[Title/Abstract]) OR "Sudden-Onset Diabetes Mellitus"[Title/Abstract]) OR "Type 1 Diabetes Mellitus"[Title/Abstract]) OR "Insulin-Dependent Diabetes Mellitus 1"[Title/Abstract]) OR "Insulin Dependent Diabetes Mellitus 1"[Title/Abstract]) OR "Type 1 Diabetes"[Title/Abstract]) OR "Diabetes, Type 1"[Title/Abstract]) OR "Autoimmune Diabetes"[Title/Abstract]) OR "Brittle Diabetes Mellitus"[Title/Abstract]) OR "Ketosis-Prone Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Type 1"[Mesh])) OR ((((((((((((((((("Diabetes Mellitus, Type 2"[Title/Abstract]) OR "Ketosis-Resistant Diabetes Mellitus"[Title/Abstract]) OR "Non-Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Stable Diabetes Mellitus"[Title/Abstract]) OR "NIDDM"[Title/Abstract]) OR "Maturity-Onset Diabetes Mellitus"[Title/Abstract]) OR "Maturity Onset Diabetes Mellitus"[Title/Abstract]) OR "MODY"[Title/Abstract]) OR "Type 2 Diabetes Mellitus"[Title/Abstract]) OR "Noninsulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Noninsulin Dependent Diabetes Mellitus"[Title/Abstract]) OR "Maturity-Onset Diabetes"[Title/Abstract]) OR "Maturity Onset Diabetes"[Title/Abstract]) OR "Type 2 Diabetes"[Title/Abstract]) OR "Adult-Onset Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Type 2"[Mesh])) OR (("Diabetes Mellitus"[Mesh]) OR "Diabetes Mellitus"[Title/Abstract])))))) OR ((((((("Gestational Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Gestational"[Title/Abstract]) OR

"Gestational Diabetes"[Title/Abstract]) OR "Pregnancy-Induced Diabetes"[Title/Abstract]) OR "Diabetes, Gestational"[Mesh])) 523490

#3 ((((("Observational Studies as Topic"[Mesh]) OR "Observational Study"[Publication Type])))) OR ((((((((((((((((((((("Case-Control Studies"[Mesh]) OR "Case-Control Studies"[Title/Abstract]) OR "Case-Control Study"[Title/Abstract]) OR "Case-Comparison Studies"[Title/Abstract]) OR "Case Comparison Studies"[Title/Abstract]) OR "Case-Comparison Study"[Title/Abstract]) OR "Case-Compeer Studies"[Title/Abstract]) OR "Case-Referent Studies"[Title/Abstract]) OR "Case Referent Studies"[Title/Abstract]) OR "Case-Referent Study"[Title/Abstract]) OR "Case-Base Studies"[Title/Abstract]) OR "Case Base Studies"[Title/Abstract]) OR "Case Control Studies"[Title/Abstract]) OR "Case Control Study"[Title/Abstract]) OR "Nested Case-Control Studies"[Title/Abstract]) OR "Case-Control Studies, Nested"[Title/Abstract]) OR "Nested Case Control Studies"[Title/Abstract]) OR "Nested Case-Control Study"[Title/Abstract]) OR "Matched Case-Control Studies"[Title/Abstract]) OR "Matched Case Control Studies"[Title/Abstract]) OR "Matched Case-Control Study"[Title/Abstract]))) OR ((((((((((((("Cohort Studies"[Mesh]) OR "Cohort Studies"[Title/Abstract]) OR "Cohort Study"[Title/Abstract]) OR "Concurrent Studies"[Title/Abstract]) OR "Concurrent Study"[Title/Abstract]) OR "Closed Cohort Studies"[Title/Abstract]) OR "Closed Cohort Study"[Title/Abstract]) OR "Cohort Analysis"[Title/Abstract]) OR "Cohort Analyses"[Title/Abstract]) OR "Historical Cohort Studies"[Title/Abstract]) OR "Historical Cohort Study"[Title/Abstract]) OR "Incidence Studies"[Title/Abstract]) OR "Incidence Study"[Title/Abstract]) OR "Cohort*"[Title/Abstract]))) 2451208

#4 #1 and #2 and #3 105 **(search results)**

Cochrane library:

ID Search

#1 (Ovarian Neoplasms):ti,ab,kw OR (Neoplasm, Ovarian):ti,ab,kw OR (Ovarian Neoplasm):ti,ab,kw OR (Ovary Neoplasms):ti,ab,kw OR (Neoplasm, Ovary):ti,ab,kw (Word variations have been searched)

#2 (Neoplasms, Ovary):ti,ab,kw OR (Ovary Neoplasm):ti,ab,kw OR (Neoplasms, Ovarian):ti,ab,kw OR (Ovary Cancer):ti,ab,kw OR (Cancer, Ovary):ti,ab,kw (Word variations have been searched)

#3 (Cancers, Ovary):ti,ab,kw OR (Ovary Cancers):ti,ab,kw OR (Ovarian Cancer):ti,ab,kw OR (Cancer, Ovarian):ti,ab,kw OR (Cancers, Ovarian):ti,ab,kw (Word variations have been searched)

#4 (Ovarian Cancers):ti,ab,kw OR (Cancer of Ovary):ti,ab,kw OR (Cancer of the Ovary):ti,ab,kw OR (Carcinoma, Ovarian Epithelial):ti,ab,kw OR (Carcinomas, Ovarian Epithelial):ti,ab,kw (Word variations have been searched)

#5 (Epithelial Carcinoma, Ovarian):ti,ab,kw OR (Epithelial Carcinomas, Ovarian):ti,ab,kw OR (Ovarian Epithelial Carcinomas):ti,ab,kw OR (Epithelial Ovarian Cancer):ti,ab,kw OR (Ovarian Epithelial Cancer):ti,ab,kw (Word variations have been searched)

#6 (Cancer, Ovarian Epithelial):ti,ab,kw OR (Cancers, Ovarian Epithelial):ti,ab,kw OR (Epithelial Cancer, Ovarian):ti,ab,kw OR (Epithelial Cancers, Ovarian):ti,ab,kw OR (Ovarian Epithelial Cancers):ti,ab,kw (Word variations have been searched)

#7 (Ovarian Cancer, Epithelial):ti,ab,kw OR (Cancer, Epithelial Ovarian):ti,ab,kw OR (Cancers, Epithelial Ovarian):ti,ab,kw OR (Epithelial Ovarian Cancers):ti,ab,kw OR (Ovarian Cancers, Epithelial):ti,ab,kw (Word variations have been searched)

#8 (Ovarian Epithelial Carcinoma):ti,ab,kw OR (Epithelial Ovarian Carcinoma):ti,ab,kw OR (Carcinoma, Epithelial Ovarian):ti,ab,kw OR (Carcinomas, Epithelial Ovarian):ti,ab,kw OR (Epithelial Ovarian Carcinomas):ti,ab,kw (Word variations have been searched)

#9 (Ovarian Carcinoma, Epithelial):ti,ab,kw OR (Ovarian Carcinomas, Epithelial):ti,ab,kw OR (ovarian carcinoma):ti,ab,kw OR (Ovar*):ti,ab,kw (Word variations have been searched)

#10 MeSH descriptor: [Ovarian Neoplasms] explode all trees

#11 MeSH descriptor: [Carcinoma, Ovarian Epithelial] explode all trees

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 17934

#13 (Diabetes mellitus):ti,ab,kw OR (Diabetes Mellitus, Type 2):ti,ab,kw OR (Diabetes Mellitus, Noninsulin-Dependent):ti,ab,kw OR (Diabetes Mellitus, Ketosis-Resistant):ti,ab,kw OR (Diabetes Mellitus, Ketosis Resistant):ti,ab,kw (Word variations have been searched)

#14 (Ketosis-Resistant Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Non Insulin Dependent):ti,ab,kw OR (Diabetes Mellitus, Non-Insulin-Dependent):ti,ab,kw OR (Non-Insulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Stable):ti,ab,kw (Word variations have been searched)

#15 (Stable Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR

(NIDDM):ti,ab,kw OR (Diabetes Mellitus, Noninsulin Dependent):ti,ab,kw OR (Diabetes Mellitus, Maturity-Onset):ti,ab,kw (Word variations have been searched)
#16 (Diabetes Mellitus, Maturity Onset):ti,ab,kw OR (Maturity-Onset Diabetes Mellitus):ti,ab,kw OR (Maturity Onset Diabetes Mellitus):ti,ab,kw OR (MODY):ti,ab,kw OR (Diabetes Mellitus, Slow-Onset):ti,ab,kw (Word variations have been searched)
#17 (Diabetes Mellitus, Slow Onset):ti,ab,kw OR (Slow-Onset Diabetes Mellitus):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Noninsulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Noninsulin Dependent Diabetes Mellitus):ti,ab,kw (Word variations have been searched)
#18 (Maturity-Onset Diabetes):ti,ab,kw OR (Diabetes, Maturity-Onset):ti,ab,kw OR (Maturity Onset Diabetes):ti,ab,kw OR (Type 2 Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw (Word variations have been searched)
#19 (Diabetes Mellitus, Adult-Onset):ti,ab,kw OR (Adult-Onset Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Adult Onset):ti,ab,kw OR (Diabetes Mellitus, Type 1):ti,ab,kw OR (Diabetes Mellitus, Insulin-Dependent):ti,ab,kw (Word variations have been searched)
#20 (Diabetes Mellitus, Insulin Dependent):ti,ab,kw OR (Insulin-Dependent Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Juvenile-Onset):ti,ab,kw OR (Diabetes Mellitus, Juvenile Onset):ti,ab,kw OR (Juvenile-Onset Diabetes Mellitus):ti,ab,kw (Word variations have been searched)
#21 (IDDM):ti,ab,kw OR (Juvenile-Onset Diabetes):ti,ab,kw OR (Diabetes, Juvenile-Onset):ti,ab,kw OR (Juvenile Onset Diabetes):ti,ab,kw OR (Diabetes Mellitus, Sudden-Onset):ti,ab,kw (Word variations have been searched)
#22 (Diabetes Mellitus, Sudden Onset):ti,ab,kw OR (Sudden-Onset Diabetes Mellitus):ti,ab,kw OR (Type 1 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Insulin-Dependent, 1):ti,ab,kw OR (Insulin-Dependent Diabetes Mellitus 1):ti,ab,kw (Word variations have been searched)
#23 (Insulin Dependent Diabetes Mellitus 1):ti,ab,kw OR (Type 1 Diabetes):ti,ab,kw OR (Diabetes, Type 1):ti,ab,kw OR (Diabetes Mellitus, Type I):ti,ab,kw OR (Diabetes, Autoimmune):ti,ab,kw (Word variations have been searched)
#24 (Autoimmune Diabetes):ti,ab,kw OR (Diabetes Mellitus, Brittle):ti,ab,kw OR (Brittle Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Ketosis-Prone):ti,ab,kw OR (Diabetes Mellitus, Ketosis Prone):ti,ab,kw (Word variations have been searched)
#25 (Ketosis-Prone Diabetes Mellitus):ti,ab,kw OR (Diabetes, Gestational):ti,ab,kw OR (Diabetes, Pregnancy-Induced):ti,ab,kw OR (Diabetes, Pregnancy Induced):ti,ab,kw OR (Pregnancy-Induced Diabetes):ti,ab,kw (Word variations have been searched)
#26 (Gestational Diabetes):ti,ab,kw OR (Diabetes Mellitus, Gestational):ti,ab,kw OR (Gestational Diabetes Mellitus):ti,ab,kw OR (diabete):ti,ab,kw OR (diabet*):ti,ab,kw (Word variations have been searched)
#27 MeSH descriptor: [Diabetes Mellitus] explode all trees
#28 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#29 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees

#30 MeSH descriptor: [Diabetes, Gestational] explode all trees
#31 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 **89079**

#32 (Cohort Studies):ti,ab,kw OR (Cohort Study):ti,ab,kw OR (Studies, Cohort):ti,ab,kw OR (Study, Cohort):ti,ab,kw OR (Concurrent Studies):ti,ab,kw (Word variations have been searched)
#33 (Studies, Concurrent):ti,ab,kw OR (Concurrent Study):ti,ab,kw OR (Study, Concurrent):ti,ab,kw OR (Closed Cohort Studies):ti,ab,kw OR (Cohort Studies, Closed):ti,ab,kw (Word variations have been searched)
#34 (Closed Cohort Study):ti,ab,kw OR (Cohort Study, Closed):ti,ab,kw OR (Study, Closed Cohort):ti,ab,kw OR (Studies, Closed Cohort):ti,ab,kw OR (Analysis, Cohort):ti,ab,kw (Word variations have been searched)
#35 (Cohort Analysis):ti,ab,kw OR (Analyses, Cohort):ti,ab,kw OR (Cohort Analyses):ti,ab,kw OR (Historical Cohort Studies):ti,ab,kw OR (Cohort Study, Historical):ti,ab,kw (Word variations have been searched)
#36 (Historical Cohort Study):ti,ab,kw OR (Study, Historical Cohort):ti,ab,kw OR (Cohort Studies, Historical):ti,ab,kw OR (Studies, Historical Cohort):ti,ab,kw OR (Incidence Studies):ti,ab,kw (Word variations have been searched)
#37 (Incidence Study):ti,ab,kw OR (Studies, Incidence):ti,ab,kw OR (Study, Incidence):ti,ab,kw AND (Cohort*):ti,ab,kw (Word variations have been searched)
#38 MeSH descriptor: [Cohort Studies] explode all trees
#39 #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 (Case-Control Studies):ti,ab,kw OR (Case-Control Study):ti,ab,kw OR (Studies, Case-Control):ti,ab,kw OR (Study, Case-Control):ti,ab,kw OR (Case-Comparison Studies):ti,ab,kw (Word variations have been searched)
#41 (Case Comparison Studies):ti,ab,kw OR (Case-Comparison Study):ti,ab,kw OR (Studies, Case-Comparison):ti,ab,kw OR (Study, Case-Comparison):ti,ab,kw OR (Case-Compeer Studies):ti,ab,kw (Word variations have been searched)
#42 (Studies, Case-Compeer):ti,ab,kw OR (Case-Referrent Studies):ti,ab,kw OR (Case Referrent Studies):ti,ab,kw OR (Case-Referrent Study):ti,ab,kw OR (Studies, Case-Referrent):ti,ab,kw (Word variations have been searched)
#43 (Study, Case-Referrent):ti,ab,kw OR (Case-Referent Studies):ti,ab,kw OR (Case Referent Studies):ti,ab,kw OR (Case-Referent Study):ti,ab,kw OR (Studies, Case-Referent):ti,ab,kw (Word variations have been searched)
#44 (Study, Case-Referent):ti,ab,kw OR (Case-Base Studies):ti,ab,kw OR (Case Base Studies):ti,ab,kw OR (Studies, Case-Base):ti,ab,kw OR (Case Control Studies):ti,ab,kw (Word variations have been searched)
#45 (Case Control Study):ti,ab,kw OR (Studies, Case Control):ti,ab,kw OR (Study, Case Control):ti,ab,kw OR (Nested Case-Control Studies):ti,ab,kw OR (Case-Control Studies, Nested):ti,ab,kw (Word variations have been searched)
#46 (Case-Control Study, Nested):ti,ab,kw OR (Nested Case Control Studies):ti,ab,kw OR (Nested Case-Control Study):ti,ab,kw OR (Studies, Nested Case-Control):ti,ab,kw OR (Study, Nested Case-Control):ti,ab,kw (Word variations have been searched)

#47 (Matched Case-Control Studies):ti,ab,kw OR (Case-Control Studies, Matched):ti,ab,kw OR (Case-Control Study, Matched):ti,ab,kw OR (Matched Case Control Studies):ti,ab,kw OR (Matched Case-Control Study):ti,ab,kw (Word variations have been searched)
#48 (Study, Matched Case-Control):ti,ab,kw OR (Studies, Matched Case-Control):ti,ab,kw OR (Case-Control):ti,ab,kw OR (Case Control):ti,ab,kw (Word variations have been searched)
#49 MeSH descriptor: [Case-Control Studies] explode all trees
#50 #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 104520
#51 MeSH descriptor: [Observational Study] explode all trees
#52 (Observational Study):ti,ab,kw OR (observation*):ti,ab,kw (Word variations have been searched)
#53 #51 or #52 224361
#54 #39 or #50 or #53 487408
#55 #12 and #31 and #54 **165** **(search results)**

Embase Session Results (9 Apr 2020) （search results: 273）

No.	Query	Results	Date
#196.	#48 AND #120 AND #195	273	9 Apr 2020
#195.	#121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #178 OR #179 OR #180 OR #181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194	1,012,386	9 Apr 2020
#194.	'cohort analysis'/exp	563,360	9 Apr 2020
#193.	'case control study'/exp	170,234	9 Apr 2020
#192.	'observational study'/exp	192,953	9 Apr 2020
#191.	'observational study':ab,ti	124,700	9 Apr 2020
#190.	'study, matched case-control':ab,ti	6	9 Apr 2020
#189.	'studies, matched case-control':ab,ti	2	9 Apr 2020
#188.	'matched case-control study':ab,ti	4,504	9 Apr 2020
#187.	'matched case control studies':ab,ti	242	9 Apr 2020
#186.	'case-control study, matched':ab,ti	115	9 Apr 2020
#185.	'case-control studies, matched':ab,ti	7	9 Apr 2020
#184.	'matched case-control studies':ab,ti	242	9 Apr 2020
#183.	'study, nested case-control':ab,ti	13	9 Apr 2020
#182.	'studies, nested case-control':ab,ti	15	9 Apr 2020
#181.	'nested case-control study':ab,ti	8,227	9 Apr 2020
#180.	'nested case control studies':ab,ti	668	9 Apr 2020
#179.	'case-control study, nested':ab,ti	1,239	9 Apr 2020
#178.	'case-control studies, nested':ab,ti	80	9 Apr 2020
#177.	'nested case-control studies':ab,ti	668	9 Apr 2020
#176.	'study, case control':ab,ti	212	9 Apr 2020
#175.	'studies, case control':ab,ti	513	9 Apr 2020
#174.	'case control study':ab,ti	107,936	9 Apr 2020
#173.	'case control studies':ab,ti	19,908	9 Apr 2020
#172.	'studies, case-base':ab,ti	1	9 Apr 2020
#171.	'case base studies':ab,ti	8	9 Apr 2020
#170.	'case-base studies':ab,ti	8	9 Apr 2020
#169.	'study, case-referent':ab,ti	1	9 Apr 2020

#168.'studies, case-referent':ab,ti	1	9 Apr 2020
#167.'case-referent study':ab,ti	523	9 Apr 2020
#166.'case referent studies':ab,ti	84	9 Apr 2020
#165.'case-referent studies':ab,ti	84	9 Apr 2020
#164.'study, case-referrent':ab,ti		9 Apr 2020
#163.'studies, case-referrent':ab,ti		9 Apr 2020
#162.'case-referrent study':ab,ti	1	9 Apr 2020
#161.'case referrent studies':ab,ti		9 Apr 2020
#160.'case-referrent studies':ab,ti		9 Apr 2020
#159.'studies, case-compeer':ab,ti	1	9 Apr 2020
#158.'case-compeer studies':ab,ti	1	9 Apr 2020
#157.'study, case-comparison':ab,ti		9 Apr 2020
#156.'studies, case-comparison':ab,ti		9 Apr 2020
#155.'case-comparison study':ab,ti	215	9 Apr 2020
#154.'case comparison studies':ab,ti	9	9 Apr 2020
#153.'case-comparison studies':ab,ti	9	9 Apr 2020
#152.'study, case-control':ab,ti	212	9 Apr 2020
#151.'studies, case-control':ab,ti	513	9 Apr 2020
#150.'case-control study':ab,ti	107,936	9 Apr 2020
#149.'case-control studies':ab,ti	19,908	9 Apr 2020
#148.'study, incidence':ab,ti	662	9 Apr 2020
#147.'studies, incidence':ab,ti	140	9 Apr 2020
#146.'incidence study':ab,ti	1,373	9 Apr 2020
#145.'incidence studies':ab,ti	750	9 Apr 2020
#144.'studies, historical cohort':ab,ti	2	9 Apr 2020
#143.'cohort studies, historical':ab,ti		9 Apr 2020
#142.'study, historical cohort':ab,ti	20	9 Apr 2020
#141.'historical cohort study':ab,ti	2,683	9 Apr 2020
#140.'cohort study, historical':ab,ti	5	9 Apr 2020
#139.'historical cohort studies':ab,ti	70	9 Apr 2020
#138.'cohort analyses':ab,ti	809	9 Apr 2020
#137.'analyses, cohort':ab,ti	30	9 Apr 2020
#136.'cohort analysis':ab,ti	11,330	9 Apr 2020
#135.'analysis, cohort':ab,ti	473	9 Apr 2020
#134.'studies, closed cohort':ab,ti		9 Apr 2020
#133.'study, closed cohort':ab,ti	1	9 Apr 2020
#132.'cohort study, closed':ab,ti		9 Apr 2020
#131.'closed cohort study':ab,ti	41	9 Apr 2020
#130.'cohort studies, closed':ab,ti		9 Apr 2020
#129.'closed cohort studies':ab,ti	2	9 Apr 2020
#128.'study, concurrent':ab,ti	148	9 Apr 2020
#127.'concurrent study':ab,ti	239	9 Apr 2020
#126.'studies, concurrent':ab,ti	46	9 Apr 2020
#125.'concurrent studies':ab,ti	198	9 Apr 2020

#124.'study, cohort':ab,ti	21,934	9 Apr 2020
#123.'studies, cohort':ab,ti	490	9 Apr 2020
#122.'cohort study':ab,ti	260,094	9 Apr 2020
#121.'cohort studies':ab,ti	31,752	9 Apr 2020
#120.#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119	1,047,969	9 Apr 2020
#119.'pregnancy diabetes mellitus'/exp	36,590	9 Apr 2020
#118.'non insulin dependent diabetes mellitus'/exp	253,232	9 Apr 2020
#117.'insulin dependent diabetes mellitus'/exp	117,492	9 Apr 2020
#116.'diabetes mellitus'/exp	1,001,964	9 Apr 2020
#115.'gestational diabetes mellitus':ab,ti	11,376	9 Apr 2020
#114.'diabetes mellitus, gestational':ab,ti	91	9 Apr 2020
#113.'gestational diabetes':ab,ti	22,863	9 Apr 2020
#112.'pregnancy-induced diabetes':ab,ti	14	9 Apr 2020
#111.'diabetes, pregnancy induced':ab,ti	57	9 Apr 2020
#110.'diabetes, pregnancy-induced':ab,ti	57	9 Apr 2020
#109.'diabetes, gestational':ab,ti	313	9 Apr 2020
#108.'ketosis-prone diabetes mellitus':ab,ti	16	9 Apr 2020
#107.'diabetes mellitus, ketosis prone':ab,ti		9 Apr 2020
#106.'diabetes mellitus, ketosis-prone':ab,ti		9 Apr 2020
#105.'brittle diabetes mellitus':ab,ti	26	9 Apr 2020
#104.'diabetes mellitus, brittle':ab,ti	3	9 Apr 2020
#103.'autoimmune diabetes':ab,ti	4,106	9 Apr 2020
#102.'diabetes, autoimmune':ab,ti	213	9 Apr 2020
#101.'diabetes, type 1':ab,ti	1,452	9 Apr 2020
#100.'type 1 diabetes':ab,ti	60,696	9 Apr 2020
#99. 'insulin dependent diabetes mellitus 1':ab,ti	31	9 Apr 2020
#98. 'insulin-dependent diabetes mellitus 1':ab,ti	31	9 Apr 2020
#97. 'diabetes mellitus, insulin-dependent, 1':ab,ti		9 Apr 2020
#96. 'type 1 diabetes mellitus':ab,ti	14,962	9 Apr 2020
#95. 'sudden-onset diabetes mellitus':ab,ti	1	9 Apr 2020
#94. 'diabetes mellitus, sudden onset':ab,ti	1	9 Apr 2020
#93. 'diabetes mellitus, sudden-onset':ab,ti	1	9 Apr 2020
#92. 'juvenile onset diabetes':ab,ti	494	9 Apr 2020

#91. 'diabetes, juvenile-onset':ab,ti	4	9 Apr 2020
#90. 'juvenile-onset diabetes':ab,ti	494	9 Apr 2020
#89. 'iddm':ab,ti	7,833	9 Apr 2020
#88. 'juvenile-onset diabetes mellitus':ab,ti	232	9 Apr 2020
#87. 'diabetes mellitus, juvenile onset':ab,ti	3	9 Apr 2020
#86. 'diabetes mellitus, juvenile-onset':ab,ti	3	9 Apr 2020
#85. 'insulin-dependent diabetes mellitus':ab,ti	17,759	9 Apr 2020
#84. 'diabetes mellitus, insulin dependent':ab,ti	47	9 Apr 2020
#83. 'diabetes mellitus, insulin-dependent':ab,ti	47	9 Apr 2020
#82. 'diabetes mellitus, type 1':ab,ti	1,786	9 Apr 2020
#81. 'diabetes mellitus, adult onset':ab,ti	3	9 Apr 2020
#80. 'adult-onset diabetes mellitus':ab,ti	193	9 Apr 2020
#79. 'diabetes mellitus, adult-onset':ab,ti	3	9 Apr 2020
#78. 'diabetes, type 2':ab,ti	2,279	9 Apr 2020
#77. 'type 2 diabetes':ab,ti	185,187	9 Apr 2020
#76. 'maturity onset diabetes':ab,ti	2,618	9 Apr 2020
#75. 'diabetes, maturity-onset':ab,ti	43	9 Apr 2020
#74. 'maturity-onset diabetes':ab,ti	2,618	9 Apr 2020
#73. 'noninsulin dependent diabetes mellitus':ab,ti	1,037	9 Apr 2020
#72. 'noninsulin-dependent diabetes mellitus':ab,ti	1,037	9 Apr 2020
#71. 'type 2 diabetes mellitus':ab,ti	61,709	9 Apr 2020
#70. 'slow-onset diabetes mellitus':ab,ti		9 Apr 2020
#69. 'diabetes mellitus, slow onset':ab,ti	1	9 Apr 2020
#68. 'diabetes mellitus, slow-onset':ab,ti	1	9 Apr 2020
#67. 'mody':ab,ti	2,136	9 Apr 2020
#66. 'maturity onset diabetes mellitus':ab,ti	183	9 Apr 2020
#65. 'maturity-onset diabetes mellitus':ab,ti	183	9 Apr 2020
#64. 'diabetes mellitus, maturity onset':ab,ti	14	9 Apr 2020
#63. 'diabetes mellitus, maturity-onset':ab,ti	14	9 Apr 2020
#62. 'diabetes mellitus, noninsulin dependent':ab,ti	4	9 Apr 2020
#61. 'niddm':ab,ti	7,991	9 Apr 2020
#60. 'diabetes mellitus, type ii':ab,ti	1,081	9 Apr 2020
#59. 'stable diabetes mellitus':ab,ti	28	9 Apr 2020
#58. 'diabetes mellitus, stable':ab,ti	16	9 Apr 2020
#57. 'non-insulin-dependent diabetes mellitus':ab,ti	7,743	9 Apr 2020
#56. 'diabetes mellitus, non-insulin-dependent':ab,ti	40	9 Apr 2020
#55. 'diabetes mellitus, non insulin dependent':ab,ti	40	9 Apr 2020
#54. 'ketosis-resistant diabetes mellitus':ab,ti	2	9 Apr 2020
#53. 'diabetes mellitus, ketosis resistant':ab,ti		9 Apr 2020
#52. 'diabetes mellitus, ketosis-resistant':ab,ti		9 Apr 2020
#51. 'diabetes mellitus, noninsulin-dependent':ab,ti	4	9 Apr 2020
#50. 'diabetes mellitus, type 2':ab,ti	4,600	9 Apr 2020
#49. 'diabetes mellitus':ab,ti	278,869	9 Apr 2020
#48. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR	161,803	9 Apr 2020

#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47		
#47. 'ovary cancer'/exp	120,100	9 Apr 2020
#46. 'ovary tumor'/exp	150,462	9 Apr 2020
#45. 'ovary tumor':ab,ti	129	9 Apr 2020
#44. 'ovarian tumor':ab,ti	7,638	9 Apr 2020
#43. 'ovarian carcinoma':ab,ti	17,377	9 Apr 2020
#42. 'ovarian carcinomas, epithelial':ab,ti	1	9 Apr 2020
#41. 'ovarian carcinoma, epithelial':ab,ti	6	9 Apr 2020
#40. 'epithelial ovarian carcinomas':ab,ti	459	9 Apr 2020
#39. 'carcinomas, epithelial ovarian':ab,ti	2	9 Apr 2020
#38. 'carcinoma, epithelial ovarian':ab,ti	6	9 Apr 2020
#37. 'epithelial ovarian carcinoma':ab,ti	2,143	9 Apr 2020
#36. 'ovarian epithelial carcinoma':ab,ti	290	9 Apr 2020
#35. 'ovarian cancers, epithelial':ab,ti	1	9 Apr 2020
#34. 'epithelial ovarian cancers':ab,ti	1,189	9 Apr 2020
#33. 'cancers, epithelial ovarian':ab,ti	7	9 Apr 2020
#32. 'cancer, epithelial ovarian':ab,ti	21	9 Apr 2020
#31. 'ovarian cancer, epithelial':ab,ti	43	9 Apr 2020
#30. 'ovarian epithelial cancers':ab,ti	100	9 Apr 2020
#29. 'epithelial cancers, ovarian':ab,ti	1	9 Apr 2020
#28. 'epithelial cancer, ovarian':ab,ti	4	9 Apr 2020
#27. 'cancers, ovarian epithelial':ab,ti		9 Apr 2020
#26. 'cancer, ovarian epithelial':ab,ti	3	9 Apr 2020
#25. 'ovarian epithelial cancer':ab,ti	414	9 Apr 2020
#24. 'epithelial ovarian cancer':ab,ti	13,087	9 Apr 2020
#23. 'ovarian epithelial carcinomas':ab,ti	84	9 Apr 2020
#22. 'epithelial carcinomas, ovarian':ab,ti		9 Apr 2020
#21. 'epithelial carcinoma, ovarian':ab,ti	1	9 Apr 2020
#20. 'carcinomas, ovarian epithelial':ab,ti	1	9 Apr 2020
#19. 'carcinoma, ovarian epithelial':ab,ti	2	9 Apr 2020
#18. 'cancer of the ovary':ab,ti	735	9 Apr 2020
#17. 'cancer of ovary':ab,ti	32	9 Apr 2020
#16. 'ovarian cancers':ab,ti	8,913	9 Apr 2020
#15. 'cancers, ovarian':ab,ti	139	9 Apr 2020
#14. 'cancer, ovarian':ab,ti	1,121	9 Apr 2020
#13. 'ovarian cancer':ab,ti	76,611	9 Apr 2020
#12. 'ovary cancers':ab,ti	89	9 Apr 2020
#11. 'cancers, ovary':ab,ti	12	9 Apr 2020
#10. 'cancer, ovary':ab,ti	65	9 Apr 2020

#9.	'ovary cancer':ab,ti	595	9 Apr 2020
#8.	'neoplasms, ovarian':ab,ti	23	9 Apr 2020
#7.	'ovary neoplasm':ab,ti	7	9 Apr 2020
#6.	'neoplasms, ovary':ab,ti	5	9 Apr 2020
#5.	'neoplasm, ovary':ab,ti	2	9 Apr 2020
#4.	'ovarian neoplasm':ab,ti	760	9 Apr 2020
#3.	'ovary neoplasms':ab,ti	14	9 Apr 2020
#2.	'neoplasm, ovarian':ab,ti	13	9 Apr 2020
#1.	'ovarian neoplasms':ab,ti	1,859	9 Apr 2020

Additional file 3 Quality assessment of included studies based on the Newcastle-Ottawa Scale score

Cohort studies

Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis∞	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total stars
Weiderpass 2002	★	★	★	★	★	★	★	★	8
Zendehdel 2003	★	★	★	★	★	★	★	…	7
Swerdlow 2005	★	★	★	…	★	★	★	★	7
Inoue 2006	★	★	★	★	★	★	★	★	8
Khan 2006	★	★	★	★	★	★	…	★	7
Hemminki 2010	★	★	★	★	★	★	★	…	7
Chodick 2010	★	★	★	★	★	★	…	★	7
Shu 2010	★	★	★	★	★	★	★	★	8
Wotton 2011	…	★	★	★	★	★	★	★	7
Johnson 2011	★	★	★	★	★	★	…	★	7
Lambe 2011	★	★	★	★	★	★	★	★	8
Gapstur 2012	★	★	★	★	★	★	…	★	7
Lo 2013	★	★	★	★	★	★	…	★	7
Chen 2014	★	★	★	★	★★	★	★	★	9
Hsu 2015	★	★	★	★	★	★	…	★	7

Harding 2015	★	★	★	★	…	★	★	★	7
Dankner 2016	★	★	★	★	★	★	★	★	8
Carstensen 2016	★	★	★	★	★	★	★	…	7
Fuchs 2017	★	★	★	★	…	★	★	★	7
Ballotari 2017	★	★	★	…	★	★	★	…	6
He 2018	★	★	★	★	★	★	…	★	7
Han 2018	★	★	★	★	★	★	★	★	8
Bao 2018	…	★	★	★	★	★	…	★	6
Saarela 2019	★	★	★	★	…	★	★	…	6
Linkeviciute-Ulinskiene 2019	★	★	★	★	…	★	★	★	7
Peng 2019	★	★	★	★	★	★	…	★	7
Pace 2020	★	★	★	★	★	★	★	…	7

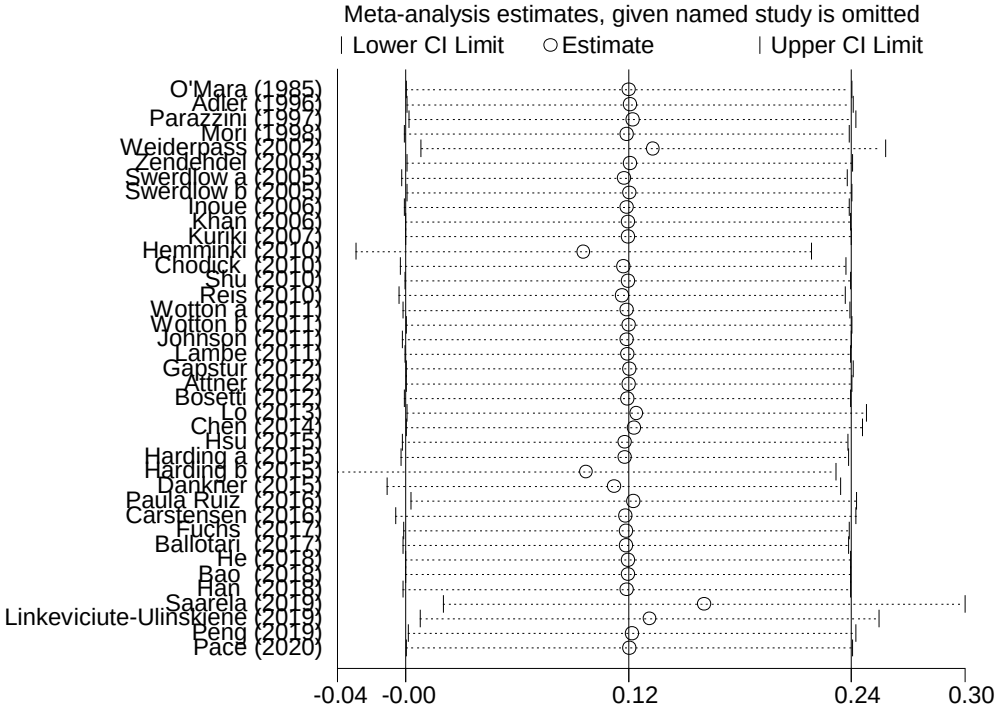
Case-control studies

Study ID	Is the case definition adequate	Representativeness of the cases	Selection of the controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total stars
O'Mara 1985	★	★	…	★	★	…	★	…	5
Adler 1996	★	★	★	…	…	★	★	…	5
Parazzini 1997	★	★	…	★	★	…	★	…	5
Mori 1998	★	★	★	★	★	…	★	★	7
Kuriki 2007	★	★	★	…	…	★	★	★	6
Reis 2010	★	★	…	★	…	★	★	★	6
Attner 2012	★	★	★	★	★	★	★	…	7
Bosetti 2012	★	★	…	★	★	…	★	…	5
Ruiz 2016	★	★	…	★	★	…	★	…	5

One star is awarded if matched on, or adjusted for maternal age; another star is awarded if other confounders are taken into account.

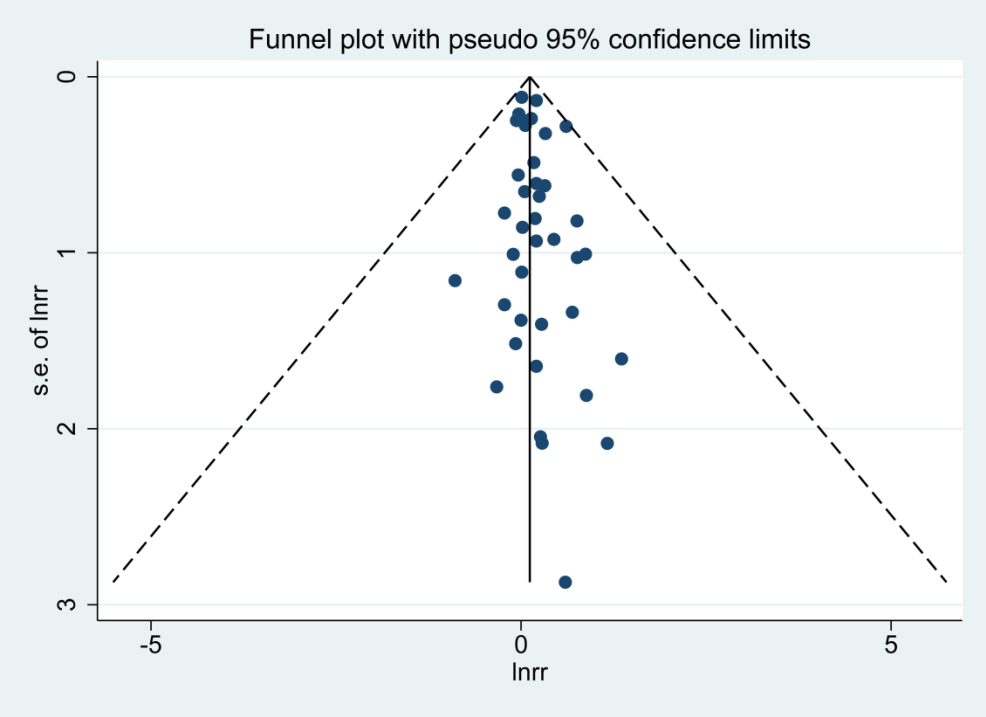
Additional file 4 Sensitivity analysis and assessment of reporting biases & Forest plots for the subgroup analyses of DM and subsequent risk of OC

Sensitivity analysis



Assessment of reporting biases

Funnel plot



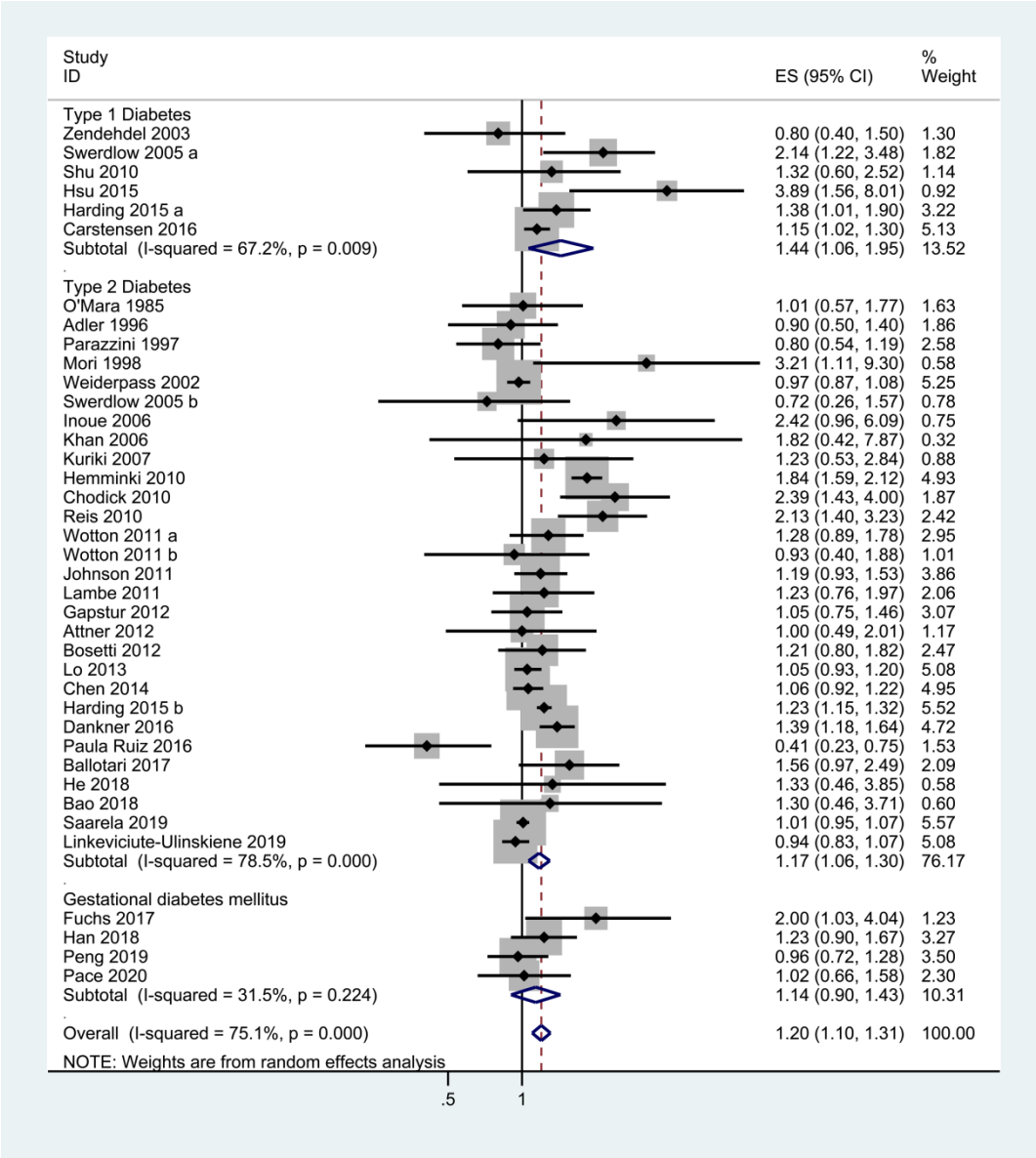
Begg's Test

Begg's Test

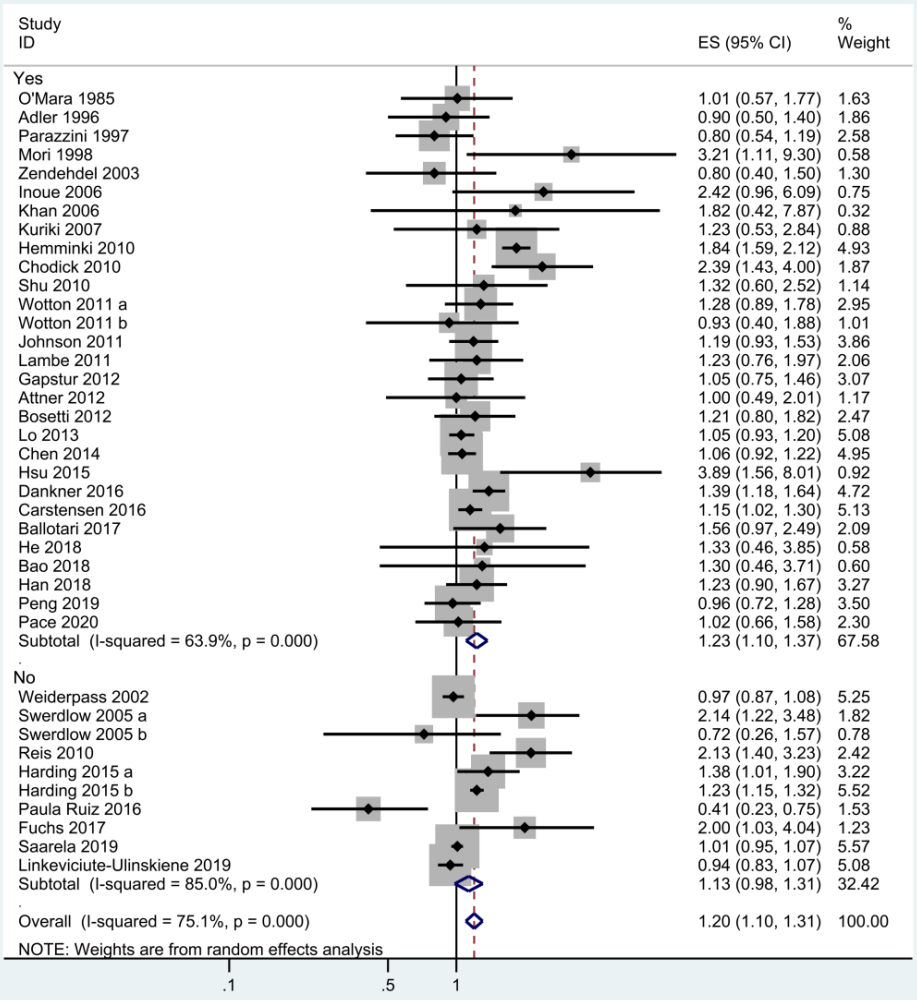
adj. Kendall's Score (P-Q) = 97
Std. Dev. of Score = 82.67
Number of Studies = 39
z = 1.17
Pr > |z| = 0.241
z = 1.16 (continuity corrected)
Pr > |z| = 0.246 (continuity corrected)

Egger's test

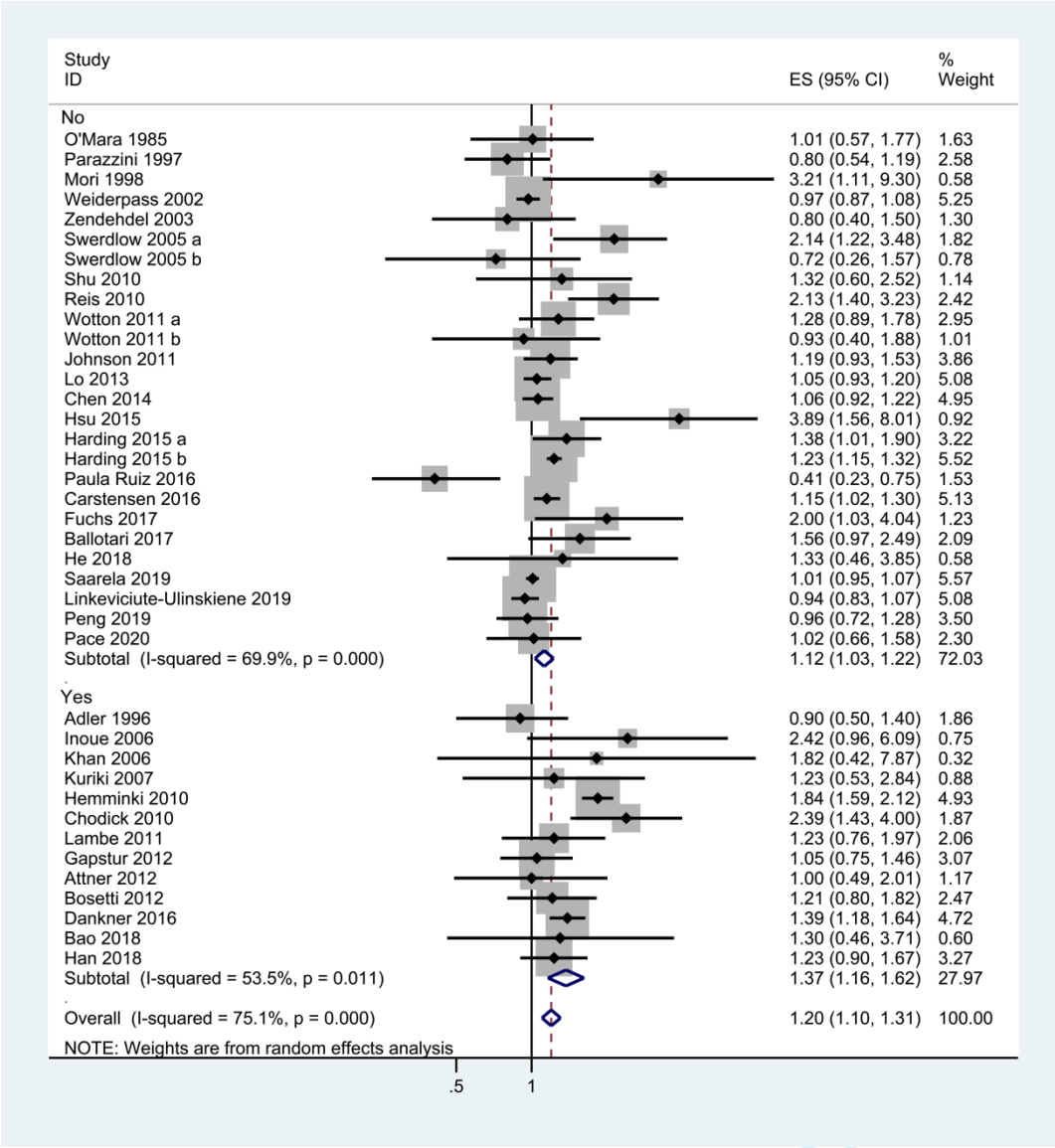
Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0705791	.0441485	1.60	0.118	-.0188741	.1600324
bias	.6885655	.4468107	1.54	0.132	-.2167589	1.59389



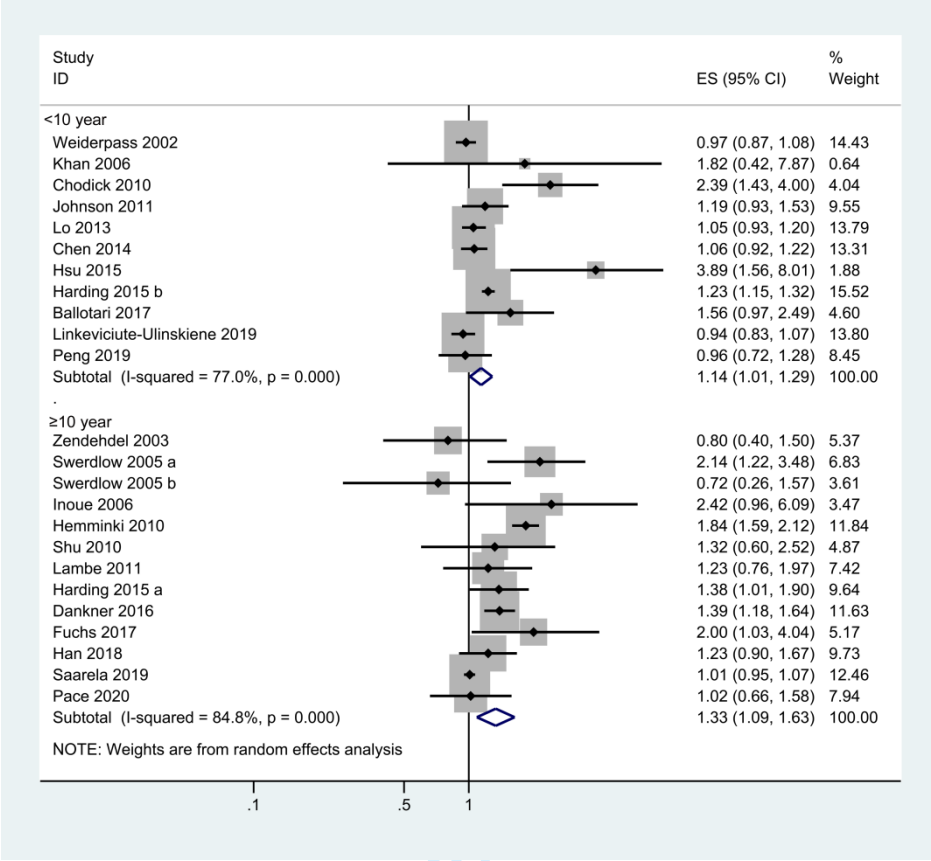
a. Subgroup analysis based on the DM types (type 1 DM vs. type 2 DM vs. GDM). RR relative risk, CI confidence interval, DM diabetes mellitus, GDM gestational DM.



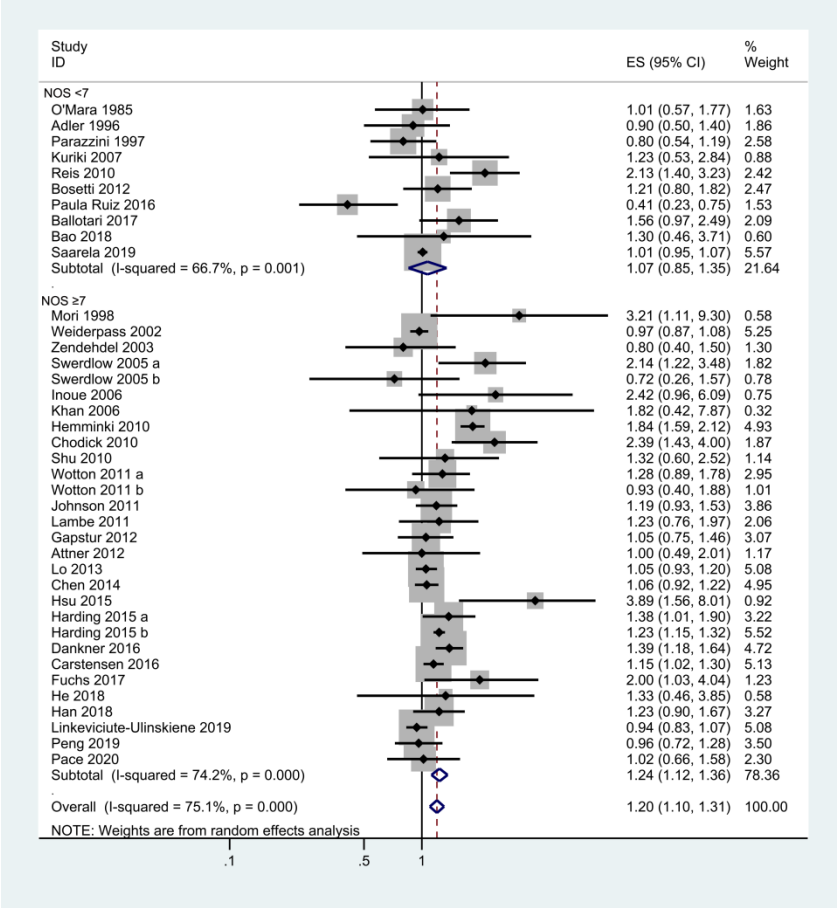
b. Subgroup analysis based on the level of adjustment (unadjusted vs. adjusted). RR relative risk, CI confidence interval.



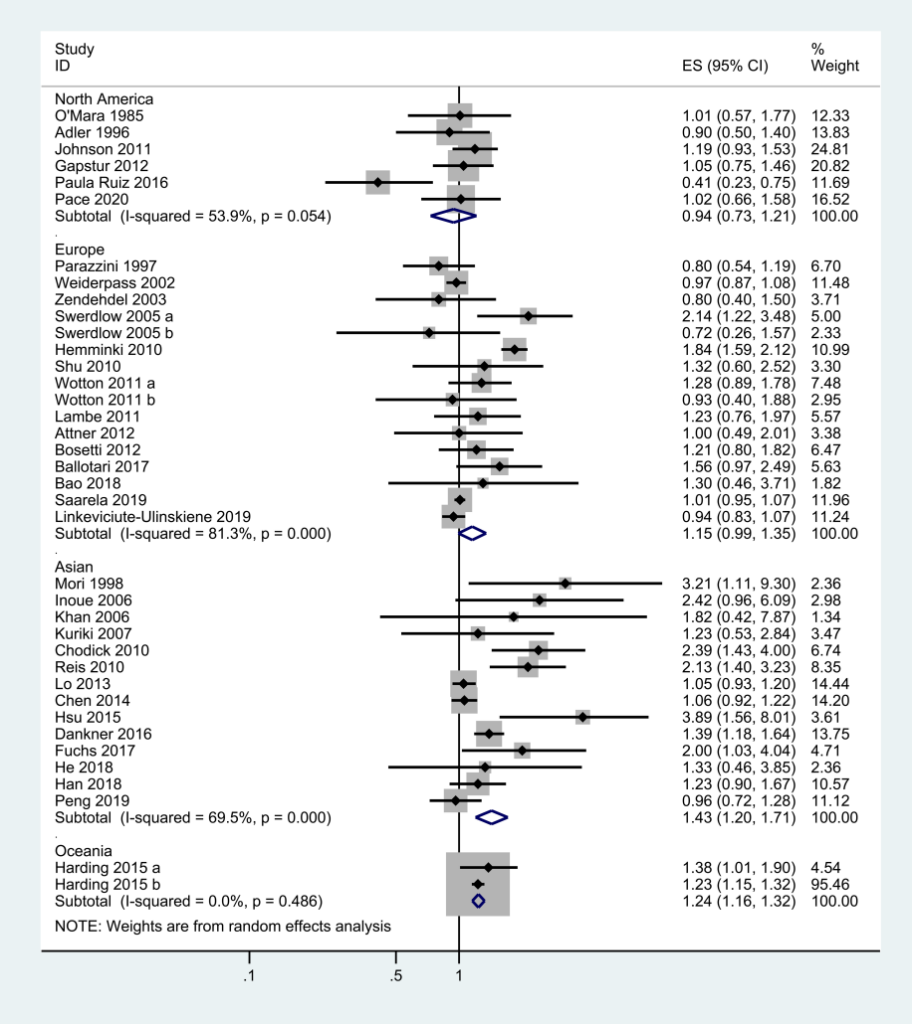
c. Subgroup analysis based on whether the study adjusted for BMI (yes vs. no). RR relative risk, CI confidence interval, BMI body mass index.



d. Subgroup analysis based on the duration of follow-up (<10 year vs. ⩾10 year). RR relative risk, CI confidence interval.



e. Subgroup analysis based on the study quality (NOS <7 vs. ⩾7 points). RR relative risk, CI confidence interval, NOS the Newcastle-Ottawa Scale score.



f. Subgroup analysis based on the geographic areas (North America vs. Europe vs. Asian vs. Oceania). RR relative risk, CI confidence interval.