Risk factors for recurrence of GDM: A meta-analysis

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Abstract: The incidence of gestational diabetes mellitus (GDM) is increasing every year. Many pregnant women with GDM experience recurrence in subsequent pregnancies. In addition, GDM poses a risk to both the mother and the child, and GDM is an important risk factor for type 2 diabetes(T2DM), so it is necessary to find risk factors for recurrence of GDM. This meta-analysis aims to identify the risk factors associated with recurrence of GDM, to reduce the recurrence rate and to improve the prognosis of patients. This meta-analysis was conducted by a systematic search of the PubMed, Cochrane, Embase and Web of science libraries for original eligible studies published in English up to October 2021. All search results were examined against our inclusion and exclusion criteria. We calculated pooled odds ratios (ORs) or standardised mean differences (SMDs) with their corresponding 95% confidence intervals (CIs) to assess the impact of included risk factors on GDM recurrence. A total of 15 studies involving 9276 patients with GDM published by October 2021 were ultimately included. The results of our meta-analysis showed that recurrence of GDM was associated with family history of diabetes (OR=1.68, 95% CI: 1.37-2.07, p<0.001), insulin therapy at index pregnancy (OR=2.52, 95% CI: 1.99-3.19, p<0.001), maternal age at index pregnancy (SMD=1.30. 95% CI: 0.22-0.38, P<0. 001), pregnancy BMI at index pregnancy (SMD=1.23, 95%CI:0.37-2.09, P=0.005), parity at index pregnancy (SMD=0.44, 95%CI:0.02-0.98, P<0.001), fasting glucose level at index pregnancy (SMD=0.36, 95%CI:0.18-0.53, P<0.001), HbA1c level at index pregnancy (SMD= 0.47, 95% CI:0.05-0.88, P=0.03) and gestational interval (SMD=0.34, 95% CI:0.11-0.57, P=0.004). Recurrence of GDM was not associated with gestational hypertension at index pregnancy (OR=2.53, 95% CI: 0.53-12.18, P=0.25), pre-pregnancy weight at index pregnancy (SMD=0.3, 95% CI: -0.13-0.73, P=0.17), weight gained during pregnancy at index pregnancy (SMD=-0.11, 95% CI: -0.33 -0.10, P=0.72), and neonatal birth weight at index pregnancy (SMD=-0.03, 95% CI: -0.24-0.18, P=0.78). Meta-analysis showed that family history of diabetes, age, severe insulin resistance in pregnant women and long pregnancy intervals were risk factors for recurrence of GDM. However, the impact of other potential risk factors, including gestational hypertension, on the recurrence of GDM requires further study. Although maternal pre-pregnancy weight and fetal birth weight at index pregnancy are not associated with the recurrence of GDM, BMI, which reflects obesity, is associated with the recurrence of GDM.

1. Introduction

Pregnancy is a complex process with changes in the metabolism of sugars, proteins and lipids [1]. Gestational diabetes mellitus (GDM) is a varying degree of glucose intolerance that develops or is first detected during pregnancy, mainly between 24 and 28 weeks of gestation [2]. The prevalence of GDM has increased yearly due to improvements in living standards and changes in dietary patterns, particularly the intake of high-calorie foods during pregnancy [3]. GDM is a major cause of perinatal (fetal macrosomia, obstructed shoulder labour, birth trauma, asphyxia, stillbirth and multiple pregnancies), neonatal (respiratory distress syndrome, hypoglycaemia, hyperbilirubinemia, prematurity and polycythemia) and maternal (pre-eclampsia, surgical deliveries and urinary tract infections) are the main causes of morbidity [4-6]. With the opening of the second-child policy in various countries, GDM recurrence requires attention and poses a new challenge to the management

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strategy of GDM [7]. There are few meta-analysis studies on GDM recurrence; therefore, it is important to identify risk factors for GDM recurrence so that clinical recommendations can be made to prevent GDM recurrence [8,9]. This group of women has a complex composition, including individuals with different medical conditions. Additional pregnancies in this population increase the investment of health resources and economic burden, posing a significant challenge to health services. The aim of this meta-analysis was to identify risk factors associated with recurrence of GDM in order to reduce recurrence rates and improve patient prognosis.

2. Materials and methods

In this systematic review and meta-analysis, we aimed to explore studies on risk factors for GDM recurrence and to quantify GDM recurrence rates.

2.1. Literature search strategy

Two evaluators (Ziyu LI and Liru Cao) systematically and independently searched PubMed, EMBASE, Cochrane and Web of science libraries for literature published before October 2021 to find relevant original English articles examining risk factors for recurrence of GDM. We combined the mesh keywords 'gestational diabetes', 'recurrence' and all relevant free search terms to search for potential articles. The detailed search strategy and process can be found in the supplementary file. In addition, a detailed manual check of the reference list for each study included in this meta-analysis was conducted to further identify other potentially eligible literature.

2.2. Inclusion and exclusion criteria

All search results were first screened for titles and abstracts, and then the full text of eligible literature was independently reviewed by two reviewers (Ziyu LI and Liru Cao). Studies included in this meta-analysis had to meet the following criteria. (1) all studies involving patients with GDM were divided into recurrent and non-recurrent groups based on recurrence at the time of re-pregnancy following the index pregnancy; (2) the diagnosis of patients with GDM included in the study was based on glucose tolerance screening during pregnancy. (3) The outcome was GDM recurrence, defined as the occurrence of GDM in a pregnant woman at the time of the index pregnancy and the occurrence of GDM in a subsequent pregnancy; (4) There were sufficient data reported on the risk factors for GDM recurrence studied in this meta-analysis; and (5) Retrospective or prospective original studies in English. The following studies were excluded. (1) insufficient data studied in this meta-analysis; (2) unclear definition of relapse or diagnosis of GDM; (3) continuous-type data done in segments, which may limit meta-analysis of risk factors; (4) reviews, letters, conference abstracts. Supplementary information and case reports.

2.3. Statistical analysis

Pooled odds ratios (ORs) or standardised mean differences (SMDs) and their corresponding 95% confidence intervals (CIs) were calculations to estimate the effect of each included risk factor on GDM recurrence. Heterogeneity of all included studies was assessed and quantified using Cochrane Q statistics and I2 statistics, respectively [10]. I2 > 50% suggested that heterogeneity between the studies included was significant, so a random effects model was subsequently used to pool these results. When heterogeneity was not significant (I2<50%), a fixed-effects model was applied. All statistical analyses involved in this meta-analysis were performed using the statistical software 'Review Manager 5.3'.

3. Results

3.1. Study selection and study characteristics

A literature search in Pubmed, Cochrane, Embase, and Web of science initially identified 726 possible articles. After excluding 56 duplicates, 600 studies were further excluded by screening the titles and abstracts of the articles and a total of 70 studies were associated with recurrence of

gestational diabetes. After obtaining the full text, a total of 15 studies met the inclusion and non-exclusion criteria and were included in this meta-analysis [11-25]. Figure 1 shows the flow chart of the literature screening for this study. The baseline characteristics of the 15 included studies are presented in Table 1. The study involved 9276 pregnant women with a history of gestational diabetes and two pregnancies, 3906 in the GDM recurrence group and 5370 in the GDM non-recurrence group.

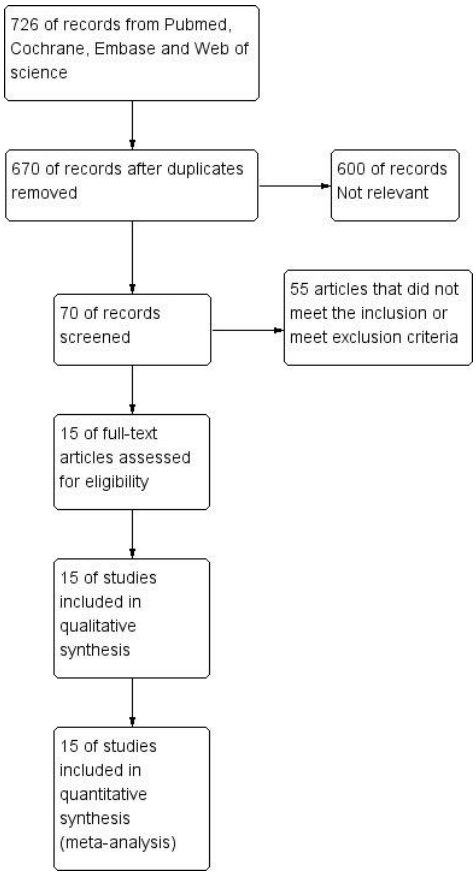

Figure 1. Flowchart of article selection for the meta-analysis.

Table 1. Baseline characteristics of all included studies in our meta-analysis

Literature	Publication (Year)	Geographic region	Sample size (Recurrence/Non-recurrence)	NOS scores
Elliot H. Philipson	1989	United States	20/10	8
ROBERT G. MOSES	1996	Australia	35/65	9
C.Y. Spong	1998	United States	111/53	9
Tomoyoshi Nohira	2004	Japan	21/9	9
Soo Heon Kwak	2008	Korea	50/61	9
Heather J. Holmes	2010	United States	137/207	8
A. Z. Khambalia	2013	Australia	2192/3123	7
Nansi S. Boghossian	2013	United States	254/996	7
Anne R. Kruse	2015	Denmark	34/38	8
Naama Schwartz	2016	Israel	432/356	8
Naama Schwartz	2017	Israel	257/169	8
Na Wang	2017	China	56/72	8
Yin-Yu Wang	2019	China	78/64	9
Kristiina Rönö	2020	Finland	191/113	7
Mamoru Morikawa	2021	Japan	38/34	7

3.2. GDM recurrence rate

Prior to the combined analysis of 15 studies involving 9276 pregnant women, heterogeneity was found and therefore a random effects model was used with a combined recurrence rate of 50% (95% CI: 0.42-0.58, P<0.001). The results of the combined recurrence rate for women with GDM are shown in Figure 2.

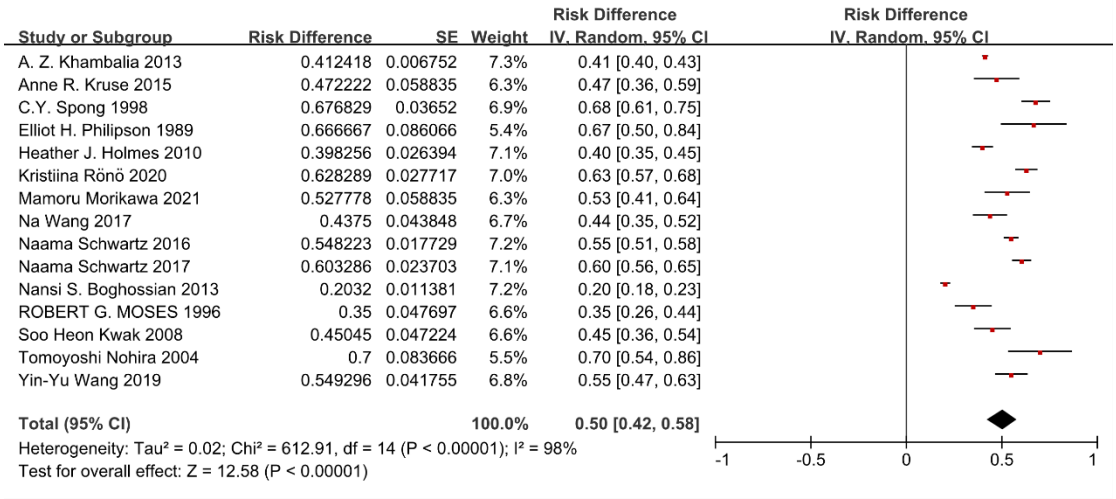

Figure 2. Forest plot for the prevalence of GDM recurrence.

3.3. Family history

Through the analysis of seven studies involving 1750 pregnant women, we examined the relationship between family history of diabetes and recurrence of GDM in the next pregnancy. The results showed that pregnant women with GDM who had a family history of diabetes were more likely to have a recurrence of GDM in their next pregnancy (OR=1.68, 95% CI: 1.37-2.07, p<0.001) (Figure 3). As there was no heterogeneity in these seven studies (I2=0%, P=0.90), a fixed effects model was used.

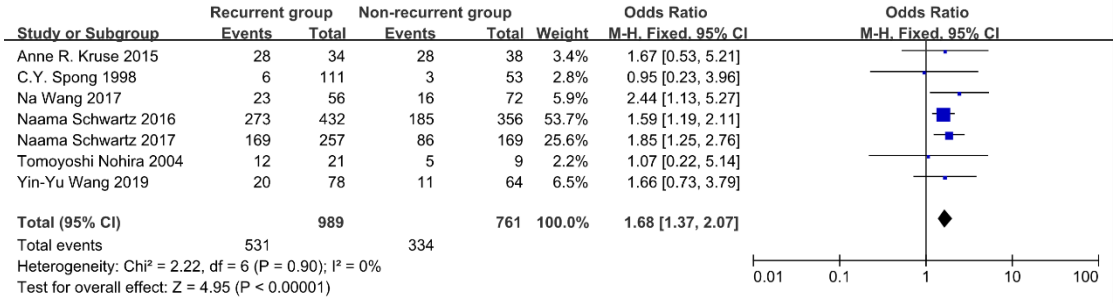

Figure 3. Forest plot with OR differences of family history.

3.4. Gestational hypertension

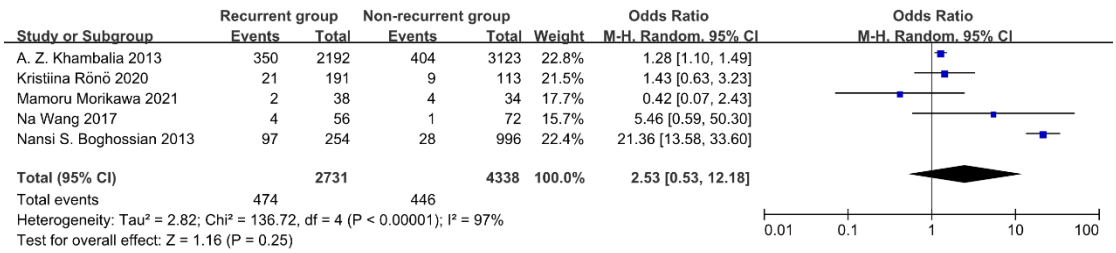

Figure 4. Forest plot with OR differences of gestational hypertension in Index pregnancy.

Through the analysis of five studies involving 7069 pregnant women, we examined the relationship between the occurrence of gestational hypertension in the index pregnancy and the recurrence of GDM in the next pregnancy. The results were not statistically significant (OR=2.53,

95% CI: 0.53-12.18, p=0.25) (Figure 4). Due to the heavy heterogeneity in these 5 studies (I2=97%, P<0.001), a random effects model was used. The reliability of the results is limited due to the heavy heterogeneity of the included studies.

3.5. Insulin therapy

In five studies involving 1539 pregnant women, this study examined the relationship between the use of insulin therapy in the index pregnancy and the recurrence of GDM in the second pregnancy. The results showed that pregnant women with GDM treated with insulin in the index pregnancy were approximately 150% more likely to have a recurrence of GDM in the second pregnancy (OR=2.52, 95% CI: 1.99-3.19, P<0.001) (Figure 5). No heterogeneity was found in the included studies (I2=15%, p=0.32), therefore a fixed effects model was used.

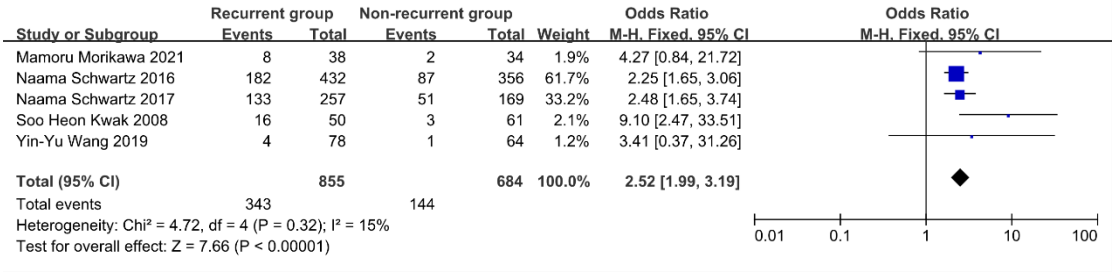

Figure 5. Forest plot with OR differences of insulin therapy in Index pregnancy.

3.6. Maternal age

In 12 studies involving 2639 pregnant women, this study examined the relationship between age at index pregnancy and recurrence of GDM in the second pregnancy. The results showed that higher age at the time of the index pregnancy was associated with a higher likelihood of GDM recurrence in the second pregnancy (SMD=0.30, 95% CI:0.22-0.38, p<0.001) (Figure 6). Mild heterogeneity was found in the included studies (I2=39%, p=0.08), so a fixed effects model was used.

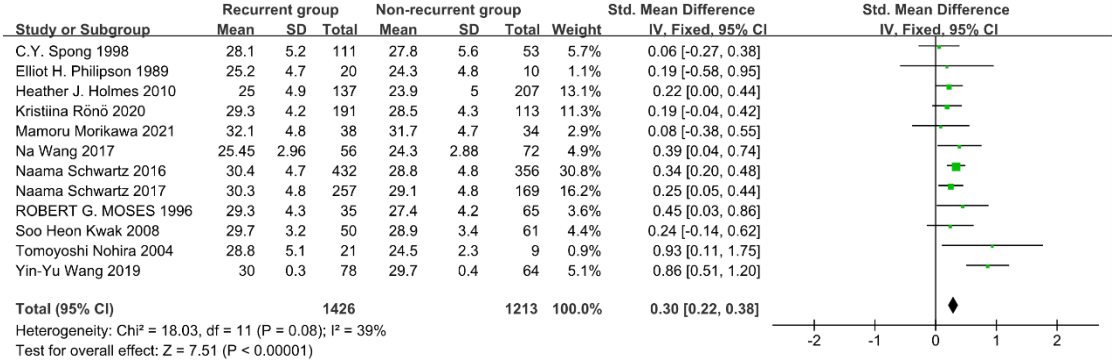

Figure 6. Forest plot with standardized mean differences of maternal age.

3.7. Pregestational weight

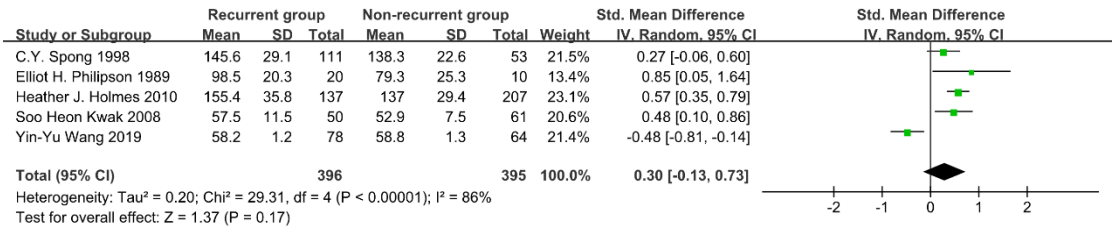

Figure 7. Forest plot with standardized mean differences of pregestational weight.

The effect of pre-pregnancy weight at index pregnancy on the recurrence of GDM at the second pregnancy was investigated through the analysis of five studies involving 791 pregnant women, which showed that pre-pregnancy weight at index pregnancy had no effect on the recurrence of GDM at the second pregnancy (SMD=0.3, 95% CI: -0.13-0.73, p=0.17) (Figure 7). The reliability

of the results was limited due to the high heterogeneity of the included studies (I2=86%, p<0.001).

3.8. Gestational weight gain

Through analysis of four studies involving 341 pregnant women, we investigated the effect of pregnancy weight gain at index pregnancy on recurrence of GDM at second pregnancy. The results of the study showed that pregnancy weight gain at index pregnancy had no effect on recurrence of GDM at second pregnancy (SMD=-0.11, 95% CI: -0.33-0.10, p=0.72) (Figure 8). As there was mild heterogeneity in the included studies (I2=49%, p=0.12), a fixed effects model was used.

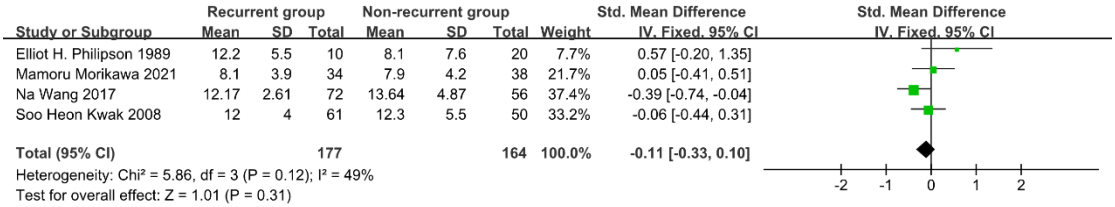

Figure 8. Forest plot with standardized mean differences of gestational weight gain.

3.9. Pregestational BMI

In seven studies involving 2145 pregnant women, this study examined the relationship between pre-pregnancy BMI at the time of index pregnancy and recurrence of GDM at the second pregnancy. The results showed that a greater pre-pregnancy BMI at index pregnancy was associated with a greater likelihood of GDM recurrence at the second pregnancy (SMD=1.23, 95% CI:0.37-2.09, p=0.005) (Figure 9). A high degree of heterogeneity was found in the included studies (I2=88%, p<0.001), therefore a random effects model was used.

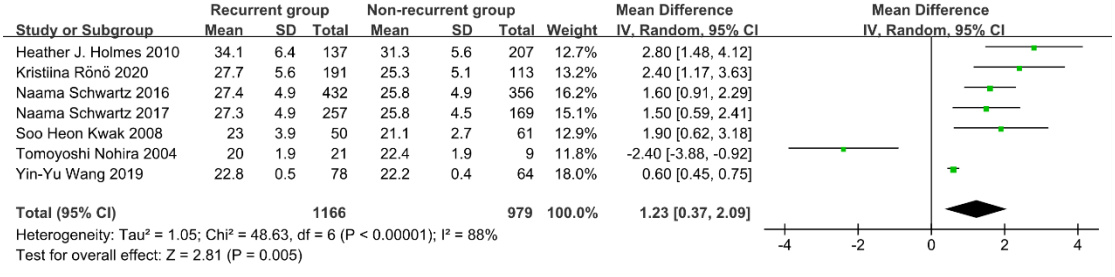

Figure 9. Forest plot with standardized mean differences of pregestational BMI.

3.10. Neonatal birth weight

We investigated the effect of fetal birth weight at index pregnancy on recurrence of GDM at second pregnancy by analysing four studies involving 341 pregnant women. The results of the study showed that fetal birth weight at index pregnancy had no effect on recurrence of GDM at second pregnancy (SMD=-0.03, 95% CI: -0.24-0.18, p=0.78) (Figure 10). A random effects model was used as there was moderate heterogeneity in the included studies (I2=73%, p=0.001).

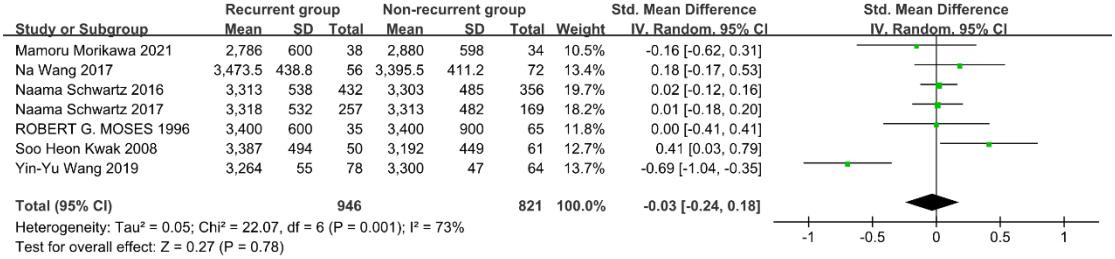

Figure 10. Forest plot with standardized mean differences of neonatal birth weight.

3.11. Parity

In four studies involving 2302 pregnant women, this study examined the relationship between gestational age at index pregnancy and recurrence of GDM in the second pregnancy. The results

showed that the higher the gestational age at the time of the index pregnancy, the higher the likelihood of GDM recurrence in the second pregnancy (SMD=0.44, 95% CI:0.02-0.98, p<0.001) (Figure 11). There was no heterogeneity in the included studies (I2=17%, p=0.31), so a fixed effects model was used.

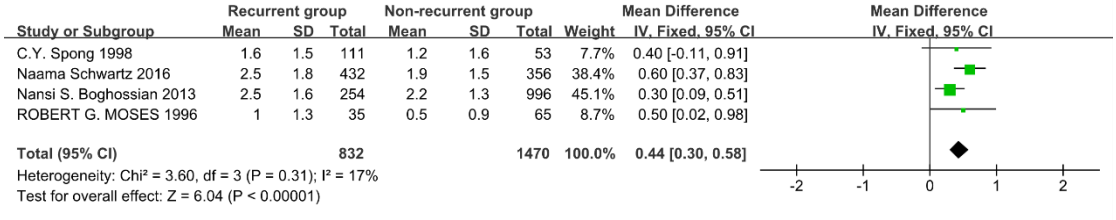

Figure 11. Forest plot with standardized mean differences of parity.

3.12. Fasting blood-glucose

In four studies involving 1630 pregnant women, this study examined the relationship between fasting glucose levels at the time of index pregnancy and recurrence of GDM in the second pregnancy. The results showed that higher fasting glucose levels at the time of the index pregnancy were associated with a higher likelihood of GDM recurrence in the second pregnancy (SMD=0.36, 95% CI:0.18-0.53, p<0.001) (Figure 12). There was moderate heterogeneity in the included studies (I2=59%, p=0.06), so a random effects model was used.

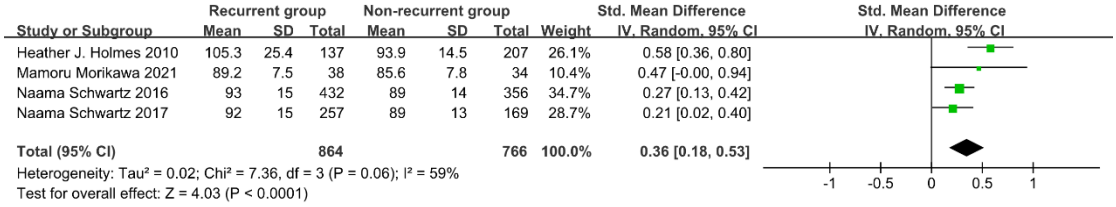

Figure 12. Forest plot with standardized mean differences of fasting blood-glucose.

3.13. HbA1c

In four studies involving 1386 pregnant women, this study examined the relationship between HbA1c levels at the time of the index pregnancy and recurrence of GDM in the second pregnancy. The results showed that higher HbA1c levels at the time of the index pregnancy were associated with a higher likelihood of GDM recurrence in the second pregnancy (SMD=0.47, 95% CI:0.05-0.88, p=0.03) (Figure 13). There was heavy heterogeneity in the included studies (I2=90%, p<0.001), so a random effects model was used.

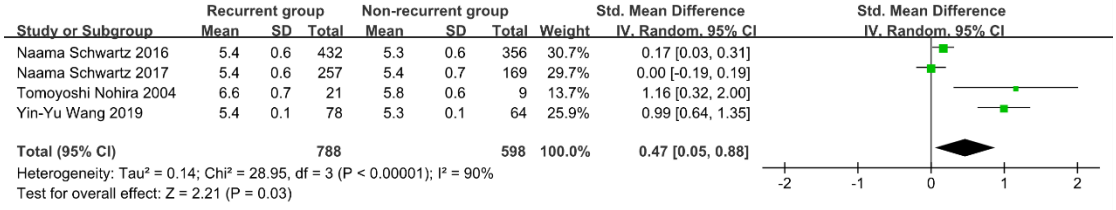

Figure 13. Forest plot with standardized mean differences of HbA1c.

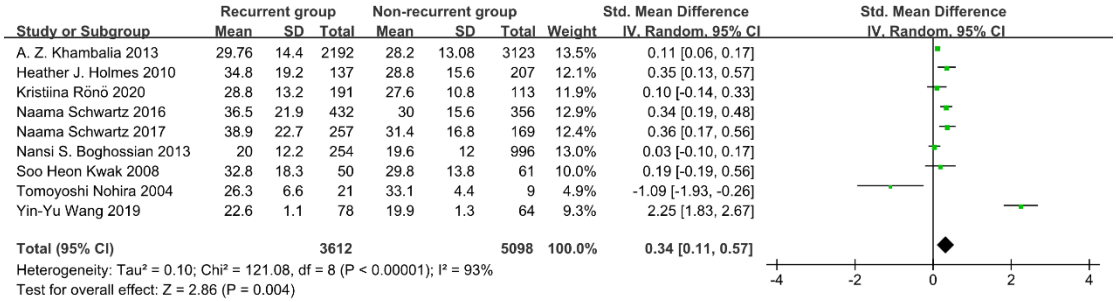

Figure 14. Forest plot with standardized mean differences of pregnancy interval.

3.14. Pregnancy interval

In nine studies involving 8710 pregnant women, this study examined the relationship between pregnancy spacing and recurrence of GDM in the second pregnancy. The results showed that the greater the interval between pregnancies, the higher the likelihood of GDM recurrence in the second pregnancy (SMD=0.34, 95% CI:0.11-0.57, p=0.004) (Figure 14). There was heavy heterogeneity in the included studies (I2=93%, p<0.001), so a random effects model was used.

4. Conclusion

GDM is a predictor of diabetes and pregnant women with GDM have a high likelihood of developing diabetes in the postnatal period. Although there is wide variation in the rate of recurrence of GDM, we found a combined recurrence rate of 50% for GDM, so it is extremely important to find risk factors for recurrence of GDM.

A family history of T2DM is a risk factor for the development of GDM [26]. In contrast, women with a history of GDM are more likely to develop T2DM postpartum [27, 28]. The link has been elaborated in a number of prospective, retrospective and cross-sectional studies that have found a strong association between a family history of T2DM and GDM [29-31]. According to Arash et al. the risk of maternal GDM was elevated for both parents and siblings with T2DM [30], and Cianni et al. found a 14.5% prevalence of GDM among those with a family history of T2DM and 7.3% among those without a family history of T2DM [32]. In the present study, a family history of diabetes was also found to be a risk factor for recurrence of GDM.

Despite the strong association between GDM and hypertension in pregnancy, the results were not statistically different in our study, although the OR was greater than 1, probably because of the high heterogeneity of the included studies. Because of the heavy heterogeneity, the reliability of the results needs further validation.

Being obese or overweight before pregnancy is one of the risk factors for the development of GDM [33]. The prevalence of GDM in obese and overweight women in the United States has gradually increased in recent decades [33]. After adjusting for ethnicity, the prevalence of GDM is higher in women who are overweight or obese [34]. In earlier studies, researchers found a positive correlation between GDM and pre-pregnancy weight BMI [33, 35-39]. In this study, maternal BMI at the time of index pregnancy was associated with recurrence of GDM in subsequent pregnancies, although no statistical difference was found between maternal weight at the time of index pregnancy and the effect of fetal birth weight on the occurrence of GDM in subsequent pregnancies. BMI is a better indicator of a pregnant woman's body fatness.

The age of the mother is associated with an increased risk of GDM. In a large prospective study in the USA (> 95% white race), the risk of developing GDM was significantly increased at age > 40 years compared to women aged < 30 years, after adjusting for other major risk factors [40]. The risk of maternal GDM appears to be higher when the fetal sex is male [41]. Some reports suggest a higher maternal risk of GDM in twin pregnancies, but this is not universal [42, 43]. Pregnancy frequency is associated with an increased risk of recurrent GDM, probably because pregnancy frequency tends to correlate positively with age.

Pregnancy spacing is a controversial factor, found to be a protective factor for recurrence of GDM in some studies, not associated with recurrence of GDM in some studies, and a risk factor for recurrence of GDM in some studies. Our combined analysis showed that longer pregnancy intervals were associated with recurrence of GDM, possibly because the interval between pregnancies was associated with age, and the older the woman, the more insulin resistant she was and the weaker her regulation of blood glucose.

Blood glucose and HbA1c levels and insulin use in pregnant women with GDM at the time of the index pregnancy reflect the degree of insulin resistance in the body, which also affects the recurrence of GDM in subsequent pregnancies.

5. Limitations

Because the data from some of the retrieved literature was segmented and could not be used for analysis, the number of studies included for some of the risk factors was low, which has an impact on the reliability of the results. In addition the diagnostic criteria for diabetes are always changing as well as varying from country to country, resulting in differences between studies. As time progresses, the stricter the diagnostic criteria for GDM will lead to an increase in the number of pregnant women with GDM, which will affect the calculation of GDM recurrence rates and the analysis of risk factors. There is also the problem of covariation between variables, such as age and pregnancy spacing, which can overestimate the role of certain risk factors.

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