Long-term follow-up on morbidity among women with a history of gestational diabetes mellitus: a systematic review

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ABSTRACT

Background. Gestational diabetes mellitus (GDM) complicates up to 10% of pregnancies and is a well-known risk factor of type 2 diabetes mellitus (T2DM) and cardiovascular disease. Little is known about possible long-term risks of other diseases. The aim was to review the literature for evidence of associations with morbidity other than T2DM and cardiovascular disease and with long-term mortality.

Methods. A systematic review based on searches in Medline, Embase and Cochrane Library until 31st March 2021, using a broad range of keywords. We extracted study characteristics and results on associations between GDM and disease occurrence at least 10 years postpartum, excluding studies on women with diabetes prior to pregnancy or only diabetes prior to outcome. The results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Newcastle-Ottawa Scale was used to assess risk of bias.

Results. We screened 3,084 titles, 81 articles were assessed full-text, and 15 included in the review. The strongest evidence for an association was for kidney diseases, particularly in black women. We found indication of an association with liver disease, possibly restricted to women with T2DM postpartum. The association between GDM and breast cancer had been studied extensively, but in most cases based on self-reported diagnosis and with conflicting results. Only sparse and inconsistent results were found for other cancers. No study on thyroid diseases was found, and no study reported on short-term or long-term mortality in women with a history of GDM.

Conclusion. Given the frequency of GDM, there is a need for better evidence on possible long-term health consequences, in particular, studies based on comprehensive records of diagnosis of GDM and long-term health outcomes.

Keywords: gestational diabetes, morbidity, cancer, long-term risk, cardiovascular disease
INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as abnormal glucose intolerance diagnosed during pregnancy, and is a condition that complicates approximately 5% of pregnancies in Denmark (1), in line with the 2-9% of pregnancies reported in other parts of Europe, and in Australia and North America (2). Several recent studies suggest that the prevalence of GDM is increasing world-wide, making GDM the most common medical complication of pregnancy (3–5). In most women, the glucose tolerance returns to normal within a few days after giving birth. Women with a history of GDM are at significantly increased risk of developing diabetes mellitus (DM) later in life, particularly type 2 DM (T2DM) (6). It is well-known that T2DM is associated with increased risk of morbidity and mortality, e.g. from cardiovascular events such as myocardial infarction, heart and renal failure (7–9). It is therefore not surprising that women with a history of GDM are also at significantly increased risk of cardiovascular diseases and heart failure (10,11) following increased occurrence of hypertension and hyperlipidemia already in fertile age (12).

However, little is known about the risk of other types of morbidity, such as cancer in women with a history of GDM. Studies based on a median follow-up of 8 years of women with GDM have shown an increased risk of thyroid cancer but a reduced risk of premenopausal breast cancer as compared with women without GDM (13). In a 1-9 year follow-up, development of non-alcoholic fatty liver disease (NAFLD) was also significantly associated with a history of GDM (14). Most studies do not have a follow-up longer than 10 years, and therefore the possible long-term consequences of GDM apart from T2DM and cardiovascular disease are poorly described (15,16).

Therefore, the aim of the present systematic review was to investigate whether women with a history of GDM as compared with other women have 1) an increased long-term risk of chronic diseases independently of and apart from T2DM and cardiovascular diseases; and 2) an increased long-term risk of premature mortality. The review was restricted to studies with a mean follow-up period of at least 10 years after a pregnancy complicated by GDM.

METHODS

Search strategy

We conducted a systematic search in the databases Medline (from 1950), Embase (from 1949) and the Cochrane Library (from 1993). Search strategies were developed and conducted in collaboration with a professional librarian, using a combination of medical subject headings (MeSH-) terms and free text search terms in titles, keywords, key headings and abstract fields. We suspected that our findings would be limited, and therefore we conducted a broad search strategy. For GDM the
MeSH-terms used were ‘Diabetes’ and ‘Gestational’, and other terms were (gestation*adj2 diabet*).ab,kf,ti., gdm.ab,kf,ti., (pregnan*adj2 induce*adj2 diabet*).ab,kf,ti. For the full list of search terms used for outcomes, see Supplementary table 1 (17). In addition to searches, the reference lists of relevant studies were checked manually for missing studies, which we imported for screening. Searches were conducted until 31st March 2021.

Inclusion and Exclusion Criteria

We included peer-reviewed original articles of cohort studies, case-control studies and clinical trials, in which women diagnosed with and/or had self-reported GDM in a previous pregnancy, were investigated for subsequent long-term morbidity or mortality. We chose to include outcomes related to organs other than the heart, well known to be affected by GDM; hence included outcomes were liver disease (non-alcoholic fatty liver disease, fibrosis and cirrhosis of the liver, liver failure, and liver transplant), renal disease (chronic renal failure and renal insufficiency), cancer (breast, endometrial, ovarian, cervix uteri, kidney, bladder, thyroid, and urological cancer), thyroid disease (hypothyroidism, hyperthyroidism and thyrotoxicosis), and deaths from these causes. We excluded studies on women with diabetes (without any differentiation of type) prior to pregnancy or only diabetes prior to outcomes, studies investigating only outcomes in offspring, as well as studies with short-term follow-up (a reported mean or median of less than 10 years postpartum). Review articles, book chapters, protocols of ongoing studies, conference abstracts and letters were also excluded. Only articles written in English, Danish, Swedish or Norwegian were included, which are the languages the reviewers comprehend. No limitation regarding publication year was used.

Study Selection

Title and abstract screening and subsequently full-text screening were performed manually by two independent reviewers (LRFM and SG-K) with disagreements resolved by consensus. Findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (Figure 1).

Data Extraction

Characteristics of each study were retrieved manually and organized in Table 1. Results were retrieved manually and organized in Table 2. For each study, two reviewers (LRFM and EL), independently reported the number of studied women with a history of GDM and number of women without. For each group we reported the number of women with the studied outcome in the follow-up period. We reported the association between GDM and the outcome studied, using the association measure reported in the original study; odds ratio (OR), rate ratio (RR), or hazard
ratio (HR), together with the reported 95% confidence interval (CI). Where available in the original papers, we included both crude results, adjusted results, and results stratified by ethnicity and/or a DM diagnosis subsequent to the GDM diagnosis.

As disease outcomes were defined differently across the studies and/or reported for different subgroups, it was not meaningful to attempt summarizing the results statistically in meta-analyses, including tests of heterogeneity, and hence it was not possible to meaningfully perform any subanalyses.

Assessment of Risk of Bias

Two reviewers (LRFM and JL) assessed the risk of bias in each included study independently. Discrepancies were resolved through discussion and consensus. The Newcastle-Ottawa Scale (NOS) was used systematically for the assessment of risk of bias, for cohort studies as well as for case-control studies as recommended by the Cochrane Non-Randomized Studies Methods Working Group. The NOS assessment scores the selection, comparability, and ascertainment of exposure and outcome, and summarizes the quality with a total score between 0 and 9 (18). The outcome of this assessment is reported in Supplementary table 2 (17).

RESULTS

We imported a total of 3,084 studies for screening from databases and reference lists (PRISMA flow diagram Figure 1). After exclusion of 1,344 duplicates, 1,740 studies remained for manual screening by title and abstract, of which 1,659 were found irrelevant and 81 studies were assessed for full-text eligibility. Sixty-six studies were excluded for the reasons listed in Figure 1. A final selection of 15 original articles matching our criteria was included in the review. Descriptive data of the studies are summarized in Table 1.

Kidney disease

Four studies on the long-term association between GDM history and kidney diseases were identified, all cohort studies (19–22).

Bomback et al. 2010 (19) examined whether GDM, in the absence of subsequent overt DM, increased the risk of abnormal urinary albumin excretion and impaired glomerular filtration rate among the participants of the National Kidney Foundation’s Kidney Early Evaluation Program (KEEP). This was a screening study of US adults at high risk of chronic kidney disease (CKD). Among women without DM, 571 had a self-reported history of GDM while 25,045 did not. They found an increased risk of microalbuminuria (OR 1.36 (95% CI: 1.03–1.80)) and CKD stages 1-2 (OR 1.54 (95% CI: 1.16–2.05)), while no association was found between a history of GDM and macroalbuminuria (OR 1.13 (95% CI: 0.41–3.09)) or CKD stages 3-5 (OR 0.94 (95% CI: 0.71–1.25)). Stratification by race showed a significantly increased risk of CKD...
stages 1-2 among African American women (OR 2.32 (95% CI: 1.50–3.60)), but not in white women; (OR 1.12 (95% CI: 0.68–1.84)).

Beharier et al. 2015 (20) conducted a population-based cohort study in Israel including 9,542 women with a history of GDM and 88,426 women without. Mean follow-up was 11 years, and 23 GDM women developed renal morbidity compared with 91 women without GDM. In unadjusted analyses, GDM was found to be a significant risk factor for renal morbidity (OR 2.34 (95% CI: 1.4-3.7)) based on a significantly increased risk of hypertensive renal disease, while renal failure, chronic renal failure and end-stage renal disease were not individually associated with increased risk. In analyses adjusted for maternal age and parity GDM was associated with increased risk of hospitalization for renal disease: HR 1.7 (95% CI: 1.05-2.6).

Dehmer et al. 2018 (21) studied the association between self-reported history of GDM and CKD in the CARDIA cohort. They extracted data from 820 women, who were nulliparous at enrollment, delivered at least once during the follow-up period and had kidney function measured during the 25 years of follow-up. There were 17 cases of CKD in women with GDM, and 88 in women without GDM, with an overall adjusted HR of 1.33 (95% CI: 0.78-2.26), and HR 1.96 (95% CI: 1.04-2.67) in the sub-group of black women.

Rawal et al. 2018 (22) performed a 9-16 year follow-up of women with a history of GDM within the Danish National Birth Cohort. They investigated the risk of glomerular hyperfiltration (defined as eGFR (116.4 mL/min/1.73 m²), elevated urine albumin-creatinine ratio (UACR) (defined as ≥20 mg/g) and micro- or macroalbuminuria (defined as UACR >30 mg/g). The adjusted risks were not increased; RR 1.1 (95% CI: 0.6-2.1) for glomerular hyperfiltration and RR 1.4 (95% CI: 0.6-2.9) for UACR. However, both risks were significantly increased among women with a history of GDM and subsequent DM; RR 3.2 (95% CI: 1.4-7.0) and RR 2.3 (95% CI: 1.1-5.9), respectively.

In summary, in studies of black women from the United States, a history of GDM was associated with an increased risk of later kidney disease, and an increased risk was also reported from an Israeli hospital database. Glomerular hyperfiltration and UACR were increased in Danish women, but only in those with DM subsequent to the GDM diagnosis.

Breast cancer

Eight studies were detected, investigating long-term risk of breast cancer after a pregnancy complicated with GDM (23–30), three case-control and five cohort studies.

A US population-based case-control study by Troisi et al. 1998 (23) evaluated the
risk of breast cancer following various pregnancy outcomes including self-reported history of GDM. They identified women between 20 and 44 years diagnosed with in situ or invasive breast cancer as well as matched controls and obtained in-person interviews regarding details on their pregnancies. Sixty-seven breast cancer cases reported a history of GDM. No association was found between GDM and breast cancer: unadjusted RR 0.99 (95% CI: 0.70-1.4), adjusted RR 1.1 (95% CI: 0.73-1.5).

An Israeli cohort study based on hospital records conducted by Perrin et al. 2008 (24), included 410 women with a history of GDM and 37,516 women without. Presence of GDM was determined from notes on “pre-diabetes” in the labor ward logs. At follow-up in the Israeli Cancer Register over a median of 34 years, 29 cases of breast cancer were identified in the GDM cohort, and 1,597 cases in the other women, adjusted RR 1.5 (95% CI: 1.0-2.1). Stratified by age at diagnosis, the adjusted RR was 1.0 (95% CI: 0.5-2.1) for women diagnosed below age 50, and 1.7 (95% CI: 1.1-2.5) for those diagnosed at or above age 50.

Rollison et al. 2008 (25) conducted a population-based case-control study in non-Hispanic white/Hispanic/Native American women in the US diagnosed with invasive breast cancer. Among 2,324 breast cancer patients, 75 reported a history of GDM, and among 2,523 controls, the number was 106, giving a statistically significantly decreased adjusted OR of 0.71 (95% CI: 0.52-0.98). The OR for women with onset of GDM before the age of 35 was 0.56 (95% CI: 0.38-0.82), and for those with onset at age 35 or older 1.34 (95% CI: 0.72-2.52).

In another population-based case-control study from the US, Brasky et al. 2013 (26) investigated women aged 35-79 years with a primary, histologically confirmed breast cancer and matched controls. Of the 960 breast cancer cases, 28 reported a history of GDM, and of the 1,852 controls 66 did. There was no association between a history of GDM and breast cancer: OR 0.79 (95% CI: 0.48-1.30), neither in premenopausal women (OR 0.60 (95% CI: 0.29-1.27)), nor in postmenopausal women (OR 1.03 (95% CI: 0.52-2.05)).

In the Nurses’ Health Study II, Powe et al. 2017 (27) studied 5,188 parous women with a self-reported history of GDM and 81,784 without any diabetes followed over 22 years. The self-reported GDM data had previously been validated against medical records in a subgroup of study participants with 94% of cases being confirmed (31). One hundred women with GDM and 2,277 women without developed breast cancer. There was a significantly decreased risk of invasive breast cancer in GDM women as compared with other women; HR 0.68 (95% CI: 0.55-0.84). In those who subsequently developed T2DM the HR was 0.72 (95% CI: 0.58-0.89), and in those without the HR was 0.26 (95% CI: 0.10-0.68).

Fuchs et al. 2017 (28) undertook a hospital-based cohort study in Israel comparing the incidence of long-term female malignancies (breast, ovary, uterine and cervix
cancer) in women with and without a recorded diagnosis of GDM. The cohort was followed for 26 years. In 9,893 women with GDM, 91 developed breast cancer, and in the 94,822 women without GDM, 436 developed breast cancer. There was a statistically significantly increased risk of breast cancer after a pregnancy complicated by GDM: OR 2.0 (95% CI: 1.60-2.51).

Pace et al. 2020 (29) undertook a Canadian cohort study of 34,294 women with a singleton birth and at least two diagnostic codes for GDM and a matched reference cohort of women without GDM. Cancer diagnoses (breast, reproductive organs, urological, thyroid etc.) were retrieved from discharge records after a mean follow-up of 13.1 years. Among women with a history of GDM, 346 developed breast cancer, and in those without GDM, 392 developed breast cancer. No association between a history of GDM and breast cancer was found: HR 0.93 (95% CI: 0.80-1.09).

Bertrand et al. 2020 (30) studied the association between GDM and breast cancer in the US Black Women’s Health Study. They included 41,767 parous women, of whom 2,059 reported of history of GDM. Women were followed for a maximum of 32 years. Among GDM women, 70 had developed breast cancer. There was no association between a history of GDM and risk of breast cancer: HR 0.98 (95% CI: 0.77-1.25). Restricted to women with at least 10 years since their last birth, the result was HR 0.92 (95% CI: 0.69-1.22).

In summary, among studies exploring the association between a history of GDM and risk of breast cancer, no association or a decreased risk were found in three cohort and three case-control studies from North America, while elevated risks were found in two Israeli studies based on hospital records.

**Liver disease**

Two studies on the association between prior GDM and long-term liver disease met our inclusion criteria (32,33), Table 2.

Ajmera et al. 2016 (32) evaluated the impact of a history of GDM on the prevalence of NAFLD in the Coronary Artery Risk Development in Young Adults (CARDIA) study, which was a multi-center, population-based, prospective cohort study that in 1985-1986 enrolled Caucasian (50%) and African American (50%) adults aged 18-30 years (34). Participants underwent an initial examination on anthropometric and metabolic profiling and follow-up examinations at 2, 5, 7, 10, 15, 20 and 25 years (2010-2011) with a retention rate of 72% in the surviving cohort. Of the 2,787 women in the CARDIA cohort, Ajmera et al. included 1,115 women with ≥1 births, free of diabetes, and who underwent CT quantification of hepatic steatosis at the 25-year follow-up. One hundred and twenty-four women had a self-reported history of GDM and 17 of those were diagnosed with NAFLD at follow-up. Compared with women with no history of GDM, and after adjustments for age, parity and metabolic risk...
factors, the long-term risk of NAFLD after a history of GDM was significantly increased; OR 2.29 (95% CI: 1.23-4.27). When further stratified by subsequent development of DM before diagnosis of NAFLD; the OR for having NAFLD was 1.18 (95% CI: 0.45-3.10) for those with DM, and 1.93 (95% CI: 0.72-5.14) for those without (32).

The risk of developing serious liver disease defined as liver cirrhosis, liver failure and liver transplantation after a history of GDM was investigated by Retnakaran et al. 2019 (33) in a Canadian cohort with 698,078 participants. They hypothesized that the risk would be increased, due to the well-described increased risk of liver disease in individuals diagnosed with T2DM. They found 17,932 women with GDM of whom, 15 cases per 100,000 person years developed serious liver disease during a median follow-up of 14 years. The long-term association between GDM and serious liver disease was slightly increased: HR 1.40 (95% CI: 1.01-1.94), but only in the women with a history of GDM who subsequently developed T2DM: HR 1.56 (95% CI: 1.02-2.39) vs. HR 1.15 (95% CI: 0.69-1.91) in those without T2DM.

Both studies indicated a positive association between GDM and long-term risk of liver disease, but the association was attenuated when data were stratified by subsequent development of DM, and no clear pattern was seen.

Female genital organ cancer

Three studies have examined the association between GDM and genital cancer (28,29,35).

Fuchs et al. 2017 (28) investigated a history of GDM in relation to both breast cancer (described above) and to female genital cancers. The future risks of developing ovarian and endometrial cancer after a pregnancy with GDM were significantly increased; OR 2.0 (95% CI: 1.03-4.04) and OR 2.1 (95% CI: 1.01-4.05), respectively. No association was found with cervical cancer, OR 1.1 (95% CI: 0.70-1.65).

In a hospital-based case-control study from Washington State, US, Wartko et al. 2017 (35) estimated the association between a history of GDM and risk of endometrial cancer. Among 340 women with endometrial cancer, 32 had a history of GDM, and among 5,743 matched controls, 322 had a history of GDM; OR 1.70 (95% CI: 1.14-2.55) in observed, non-imputed data, and OR 1.30 (95% CI: 0.85-1.98) when missing data were accounted for by imputation and further adjustment for BMI.

Pace et al. 2020 (29) (described above) found no association between overall risk of reproductive organ malignancies (HR 1.08 (95% CI: 0.91-1.29)), endometrial cancer (HR 0.31 (95% CI: 0.07-1.46)), ovarian cancer (HR 1.02 (95% CI: 0.76-1.92)) or cervical cancer (HR 1.21 (95% CI: 0.76-1.92)).

No consistent pattern was found for the association between a history of GDM and
later occurrence of female genital cancers, although the overall trend was toward no association in two of the three studies.

**Thyroid disease including thyroid cancer**

In this disease group, only one study was found.

Pace et al. 2020 (29) (described above) is the only study of thyroid cancer in women with a history of GDM. Among the 34,294 women with GDM, 125 were later diagnosed with thyroid cancer compared with 96 women without GDM, resulting in an increased risk in GDM women: HR 1.39 (95% CI: 1.03-1.89).

No study investigating the long-term relationship between history of GDM and subsequent development of thyroid disease (hypothyroidism, hyperthyroidism, thyrotoxicosis) was found.

**Other outcomes**

Pace et al. 2020 (29) found no association between a history of GDM and later risk of urological cancer (HR 0.60 (95% CI: 0.24-1.08)). Pace et al. 2020 also reported on a number of other cancer sites and found no HR statistically significantly different from 1. No study on long-term mortality was detected.

**DISCUSSION**

**Main finding**

In the present systematic review, we mapped potential long-term health consequences of GDM other than T2DM and cardiovascular disease. Given that GDM is among the most common medical complication of pregnancies, surprisingly few studies were identified.

We found some indication for an increased risk of liver disease following a history of GDM. It was uncertain, however, whether this risk was restricted to those with a subsequent diagnosis of DM. Three studies indicated that women, especially black women, with a history of GDM had an increased risk of subsequent kidney disease. There was also some indication of increased risk of glomerular hyperfiltration and UACR but restricted to women with subsequent DM. The possible risk of breast cancer following a history of GDM showed somewhat inconsistent results. In three cohort and three case-control studies from North America no association was found, but an increased risk was indicated in two Israeli cohort studies based on hospital records. Only sparse and somewhat inconsistent results were found for the association between a history of GDM and other cancers. No study on the association between a history of GDM and thyroid diseases was found, except one on thyroid cancer, and no study had reported on mortality in women with GDM.
Kidney diseases

The strongest indication for long-term health consequences of GDM came from studies of kidney diseases. This is consistent with the fact that inflammatory markers shown to predict both cardiovascular events and chronic kidney disease are elevated in women with a history of GDM (36), supporting the hypothesis that women with a history of GDM can develop subclinical inflammation and persistent generalized vascular dysfunction (20). Additionally, there have been indications of DM playing an important role in the development of future renal damage (22). This was not surprising, as it is well established that T2DM is a risk factor for chronic kidney disease (37,38).

The excess risk of kidney disease following a history of GDM largely came from studies in black women (19,21). Previous studies strongly indicate that African American women with GDM developed T2DM and hypertension more often than white women with GDM (39,40). This could very well explain the higher incidence of cardiovascular disease in African American women with a history of GDM.

In three of the studies indicating an association with kidney disease, the GDM diagnoses were self-reported (19–21). However, in the US CARDIA-cohort self-reported GDM had been validated by review of prenatal glucose tolerance tests for a subsample of 165 women with 200 births, showing a sensitivity of 100%, and a specificity of 92% (41). The Israeli cohort study was based on hospital records from 1988-2013 (Beharier et al. 2015 (20)). Data from this study were unfortunately not reported stratified for development of subsequent T2DM.

Breast cancer

Breast cancer was the most thoroughly studied possible long-term consequence of GDM, but the results of the eight available studies were not entirely consistent.

The US case-control studies were conducted in 1990-1992 (23), 1996-2001 (26), and 1999-2004 (25). Data on GDM were self-reported, and given that the data were collected from breast cancer patients and controls from 1990 to 2004, these self-reported data are likely to date back to pregnancies in the 1960’s. Some uncertainty must be considered as to whether GDM in pregnant women was investigated systematically at that time; and if this was the case, whether the result was conveyed to the woman; and to what extent recall bias could affect self-reported data at the time of a breast cancer diagnosis many years later. One cohort study from the US was also based only on self-reported data from 1995 onward (30), while the self-reported data from 1989-2001 in the other US cohort study had been validated against medical records (27). In the Canadian cohort study, GDM diagnoses were retrieved from health administrative records from 1999-2007 (29). In all of these six
studies, no association was found between a history of GDM and breast cancer.

The two Israeli cohort studies were both based on hospital records (24,28). Perrin et al. 2008 (24) used data from the Jerusalem Perinatal Study comprising births from 1964-1976. Data on obstetric information were copied from the labor ward log at the time of birth, and the rubric “pre-diabetes” was supposed to correspond, approximately, to GDM. The pregnant women were screened for glucosuria at each antenatal visit, and if found positive they were referred for an oral glucose tolerance test. Like in the Israeli study on kidney diseases (20), Fuchs et al., 2017 (28) used hospital records from another Israeli area from 1988-2013. Data on GDM came from the perinatal database, but further information on how GDM was defined was not provided.

The differences in time periods for diagnosis of GDM, and the differences in ascertainment of GDM diagnosis could have played a role in the inconsistencies in results across studies. The ICD8 coding system did not have a separate code for GDM. Yet, the awareness of the possible negative consequences for development of diabetes during pregnancy has been present for decades, and years before the oldest study included in this review. Furthermore, the excess risk found in the Jerusalem study was restricted to women diagnosed with breast cancer after the age of 50 years, and this study might be the only one with a sufficiently long follow-up period to cover breast cancer cases diagnosed in postmenopausal age.

Liver diseases

Based on two studies, there was some evidence for a long-term increased risk of liver diseases after a history of GDM. This was consistent with earlier results by Forbes et al. 2011 (14)(14)(14) which showed GDM to be associated with a significantly increased short-term risk of NAFLD (OR 2.77 (95% CI: 1.43–5.37)).

However, the elevated long-term risk of liver cirrhosis, failure or need of transplant after a diagnosis of GDM was significantly increased only among women who developed T2DM after GDM, reinforcing the association between DM and liver disease. Obesity and weight gain are risk factors for both GDM, T2DM, and liver disease (33). Further investigations are needed where the possible association between a history of GDM and the long-term risk of liver disease is studied with adjustment for the presence of DM and/or obesity at follow-up.

Liver biopsy is the gold standard diagnostic ascertainment method for NAFLD (32). In the Canadian cohort study, diagnoses of liver diseases were extracted from hospital records (33). However in the CARDIA study, diagnoses were based on CT-scans (32), which might imply a risk of misclassification with non-alcoholic fatty liver disease.
Female genital cancer and urological cancer

An excess risk of endometrial cancer was indicated in the cohort study based on hospital records from 1988-2013 from an Israeli hospital (28). An excess risk in a US case-control study based on hospital records disappeared when the risk assessment was based on imputed data and further adjusted for body mass index (35). Another study also failed to reach significance on increased risk of endometrial cancer, but this could be ascribed missing data (29). The attenuation of the association between GDM and endometrial cancer when controlled for body mass index is expected, as obesity is known to be the strongest non-genetic risk factor for endometrial cancer (35).

Other morbidity and mortality

Based on only one study, there might be a small long-term risk for thyroid cancer but not other thyroid diseases (29). Since thyroid disease was recently found to be associated with GDM in short-term follow-up studies (5 years postpartum) (42), further investigation of the long-term consequences is needed.

Strengths and limitations

The strength of this study is the broad scope of diagnoses explored, adding knowledge to the overall long-term morbidity, besides overt diabetes and heart disease, related to a history of GDM.

The limitation of the study is that the included studies differ on important issues such as design, outcome measures, and study period. Some studies are based on the diagnosis of GDM in hospital records, others on self-reports with the inherent risk of recall bias. Some studies included cohorts from private hospitals, others based on national registers. Some studies adjusted for intermediate DM and BMI, others did not. The time span, which the studies covered is broad with different diagnosis systems and differences in how to diagnose. Hence, we refrained from performing a meta-analysis of the reported results.

Further, we restricted our search to morbidity related to specific organs and not morbidity in general. Therefore, long-term morbidity related to, e.g. the pancreas and intestine is not covered.

We are aware of the risk of publication bias. However, the reported studies are all based on the hypothesis that GDM might cause long-term health problems. For each study, quite work demanding extra testing and/or extraction of data from existing databased were needed. On this basis, we find it unlikely that researchers have completed this work without reporting the results. By far the majority of reported results are not statistically significant, indicating that researchers have also reported results not supporting their hypothesis.
CONCLUSION

The evidence on long-term health consequences after a history of GDM for the conditions, explored in this review is sparse. The most consistent pattern for an association between GDM and long-term disease was found for kidney diseases, and especially in black women, but in three of the four studies, the diagnosis of GDM was self-reported, and the studies used different outcome measures for kidney disease. Studies based on self-reported GDM diagnosis, some published as far back as the 1960’s, dominated the evidence base for the association between GDM and breast cancer; and some diagnoses might therefore have been misclassified. Overall, the findings in this systematic review did not provide firm evidence for associations between GDM and long-term excess risks of the studied diseases.

Given the complex associations between GDM, development of different kinds of diseases after birth and long-term health outcomes, future studies based on comprehensive hospital records or well-defined cohorts are strongly recommended.
ADDITIONAL INFORMATION

Registration and protocol: The protocol for the review was not registered. However, it was prepared and can be accessed with corresponding author LRFM.

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Disclosures: No potential conflicts of interest were reported.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author LRFM, upon reasonable request.
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Legends to figure

Figure 1. Flow diagram of the literature search and selection process.
| First author, year, (ref) | Country     | Study design                                      | Ethnicity                  | Exposure: +/- number in cohort | Outcomes: +/- number in case-control | Duration of follow-up, years | GDM assessment method             |
|--------------------------|-------------|--------------------------------------------------|----------------------------|--------------------------------|--------------------------------------|-------------------------------|----------------------------------|
| **Kidney disease**       |             |                                                  |                            |                                |                                      |                               |                                   |
| Bomback 2010 (17)        | USA         | Cross-sectional, screening data for women at high risk of chronic kidney disease | White, Afro American, other| GDM+: 571                       | Microalbuminuria; Macroalbuminuria; Chronic kidney disease (CKD) | Cross-sectional screening study | Self-reported at mean age 51-53 years |
| Beharier 2015 (18)       | Israel      | Cohort, hist                                     | Non-selective population   | GDM+: 9542 GDM+: 88426         | Renal disease                        | Mean: 11.2                    | Administrative health data        |
| Dehmer 2018 (19)         | USA         | Cohort, pros, CARDIA                             | White, black               | GDM+: 101 GDM+: 719            | Chronic kidney disease (urine albumin and creatinine) | Mean: 20.8                    | Self-reported                     |
| Study            | Country | Design | Race, Ethnicity, Other | Case \# | Control \# | End Points                                                                 | Measures                                                                 | Methodology                                                                 |
|------------------|---------|--------|------------------------|---------|-----------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Breast cancer**|         |        |                        |         |           |                                                                             |                                                                           |                                                                                |
| Troisi 1998 (21) | USA     | Case-control | White, Afro-American, other | GDM | Breast cancer (medical records): BC+: 1239 BC-: 1166 | Not relevant | Self-reported                                                                 |                                                                             |
| Perrin 2008 (22) | Israel  | Cohort, hist | European, Israeli, other West Asian, North African | GDM+ : 410 GDM- : 37516 | Breast cancer (Israel Cancer Register ICD-10: C50) | Median: 34 | Labor ward logs (GDM based on screening for glucosuria at antenatal visits and subsequently OGTT) |                                                                             |
| Rollison 2008 (23) | USA     | Case-control | Non-Hispanic white, Hispanic, native American | GDM | Breast cancer (Cancer register: ICD-10: C50) BC+: 2324 BC-: 2523 | Reported at mean age 57.0 | Self-reported                                                                 |                                                                             |
| Brasky 2013 (24) | USA     | Case-control | Predominantly Caucasian | GDM | Breast cancer (Medical records, interview): BC+: 960 BC-: 1852 | Reported at mean age 58.2 | Self-reported                                                                 |                                                                             |
| Study | Year | Country | Cohort, Design | Race, Ethnicity | GDM+ | GDM- | Disease(s) | Methodology | Mean | Years since last birth | Reporting Modality |
|-------|------|---------|----------------|----------------|------|------|------------|-------------|------|-----------------------|-------------------|
| Powe 2017 (25) | USA Cohort, Pros | White, Afro-American, Asians | GDM+: 5188 GDM-: 81784 | Breast cancer (questionnaire, medical records) | >22 | Self-reported |
| Fuchs 2017 (26) | Israel Cohort, hist | Non-select population | GDM+: 9893 GDM-: 94822 | Ovary, uterus, breast, cervix cancer. Medical records | Mean: 12 | Perinatal database |
| Pace 2020 (27) | Canada Cohort, hist | European ancestry | GDM+: 34294 GDM-: 34294 | Breast cancer, thyroid cancer and other female genital organ cancer | Mean: 13.1 | Administrative health data: ICD-codes |
| Bertrand 2020 (28) | USA Cohort, Pros | Afro American | GDM+: 2059 GDM-: 39708 | Breast cancer (self-report, death certificates, cancer register records, medical records) | Years since last birth: ≥10 | Self-reported |
| Liver disease | | | | | | |
| Ajmera 2016 (30) | USA Cohort, Pros, CARDIA | Caucasian, Afro American | GDM+: 124 GDM-: 991 | NAFLD (CT scan) | 25 | Self-reported |
| Retnakaran 2019 (31) | Canada Cohort, hist | Chinese, South Asian, other | GDM+: 17932 GDM-: 680146 | Serious liver disease (hospitalized for cirrhosis, liver failure, liver transplant) | Median: 14 | Administrative health data |
| Other female genital organ and urological cancer | | | | | | |
| Study       | Location  | Study Type | Population Description                                                                 | Medical Records | Mean Age | Database Type          |
|------------|-----------|------------|----------------------------------------------------------------------------------------|-----------------|----------|------------------------|
| Fuchs 2017 | Israel    | Cohort, hist | Non-select population                                                                   | GDM+ : 9893 GDM-: 94822 | 12       | Perinatal database      |
| Wartko 2017| USA       | Case-control | Non-Hispanic white, non-Hispanic black, Ameri-can Indian/ Alaska native, Asian, native Hawaiian/Pacific islander, Hispanic | History of GDM  | 14       | ICD-9-CM 648.8 in hospital discharge records |
| Pace 2020  | Canada    | Cohort, hist | European ancestry                                                                       | GDM+ : 34294 GDM-: 34294 | 13.1     | Administrative health data: ICD-codes |

**Thyroid cancer**

| Study       | Location  | Study Type | Population Description                                                                 | Medical Records | Mean Age | Database Type          |
|------------|-----------|------------|----------------------------------------------------------------------------------------|-----------------|----------|------------------------|
| Pace 2020  | Canada    | Cohort, hist | European ancestry                                                                       | GDM+ : 34294 GDM-: 34294 | 13.1     | Administrative health data: ICD-codes |

GDM: gestational diabetes mellitus; USA: United States of America; ICD: International Classification of Diseases; Pros: Prospective; Hist: Historical; OGTT: Oral Glucose Tolerance Test; NAFLD: Non-alcoholic fatty liver disease; BC: Breast cancer; EC: Endometrial cancer
Table 2. Association between history of gestationel diabetes mellitus (GDM) and long-term morbidity outcomes

| First author, year, (ref) | Exposure Number | Outcome Number | Measure | Unadjusted (age-adjusted when specified) (95% CI) | Adjusted (95% CI) | Adjustment variables |
|---------------------------|-----------------|----------------|---------|------------------------------------------------|-------------------|---------------------|
|                           | GDM +           | GDM -          | GDM +   | GDM -                                          |                   |                     |
| Kidney disease            |                 |                |         |                                               |                   |                     |
| Bomback 2010 (17)         | 571             | 25045          | [57]    | [1928]                                        | OR                |                     |
|                           |                 |                | [4]     | [150]                                         |                   |                     |
|                           |                 |                | [55]    | [1603]                                        |                   |                     |
|                           |                 |                | [67]    | [3506]                                        |                   |                     |
|                           | Microalbuminuria: 1.34 (1.02–1.77) | Macroalbuminuria: 1.13 (0.42–3.07) | CKD stages 1–2: 1.54 (1.16–2.05) | CKD stages 3–5: 0.84 (0.65–1.09) Not reported | Microalbuminuria: 1.36 (1.03–1.80) | Macroalbuminuria: 1.13 (0.41–3.09)$^a$ | CKD stages 1–2: 1.54 (1.16–2.05)$^a$ | CKD stages 3–5: 0.94 (0.71–1.25)$^a$ | CKD stages 1-2: Afro American women: 2.32 (1.50–3.60)$^b$ | White women: 1.12 (0.68–1.84)$^b$ | a) Age, race, BMI, current smoking, alcohol use, hypertension, dyslipidaemia, eGFR, and family history of kidney disease |
|                           |                 |                |         |                                               |                   |                     |
| Beharier 2015 (18)        | 9542            | 88426          | 23      | 91                                            | OR HR             | Parity and maternal age |
|                           |                 |                |         |                                               |                   |                     |
| Dehmer 2018 (19) | 101 | 719 | 17 | 88 | HR | 1.46 (0.87-2.45) |
|---|---|---|---|---|---|---|
| 42 | 289 | 13 | 45 | Not reported | Not reported |
| 59 | 430 | 4 | 43 | | |

1.33 (0.78-2.26)\(^c\)

*Black women*: 1.96 (1.04-2.67)\(^d\)

*White women*: 0.65 (0.23-1.83)\(^d\)

\(^c\) Age, race, BMI, smoking, family history of diabetes, fasting blood glucose, baseline eGFR, education, high-density lipoprotein cholesterol, systolic blood pressure and physical activity score

\(^d\) Age, race, BMI, smoking, family history of diabetes, fasting blood glucose, baseline eGFR, education, high-density lipoprotein cholesterol, systolic blood pressure and physical activity score + interaction term for race and GDM
### Glomerular hyperfiltration:

| Study | RR (95% CI) | GDM+/DM+ | GDM+/DM- | UACR: |
|-------|-------------|----------|----------|-------|
| [601] | 1.6 (1.0-2.7) | 3.2 (1.8-5.7) | 1.0 (0.5-1.9) | 1.9 (1.0-3.6) |
| [181] | 3.2 (1.4-7.0) | 0.8 (0.4-1.6) | 1.4 (0.6-2.9) | 1.4 (0.6-2.9) |
| [420] | 1.0 (0.5-1.9) | 0.8 (0.4-1.6) | 0.8 (0.4-1.6) | 1.0 (0.4-2.3) |

### UACR:

| Study | RR (95% CI) | GDM+/DM+ | GDM+/DM- | UACR: |
|-------|-------------|----------|----------|-------|
| [601] | 1.9 (1.0-3.6) | 3.6 (1.7-7.6) | 1.3 (0.6-2.9) | 1.4 (0.6-2.9) |
| [181] | 1.3 (0.6-2.9) | 2.3 (1.1-5.9) | 1.0 (0.4-2.3) | 1.7 (1.1-2.5) |
| [420] | 1.0 (0.4-2.3) | 1.0 (0.4-2.3) | 1.0 (0.4-2.3) | 1.0 (0.4-2.3) |

### Age at index pregnancy, smoking during pregnancy (yes vs. no), education (high school or less vs. more than high school education), family history of diabetes (yes vs. no), prepregnancy BMI and hypertension before pregnancy

| Study | Cases | Controls | GDM in cases | GDM in controls | RR (95% CI) |
|-------|-------|----------|--------------|-----------------|-------------|
| Troisi 1998 (21) | [1235] | [1163] | 67 | 65 | 0.99 (0.70-1.4) |
| | | | | | Last pregnancy ≥5 years: 1.2 (0.74-1.9) |
| | | | | | Age at diagnosis<50: 1.0 (0.5-2.1) |
| | | | | | Age at diagnosis≥50: 1.7 (1.1-2.5) |
| Perrin 2008 (22) | 410 | [37516] | 29 | 1597 | 1.5 (1.0-2.1) |
| | | [37516] | 7 | 637 | Not reported |
| | | [34551] | 22 | 960 | Not reported |

### Breast cancer

| Study | Cases | Controls | GDM in cases | GDM in controls | RR (95% CI) |
|-------|-------|----------|--------------|-----------------|-------------|
| Troisi 1998 (21) | [1235] | [1163] | 67 | 65 | 1.1 (0.73-1.5) |
| | | | | | Last pregnancy ≥5 years: 1.3 (0.77-2.1) |
| | | | | | Age at diagnosis<50: 1.0 (0.5-2.1) |
| | | | | | Age at diagnosis≥50: 1.7 (1.1-2.5) |
| Perrin 2008 (22) | 410 | [37516] | 29 | 1597 | 1.5 (1.0-2.1) |
| | | [37516] | 7 | 637 | Not reported |
| | | [34551] | 22 | 960 | Not reported |

### Age, site, race, and a combination variable representing parity and age at first birth, BMI, age at menarche, mammography and alcohol intake

Age at index pregnancy, smoking during pregnancy (yes vs. no), education (high school or less vs. more than high school education), family history of diabetes (yes vs. no), prepregnancy BMI and hypertension before pregnancy

Age and birth order at first observed birth, social class, ethnic origin, education and immigration status
| Study       | Year | Design | Cases | Controls | GDM in Cases | GDM in Controls | OR                          | Note                                                                 |
|-------------|------|--------|-------|----------|--------------|-----------------|---------------------------|---------------------------------------------------------------------|
| Rollison    | 2008 | Case-control | 2324  | 2523     | Not reported | Not reported     | Age-adjusted: 0.70 (0.51-0.94) Age at GDM onset 15-34: 0.54 (0.37-0.77) Age at GDM onset ≥35: 1.35 (0.73-2.48) | BMI at age 15 years (<20, 20-24, or ≥25), number of full-term pregnancies (0, 1-2, 3-4, or ≥5), age at first pregnancy (<30 years vs. ≥30 years), age at menarche (<13, 13, or >13 years), lifetime physical activity, family history of breast cancer and breastfeeding history (ever vs. never) |
| Brasky      | 2013 | Case-control | 960   | 1852     | 28           | 13              | Age-adjusted: 0.81 (0.52-1.27) Premenopausal 0.60 (0.29-1.27) Postmenopausal 1.03 (0.52-2.05) | Age, education, history of benign breast disease, family history of breast cancer, age at first pregnancy, number of pregnancies, menopausal status and age at menopause (among postmenopausal women) |
| Power 2017 (25) |
|-----------------|
| 5188 | 81784 | 100 | 2227 |
| 5   | 2224  |
| 95  | 2224  |

HR

Age-adjusted: 0.68 (0.55-0.84)  
GDM+/T2D+: 0.23 (0.09-0.61)  
GDM+/T2D-: 0.72 (0.58-0.90)  

0.68 (0.55-0.84)  
GDM+/T2D+: 0.26 (0.10-0.68)  
GDM+/T2D-: 0.72 (0.58-0.89)  

Age, BMI at age 18 (continuous), weight gain since age 18 (continuous), height (continuous), total physical activity (MET-hours/week, quintiles), alcohol intake (none, 1-14 grams/day, ≥15 grams/day), age at menarche (≤10 years old, 11-12, 13-14, ≥15), birth index (continuous), total breastfeeding (none, <6 months, ≥6 months), menopausal status (premenopausal, postmenopausal, unknown), hormone therapy use (never, ever use of estrogen + progesterone, past: estrogen only or other, current: estrogen only or other), family history of breast cancer in mother or sister (yes/no), personal history of benign breast disease (yes/no), white race/ethnicity (yes/no), and mammography within the past 2 years (<40 years old, ≥40 and no mammography, ≥40 and mammography for screening, ≥40 and mammography for abnormality/symptoms).
| Study            | Year (Abbreviation) | n | n | | | OR | [95% CI] | Outcome/Description |
|------------------|---------------------|---|---|---|---|----|----------|-------------------|
| Fuchs            | 2017 (26)           | 9893 | 94822 | [91] | [436] | OR | [2.0 (1.60-2.51)] | Not reported |
| Pace             | 2020 (27)           | 34294 | 34294 | 346 | 392 | HR | Not reported | 0.93 (0.80-1.09) |
| Bertrand         | 2020 (28)           | 2059 | 39708 | 70 | 1609 | HR | 1.00 (0.78-1.27) | Not reported |
|                  |                     |    |     |    |     |    | 0.98 (0.77-1.25) | 10+ years since last birth |
|                  |                     |    |     |    |     |    | 0.92 (0.69-1.22) | Age, questionnaire cycle, BMI at 18, recent BMI, parity, menarche, age at first birth, oral contraceptive duration, and family history of breast cancer |
| Liver disease    |                     |    |     |    |     |    |        |                   |
| Ajmera           | 2018 (30)           | 124 | 61 | 991 | 17 | 58 | OR | 2.56 (1.44-4.55) | Not reported |
|                  |                     |    |    | 909 | [12] | [5] |    | 2.29 (1.23-4.27) | GDM+/DM+:
|                  |                     |    |    |     |     |     |    | 1.18 (0.45-3.10) | GDM+/DM-:
|                  |                     |    |    |     |     |     |    | 1.93 (0.72-5.14) | Baseline HOMA-IR, triglycerides and history of GDM |
| Retnakaran       | 2019 (31)           | 17932 | 680146 | 15/10^5 | 11/10^5 | HR | 1.40 (1.01-1.94) | Not reported |
|                  |                     |    |    |     |     |     |    | GDM+/T2D+:
|                  |                     |    |    |     |     |     |    | 1.88 (1.23-2.87) | GDM+/T2D-:
|                  |                     |    |    |     |     |     |    | 1.26 (0.76-2.09) | Age, income, region of residence, hypertension, dyslipidaemia and ethnicity |

Endometrial cancer

| Study            | Year (Abbreviation) | n | n | | | OR | [95% CI] | Outcome/Description |
|------------------|---------------------|---|---|---|---|----|----------|-------------------|
| Liver disease    |                     |    |     |    |     |    |        |                   |
| Ajmera           | 2018 (30)           | 124 | 61 | 991 | 17 | 58 | OR | 2.56 (1.44-4.55) | Not reported |
|                  |                     |    |    | 909 | [12] | [5] |    | 2.29 (1.23-4.27) | GDM+/DM+:
|                  |                     |    |    |     |     |     |    | 1.18 (0.45-3.10) | GDM+/DM-:
|                  |                     |    |    |     |     |     |    | 1.93 (0.72-5.14) | Baseline HOMA-IR, triglycerides and history of GDM |
| Retnakaran       | 2019 (31)           | 17932 | 680146 | 15/10^5 | 11/10^5 | HR | 1.40 (1.01-1.94) | Not reported |
|                  |                     |    |    |     |     |     |    | GDM+/T2D+:
|                  |                     |    |    |     |     |     |    | 1.88 (1.23-2.87) | GDM+/T2D-:
|                  |                     |    |    |     |     |     |    | 1.26 (0.76-2.09) | Age, income, region of residence, hypertension, dyslipidaemia and ethnicity |
| Study            | Year (No.) | Cases | Controls | GDM in Cases | GDM in Controls | OR (95% CI) | Analysis | Additional Factors | OR (95% CI) |
|------------------|------------|-------|----------|--------------|----------------|-------------|----------|-------------------|-------------|
| Fuchs 2017 (26)  | 9893       | 94822 | [11]     | [47]         | OR 2.1 (1.01-4.05) | Not reported |          |                   |             |
| Wartko 2017 (33) | Case-control | 340   | 5743     | GDM in Cases | GDM in Controls | OR Non-imputed, adjusted: 1.7 (1.14-2.55) | Imputed, adjusted 1.30 (0.85-1.98) | e) Race/ethnicity, year of delivery, maternal age at delivery |
| Pace 2020 (27)   | 34294      | 34294 | 7        | 3            | HR Not reported | 0.31 (0.07-1.46) | Gestational hypertension, preterm delivery, infant size, parity, prior comorbidity, maternal deprivation index and ethnicity |
| Ovarian cancer    |            |       |          |              |                |             |          |                   |             |
| Fuchs 2017 (26)  | 9893       | 94822 | [10]     | [46]         | OR 2.0 (1.03-4.04) | Not reported |          |                   |             |
| Pace 2020 (27)   | 34294      | 34294 | 24       | 32           | HR Not reported | 1.02 (0.66-1.58) | Gestational hypertension, preterm delivery, infant size, parity, prior comorbidity, maternal deprivation index and ethnicity |
| Cervical cancer   |            |       |          |              |                |             |          |                   |             |
| Fuchs 2017 (26)  | 9893       | 94822 | [23]     | [199]        | OR 1.1 (0.70-1.65) | Not reported |          |                   |             |
| Study | Year (Volume) | Sample Size | Follow-up | HR | CI | Risk Factors |
|-------|---------------|-------------|-----------|----|----|-------------|
| **Urological cancer** | | | | | | |
| *Pace* | 2020 (27) | 34294 | 44 | 38 | HR | Not reported | 1.21 (0.76-1.92) | Gestational hypertension, preterm delivery, infant size, parity, prior comorbidity, maternal deprivation index and ethnicity |
| **Thyroid cancer** | | | | | | |
| *Pace* | 2020 (27) | 34294 | 25 | 21 | HR | Not reported | 0.60 (0.24-1.48) | Gestational hypertension, preterm delivery, infant size, parity, prior comorbidity, maternal deprivation index and ethnicity |

GDM: gestational diabetes mellitus; CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; RR: Relative risk; CKD: Chronic kidney disease; UACR: urine albumin-to-creatinine ratio; BMI: Body mass index; DM: Diabetes mellitus; T2D: Type 2 diabetes; HOMA-IR: Homeostatic model assessment index
Figure 1

Identification of studies via databases and references

Records identified from databases and reference lists (n = 3084)

Records removed before screening: Duplicate records removed (n = 1344)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)

Records screened manually (n = 1740)

Records excluded (n = 1659)

Reports assessed for eligibility (n = 81)

Reports excluded:
- Conference abstracts (n = 23)
- Review articles (n = 13)
- Short-term follow-up (n = 11)
- Wrong outcomes (n = 5)
- Wrong indication (n = 4)
- Letters (n = 3)
- Protocols (n = 2)
- Wrong patient population (n = 1)
- Full-text version not published yet (n = 1)
- Outcome in offspring (n = 1)
- Article in Arabic (n = 1)
- Book chapter (n = 1)

Studies included in review (n = 15)