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META - ANALYSIS

Anwaier et al: Maternal diabetes and fetal epicardial fat thickness

Influence of maternal diabetes during pregnancy on ultrasound-measured fetal epicardial fat thickness: A meta-analysis

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ABSTRACT

Maternal diabetes during pregnancy, including gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (PDM), has been linked to alterations in fetal development. This meta-analysis aimed to investigate the impact of maternal diabetes on fetal epicardial fat thickness (fEFT), measured via ultrasound—a potential marker of cardiometabolic risk. A systematic search of PubMed, Embase, and Web of Science was conducted to identify observational studies assessing fEFT in pregnant women with and without diabetes. A random-effects model was used to calculate the mean difference (MD) in fEFT between groups. Heterogeneity was evaluated using the I^2 statistic, and sensitivity, subgroup, and meta-regression analyses were performed to explore sources of variability. Data from ten studies, comprising twelve datasets and 1,303 participants, were pooled. Women with diabetes during pregnancy had significantly higher fEFT compared to those without diabetes (MD: 0.37 mm, 95% confidence interval [CI]: 0.26 to 0.49, $p < 0.001$), with moderate heterogeneity ($I^2 = 69\%$). Sensitivity analyses, conducted by excluding one dataset at a time, confirmed the robustness of the findings (all p-values < 0.05). Meta-regression revealed a positive correlation between gestational age (GA) at fEFT measurement and fEFT differences (coefficient = 0.040, $p = 0.005$), accounting for 83.2% of the heterogeneity. Subgroup analyses demonstrated consistent results across study designs, maternal diabetes types, and demographic factors but highlighted greater fEFT differences in studies where GA at fEFT measurement was > 26 weeks.In conclusion, maternal diabetes during pregnancy is associated with increased fEFT, particularly in later gestation.

Keywords: Gestational diabetes mellitus; GDM; pregestational diabetes mellitus; PDM; fetal epicardial fat thickness; fEFT; metabolism; meta-analysis.

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder that poses significant health challenges worldwide, with increasing prevalence among women of childbearing age (1, 2). Gestational diabetes mellitus (GDM), defined as glucose intolerance first recognized during pregnancy (3), and pregestational diabetes mellitus (PDM), which encompasses type 1 or type 2 diabetes diagnosed before pregnancy (4), affect a substantial proportion of pregnancies globally. GDM alone has been reported to affect approximately 14% of pregnancies (5), while PDM incidence varies geographically, largely reflecting the prevalence of diabetes in the general population (6). Both conditions are associated with a range of adverse maternal and fetal outcomes, including preeclampsia, preterm delivery, fetal macrosomia, and perinatal complications (7-9). These complications underscore the importance of understanding and mitigating the effects of maternal DM on pregnancy and offspring health. Emerging evidence highlights the potential influence of maternal DM on the cardiometabolic risk of offspring, which may manifest in both fetal development and later life (10, 11). Fetal exposure to maternal hyperglycemia is thought to disrupt normal metabolic programming, predisposing offspring to obesity, insulin resistance, and type 2 diabetes in adolescence and adulthood (12). These observations have led to a growing interest in identifying early markers of cardiometabolic risk in fetuses exposed to maternal DM (13). Among these, fetal epicardial fat thickness (fEFT) has emerged as a promising candidate. Epicardial fat is a metabolically active visceral fat depot that envelops the myocardium and coronary arteries, and its thickness has been linked to cardiometabolic disorders in adults (14, 15). Measuring fEFT via ultrasound provides a non-invasive method to assess fetal adiposity and may offer insights into early alterations in metabolic pathways influenced by maternal factors (16). Increased fEFT in fetuses and neonates correlates with higher birth weight, greater adiposity, and metabolic markers indicating early dysfunction, such as hyperinsulinemia (17-20). These findings suggest that elevated fEFT in utero could serve as an early marker of cardiometabolic risk. Despite the biological plausibility and clinical significance of these associations, research on the influence of maternal DM on fEFT remains relatively limited. Some observational studies have demonstrated increased fEFT in fetuses of women with GDM or PDM compared to non-diabetic pregnancies (21-28).

Given the growing interest in fEFT as a potential early marker of fetal cardiometabolic risk, understanding its association with maternal diabetes is crucial. While individual studies have explored this relationship, findings remain inconsistent due to variations in study design, measurement methods, and sample characteristics. Therefore, we conducted this systematic review and meta-analysis to quantitatively assess the impact of maternal diabetes (both GDM and PDM) on ultrasound-measured fEFT and explore potential sources of heterogeneity, providing a comprehensive synthesis of the available evidence. Additionally, we

sought to investigate the modifying effects of study characteristics, such as gestational age (GA) at the time of fEFT measurement, maternal BMI, and the type of maternal DM, on this association.

MATERIAL AND METHODS

This meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) (29, 30) and the Cochrane Handbook for Systematic Reviews of Interventions (31) throughout its design, data collection, statistical analysis, and interpretation of results. This meta-analysis was registered with PROSPERO under the identifier CRD42024618929. Initially, the protocol focused on pregnancies complicated by GDM compared to controls. However, prior to data extraction, the protocol was amended to include both GDM and PDM to comprehensively evaluate the influence of maternal diabetes on fetal epicardial fat thickness. The amendment was submitted and approved by PROSPERO, in accordance with standard meta-analysis procedures.

Literature search

To identify studies relevant to the meta-analysis, we conducted a systematic search of PubMed, Embase, and Web of Science using comprehensive search terms, including ("epicardial adipose tissue" OR "epicardial fat" OR "pericardial adipose tissue" OR "pericardial fat" OR "cardiac adipose tissue" OR "cardiac fat" OR "subepicardial adipose tissue" OR "subepicardial fat" OR "heart fat" OR "heart adipose tissue") AND ("gestational diabetes" OR "GDM" OR "pregestational diabetes" OR ("gestational" OR "pregnancy" OR "pregnant") AND ("diabetes" OR "diabetic" OR "hyperglycemia")). The search was restricted to studies involving humans and published as full-length articles in peer-reviewed English-language journals. Additionally, references from relevant original and review articles were manually screened to identify potentially eligible studies. The literature search covered publications from database inception to November 12, 2024. Detailed search terms and strategies for each database are provided in **Supplemental Data**.

Inclusion and exclusion criteria

The inclusion criteria for eligible studies were as follows: (1) observational studies published as full-length articles; (2) included pregnant women with DM, either GDM or PDM, and healthy pregnant women without DM, all with singleton pregnancies; (3) assessed fEFT via ultrasound in women with and without DM; and (4) reported or allowed the calculation of differences in fEFT between women with and without DM during pregnancy. The diagnostic criteria for GDM or PDM were based on those used in the included studies. Exclusion criteria were: (1) studies that did not include pregnant women; (2) studies including pregnant women with other clinical conditions, such as pregnancy-induced hypertension or preeclampsia; (3) studies

that did not measure fEFT; and (4) preclinical studies, reviews, or editorials. In cases of overlapping populations, the study with the largest sample size was included in the meta-analysis.

Study quality evaluation and data extraction

The processes of literature search, study identification, quality assessment, and data extraction were independently performed by two authors. Disagreements, if any, were resolved through consultation with the corresponding author. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS) (32), which assesses three domains: selection of cases and controls, comparability between groups, and measurement of exposure. The NOS assigns scores ranging from 1 to 9, with higher scores indicating better quality. The following data were extracted from each study for analysis: study details (author, year, country, and design), participant characteristics (sample size, age, and BMI of pregnant women), median GA for fEFT measurement, type of maternal DM (GDM or PDM), and variables matched or adjusted in reporting the influence of maternal DM on fEFT.

Statistical analysis

The mean difference (MD) with corresponding 95% confidence intervals (CIs) was used to summarize the difference in fetal epicardial fat thickness (fEFT) between women with and without diabetes during pregnancy (33). Heterogeneity among studies was assessed using the Cochrane Q test and the I^2 statistic (33, 34). Heterogeneity was categorized as mild ($I^2 < 25\%$), moderate (I^2 25%–75%), or substantial ($I^2 > 75\%$). A random-effects model was applied to pool the results, accounting for potential between-study variability (31). Sensitivity analyses were conducted by omitting one dataset at a time to evaluate the robustness of the findings (33). Predefined univariate meta-regression analyses were performed to assess the modifying effects of study characteristics on the outcomes, including sample size, mean maternal age, mean BMI, and NOS scores. Predefined subgroup analyses explored the influence of study characteristics, such as study design, type of maternal diabetes, mean maternal age, BMI, timing of fEFT measurement, and NOS scores. For subgroup definitions, medians of continuous variables were used as cutoffs. Publication bias was initially evaluated through funnel plot construction and visual assessment of symmetry (35), complemented by Egger's regression test (35). Statistical analyses were performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Study inclusion

The study inclusion process is illustrated in Figure 1. Initially, 168 potentially relevant records were identified through a comprehensive search of the three databases. After removing 25 duplicates, 143 records remained. Screening of titles and abstracts excluded 123 studies, primarily because they did not align with the objectives of the meta-analysis. The full texts of the remaining 20 records were then assessed independently by two authors, leading to the exclusion of 10 studies for reasons detailed in Figure 1. Ultimately, 10 observational studies were deemed eligible for inclusion in the quantitative analysis (21-28, 36, 37).

Summary of study characteristics

Table 1 summarizes the characteristics of the included studies. In total, 10 observational studies were included, comprising six case-control studies (23, 24, 26-28, 36) and four cross-sectional studies (21, 22, 25, 37). These studies were published between 2016 and 2023 and were conducted in Turkey (22, 24, 27, 28, 36), the United States (21, 23), and India (25, 26, 37). Two studies (27, 28) provided separate datasets for women with GDM and PDM, resulting in 12 datasets included in the meta-analysis. A total of 1,303 women with singleton pregnancies were analyzed, with mean maternal ages ranging from 25.6 to 35.8 years and mean BMI from 27.9 to 31.3 kg/m². The ultrasonic methods for measuring fEFT varied among the included studies, (e.g., left ventricular outflow tract, four-chamber, or apical views) and reference points for defining fEFT thickness, which are described in detail in **Table 1**. The median GA for ultrasound assessment of fEFT ranged from 20.0 to 34.5 weeks. Six studies included women with GDM (22, 24-26, 36, 37), one study included women with PDM (21), and three studies included both GDM and PDM populations (23, 27, 28). In all included studies, potential confounding factors, such as GA at the time of fEFT measurement, were matched between women with and without diabetes during pregnancy. The quality of the included studies, assessed using the Newcastle-Ottawa Scale (NOS), ranged from seven to nine stars, indicating overall good methodological quality (Table 2).

Results of overall meta-analysis and sensitivity analysis

Moderate heterogeneity was observed among the included studies (I^2 = 69%). Using a random-effects model, the pooled analysis demonstrated that fEFT was significantly greater in women with DM during pregnancy compared to those without DM (MD: 0.37 mm, 95% CI: 0.26 to 0.49, $p < 0.001$; Figure 2A). Sensitivity analyses, performed by excluding one dataset at a time, confirmed the robustness of the results (MD range: 0.32 to 0.40, all $p < 0.05$).

Results of the meta-regression analysis

Univariate meta-regression analysis indicated a positive correlation between median GA at fEFT measurement and the fEFT difference between women with and without DM during pregnancy (coefficient = 0.040, p = 0.005; Table 3 and Figure 2B), explaining a substantial proportion of heterogeneity (Adjusted R^2 = 83.2%). Other variables, such as sample size, mean maternal age, mean maternal BMI, and NOS scores, did not show significant effects (all $p > 0.05$; Table 3).

Results of the subgroup analysis

Subgroup analyses revealed consistent effects of maternal DM on fEFT across study designs (case-control and cross-sectional, p for subgroup difference = 0.18; Figure 3A), types of maternal DM (GDM and PDM, p for subgroup difference = 0.55; Figure 3B), mean maternal age categories (< 29 years vs. ≥ 29 years, p = 0.69; Figure 4A), and maternal BMI categories (< 30 kg/m² vs. ≥ 30 kg/m², p = 0.59; Figure 4B). However, subgroup analysis by GA for fEFT measurement showed a significantly greater increase in fEFT in studies with GA > 26 weeks compared to those with GA ≤ 26 weeks (0.54 mm vs. 0.23 mm, p for subgroup difference = 0.002; Figure 5A). Similar findings were observed in studies with varying NOS scores (p for subgroup difference = 0.09; Figure 5B).

Publication bias

Figure 6 presents the funnel plots for the meta-analysis evaluating the difference in fEFT between women with and without DM during pregnancy. The plots appear symmetrical upon visual inspection, suggesting a low risk of publication bias. This observation is further supported by Egger's regression test, which did not indicate significant publication bias (p = 0.58).

DISCUSSION

The results of this meta-analysis reveal a significant association between maternal DM during pregnancy and increased fEFT, with a mean difference of 0.37 mm compared to pregnancies without DM. This finding was consistent across sensitivity analyses, with moderate heterogeneity observed. Meta-regression analysis identified GA at the time of fEFT measurement as a significant source of heterogeneity, suggesting that the impact of maternal DM on fEFT becomes more pronounced as pregnancy progresses. Subgroup analyses further demonstrated consistent results across various study designs, maternal demographic factors, and study quality, underscoring the robustness of the observed association.

The influence of maternal DM on fEFT can be attributed to several pathophysiological mechanisms. Hyperglycemia-induced fetal hyperinsulinemia plays a central role, as elevated insulin levels stimulate the

proliferation and hypertrophy of adipocytes, leading to increased fat deposition (38). Insulin acts as a growth-promoting hormone during fetal development, with high levels directly influencing the differentiation of preadipocytes into mature adipocytes, particularly in metabolically active depots such as epicardial fat (39). Epicardial fat, due to its proximity to the myocardium and coronary arteries, has a unique metabolic profile characterized by high lipolytic activity and the secretion of pro-inflammatory cytokines and adipokines (40). These characteristics make it particularly susceptible to the metabolic alterations associated with maternal DM. Additionally, maternal DM is associated with systemic inflammation and oxidative stress, which may exacerbate adipogenesis and impair normal fat distribution in the fetus (41). Hyperglycemia triggers the overproduction of reactive oxygen species (ROS) (42) and activates pro-inflammatory pathways such as nuclear factor-κB (NF-κB) (43). These processes lead to the upregulation of inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which can further promote adipose tissue expansion and dysfunction (44). In the fetal environment, these inflammatory signals may enhance the deposition of epicardial fat by promoting local adipocyte proliferation and hypertrophy (45). Maternal DM also affects placental function, further contributing to increased fEFT (46). The placenta acts as a mediator of nutrient transfer and endocrine signaling between the mother and fetus (47). In pregnancies complicated by DM, placental abnormalities such as increased vascular resistance and reduced mitochondrial function have been observed (47). These changes can alter the supply of glucose and lipids to the fetus, favoring excessive energy availability and fat deposition (47). Moreover, maternal hyperglycemia can upregulate placental transporters for glucose and fatty acids, leading to an increased flux of these substrates to the fetus and subsequent adipogenesis in depots such as epicardial fat (48). Finally, epigenetic modifications may also play a role in the influence of maternal DM on fEFT. Chronic hyperglycemia during pregnancy can induce changes in DNA methylation, histone modification, and non-coding RNA expression in the developing fetus (49). These epigenetic alterations can affect the expression of genes involved in adipogenesis and metabolism, potentially predisposing the fetus to increased fat deposition and cardiometabolic dysfunction later in life (50). Studies have demonstrated altered methylation patterns in genes regulating insulin signaling and lipid metabolism in offspring of diabetic pregnancies, which may contribute to the observed increase in fEFT (51, 52).

The results of the meta-regression and subgroup analyses offer important insights into the timing and magnitude of maternal DM's effects on fEFT. The positive correlation between GA and fEFT differences suggests that later gestation may represent a critical period for the influence of maternal DM on fetal adiposity. This finding has clinical implications, as it highlights the importance of early and sustained glycemic control throughout pregnancy to minimize the impact on fetal development (53). The consistency of results across study designs, maternal age, BMI, and study quality indicates that the observed association is robust and not confounded by these factors. This reinforces the validity of fEFT as a marker for assessing

the effects of maternal DM on fetal development. In addition, although our subgroup analysis did not reveal a significant difference in the effect of GDM versus PDM on fEFT, we acknowledge that these two conditions have distinct metabolic characteristics and may exert differential influences on fetal development (54). However, the shared pathophysiological pathways, including hyperglycemia-induced fetal hyperinsulinemia and inflammatory processes, likely contribute to similar changes in fEFT (55). Further studies are warranted to explore potential variations in fEFT progression between GDM and PDM pregnancies, particularly in relation to glycemic control and disease severity.

This meta-analysis has several strengths. It represents a comprehensive and up-to-date synthesis of the literature, incorporating data from multiple observational studies with matched or adjusted GA to ensure comparability. Rigorous methodological approaches, including sensitivity, subgroup, and meta-regression analyses, were employed to explore heterogeneity and identify key modifiers of the observed association (56). These analyses enhance the reliability of the findings and provide valuable insights into the factors influencing fEFT in pregnancies complicated by DM. Moreover, the inclusion of studies with high methodological quality, as assessed by the NOS scores, further supports the robustness of the results.

Despite these strengths, several limitations must be acknowledged. First, the meta-analysis included only observational studies, which are inherently subject to residual confounding despite adjustments for key variables (57). Second, unmeasured factors, such as maternal diet, physical activity, and genetic predispositions, may have influenced the results (58). Third, the study-level nature of the analysis limits the ability to explore individual-level data and precludes causal inferences. Additionally, while GA emerged as a significant modifier, the underlying mechanisms and precise role of GA in the observed association warrant further investigation. Another potential limitation is the variation in diagnostic criteria for GDM across the included studies. Most studies applied the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria (22-24, 26-28, 36, 37), while one study used the Diabetes In Pregnancy Study group India (DIPSI) criteria (25). Differences in diagnostic thresholds may introduce variability in the classification of GDM, potentially affecting the pooled estimates (59). However, due to the limited number of included studies, we were unable to assess the impact of these variations. Future meta-analyses incorporating a larger number of studies may allow for a more detailed evaluation of the influence of different GDM diagnostic criteria on fEFT. Finally, the included studies used different ultrasound techniques for fEFT measurement. These methodological differences may have contributed to heterogeneity in our meta-analysis. However, due to the absence of a standardized protocol for fEFT assessment, future studies should aim to establish uniform measurement criteria to enhance comparability across studies. The findings of this meta-analysis have potentially important clinical implications. Our findings suggest that

increased fEFT may serve as an early indicator of fetal metabolic risk in pregnancies complicated by diabetes. Given its non-invasive nature, ultrasound-based fEFT assessment could be integrated into prenatal screening protocols to identify fetuses at risk of metabolic complications (60). Furthermore, optimizing maternal glycemic control may help mitigate excessive fetal fat accumulation, potentially improving long-term cardiometabolic health in offspring (12). Future studies should explore standardized thresholds for fEFT measurement and its predictive value in clinical practice. Routine assessment of fEFT in pregnancies complicated by DM could provide valuable information for risk stratification and guide targeted interventions to optimize fetal outcomes (61). The identification of GA as a key modifier underscores the need for close monitoring during later gestation, particularly in women with poor glycemic control. Although increased fEFT has been suggested as a marker of fetal metabolic compromise, including macrosomia (62), we were unable to assess its direct relationship with these outcomes due to limited available data. Future studies should explore whether fEFT could serve as an early predictor of fetal overgrowth and metabolic dysfunction, particularly in pregnancies complicated by diabetes. Future research should focus on elucidating the long-term implications of increased fEFT on offspring health and exploring interventions to mitigate these effects (63). Longitudinal studies investigating the trajectory of fEFT from fetal to postnatal life and its association with cardiometabolic outcomes in offspring would be particularly informative (63). Additionally, randomized controlled trials evaluating the effects of glycemic control and other maternal interventions on fEFT and offspring outcomes could provide critical insights into causal pathways and potential strategies for prevention.

CONCLUSION

In conclusion, this meta-analysis demonstrates that maternal DM during pregnancy is associated with increased fEFT, with the effect becoming more pronounced in later gestation. These findings highlight the importance of glycemic control and targeted monitoring in diabetic pregnancies to mitigate long-term cardiometabolic risks in offspring. Further research is needed to clarify the mechanisms underlying this association and to explore the clinical utility of fEFT as a prognostic marker in this high-risk population.

Conflicts of interest: Authors declare no conflict of interest.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Design	No. of women included	Maternal age (years)	Maternal BMI (kg/m^2)	fEFT measuring timing	Methods for fEFT measuring	Median GA of fEFT measuring (weeks)	Type of maternal diabetes	No. of women with DM	Variables matched or adjusted
Yavuz 2016	Turkey	CS	80	27.7	27.9	GA: 24-28 weeks	Via ultrasound at end-diastole over 3 cardiac cycles from the RV wall, recording the highest value per cycle	26	GDM (IADPSG)	40	Maternal age, BMI, GA, fetal gender, and fetal abdominal circumference
Jackson 2016	USA	CS	56	28.8	30.8	GA: 20-28 weeks	Via ultrasound using LVOT views near the aortic valve, selecting the image that best	23.5	PDM	28	Maternal age, BMI, GA, and fetal abdominal circumference

							delineated the epicardial fat border				
Akkurt 2018	USA	CC	212	29.2	31.3	GA: 24-35 weeks	Via ultrasound using the LVOT view, identifying the hypoechogenic fat layer over the RV, and measuring the thickest point near a reference line drawn through the descending aorta and aortic annulus	28.2	GDM (IADPSG)	106	Maternal BMI, parity, ethnicity, GA, fetal sex, and fetal abdominal circumference
Aydin 2020	Turkey	CC	120	32.1	29	GA: 18-22 weeks	Via ultrasound using the standardized four-chamber view, measuring fEFT at the midpoint of the ventricular wall	20	GDM (IADPSG)	60	Maternal age, BMI, GA, and fetal abdominal circumference

Iskender 2022	Turkey	CC	80	28	29.1	GA: 28-39 weeks	Via ultrasound using the apical five-chamber view, measuring the hypoechoic area on the free wall of the RV with a reference line drawn from the descending aorta through the aortic annulus	34.5	GDM (IADPSG)	40	Maternal age, gravidity, and GA
Baria 2023	India	CS	70	35.8	NR	GA: 24-28 weeks	Via ultrasound using the LVOT view, identifying the hypoechogenic area between the visceral pericardium and myocardium along the right ventricle, measured	26	GDM (DIPSI)	35	Maternal age and GA

							during end-systole				
Ghuman 2023	India	CC	70	25.6	NR	GA: 24-32 weeks	Via ultrasound using a standardized four-chamber view at end-diastole over three cardiac cycles, measuring the hypoechoic space just outside the myocardium on the right ventricular free wall	28	GDM (IADPSG)	35	Maternal age, BMI, and GA
Omeroglu 2023 GDM	Turkey	CC	135	29	30.4	GA: 28-39 weeks	Via ultrasound using the LVOT view, measuring the hypoechoic area between the myocardium and visceral pericardium on the RV	32	GDM (IADPSG)	90	GA

Omeroglu 2023 PDM	Turkey	CC	90	28	29.9	GA: 28-39 weeks	Via ultrasound using the LVOT view, measuring the hypoechoic area between the myocardium and visceral pericardium on the RV	32	PDM	45	GA
Singh 2023	India	CS	60	26.4	NR	GA: 24-28 weeks	Via ultrasound using the LVOT view, measuring the hypoechoic area between the visceral pericardium and myocardium along the right ventricle at end-diastole	26	GDM (IADPSG)	30	Maternal age and GA
Sever 2023	Turkey	CC	165	29.9	30	GA: 24-28 weeks	Via ultrasound using cardiac long-axis views	26	GDM (IADPSG)	110	Maternal BMI, GA, parity,

GDM							of the LVOT near the aortic valve, measuring the thickest hypoechoic area at end-diastole				gravidity, and fetal sex
Sever 2023 PDM	Turkey	CC	165	30.6	30.1	GA: 24-28 weeks	Via ultrasound using cardiac long-axis views of the LVOT near the aortic valve, measuring the thickest hypoechoic area at end-diastole	26	PDM	110	Maternal BMI, GA, parity, gravidity, and fetal sex

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

	Adequate definition of the cases	Representativeness of the cases	Selection of Controls	Definition of Controls	Controlled for GA	Controlled for other confoundings	Ascertainment of the exposure	Same method of ascertainment of exposure for cases and controls	Non-response rate	Overall
Yavuz 2016	1	0	1	1	1	1	1	1	1	8
Jackson 2016	1	1	1	1	1	1	1	1	1	9
Akkurt 2018	0	0	1	1	1	1	1	1	1	7
Aydin 2020	1	1	1	1	1	1	1	1	1	9
Iskender	1	1	1	1	1	1	1	1	1	9

2022										
Baria 2023	1	0	1	1	1	1	1	1	1	8
Ghuman 2023	1	0	1	1	1	1	1	1	1	8
Omeroglu 2023 GDM	1	0	1	1	1	0	1	1	1	7
Omeroglu 2023 PDM	1	0	1	1	1	0	1	1	1	7
Singh 2023	1	0	1	1	1	1	1	1	1	8
Sever 2023 GDM	1	0	1	1	1	1	1	1	1	8
Sever 2023 PDM	1	0	1	1	1	1	1	1	1	8

Table 3. Results of univariate meta-regression analysis

Variables	MD of fEFT between women with and without DM in pregnancy			
	Coefficient	95% CI	p values	Adjusted R^2
Sample size	-0.00061	-0.00360 to 0.00237	0.65	-14.9%
Mean maternal age (years)	0.0035	-0.0614 to 0.0684	0.91	-14.5%
Mean maternal BMI (kg/m^2)	0.041	-0.111 to 0.194	0.56	-10.8%
Median GA at fEFT measuring (weeks)	0.040	0.015 to 0.066	0.005	83.2%
NOS	-0.15	-0.32 to 0.03	0.09	28.7%

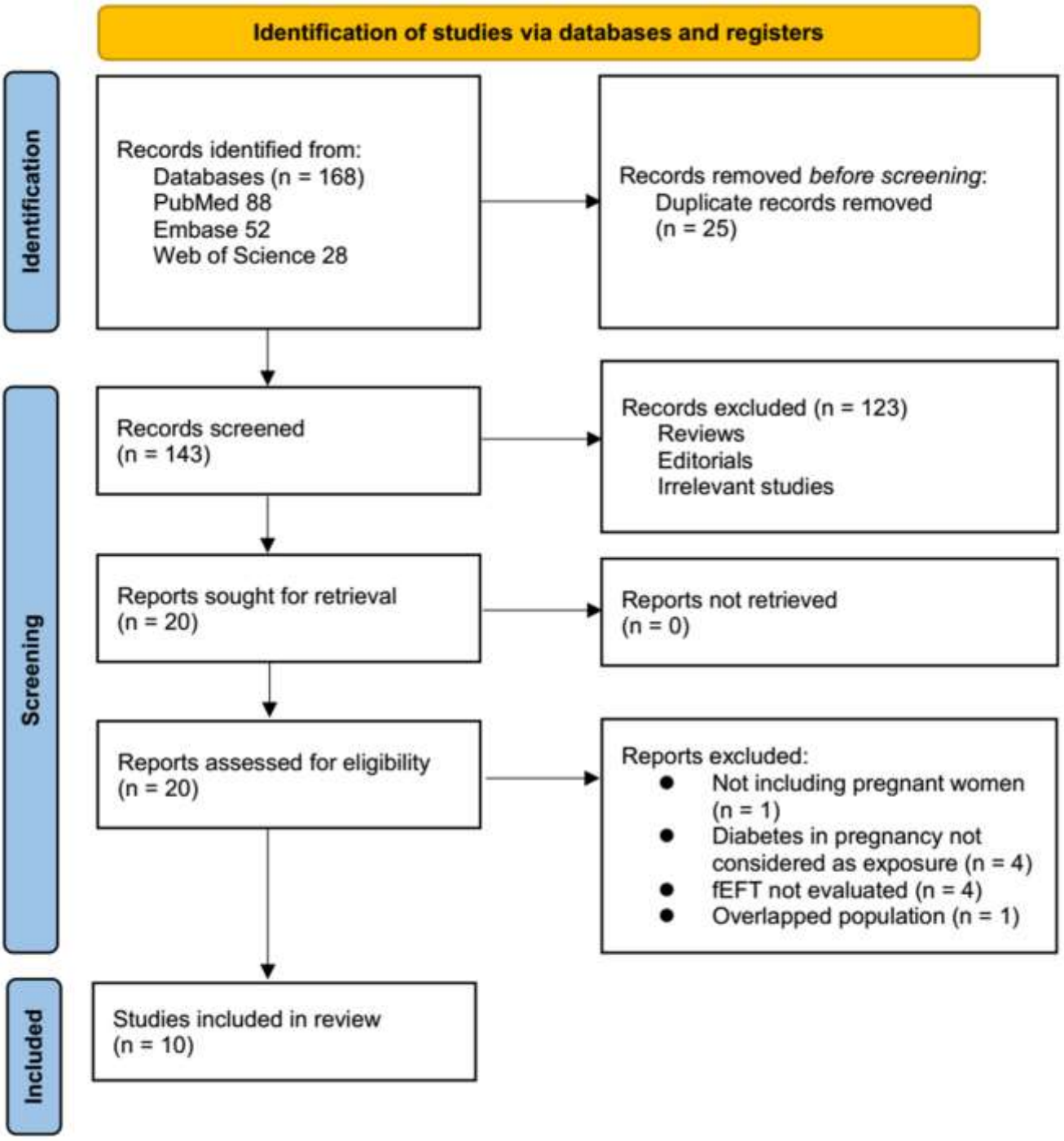
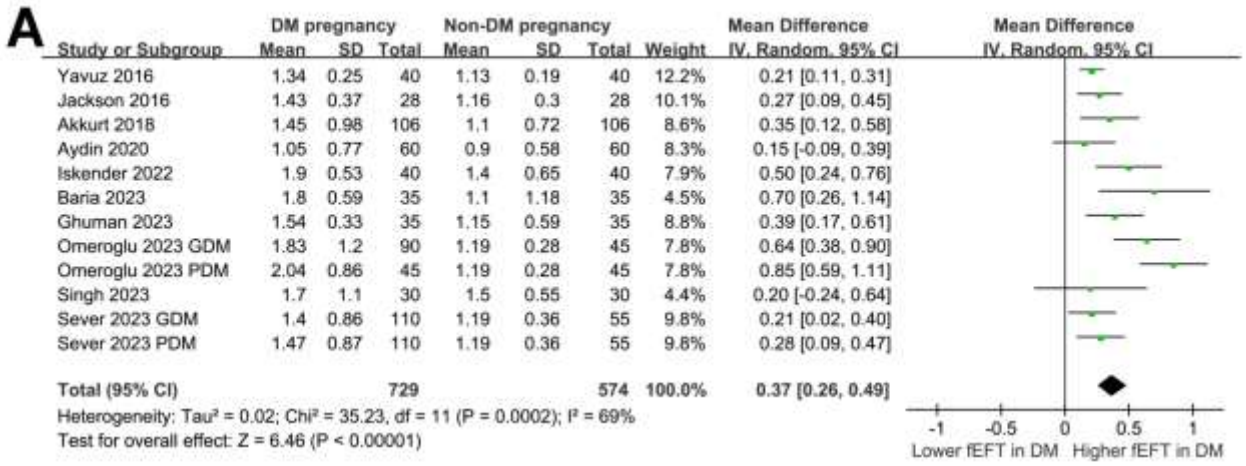


Figure 1. Flowchart illustrates the process of database search and study identification



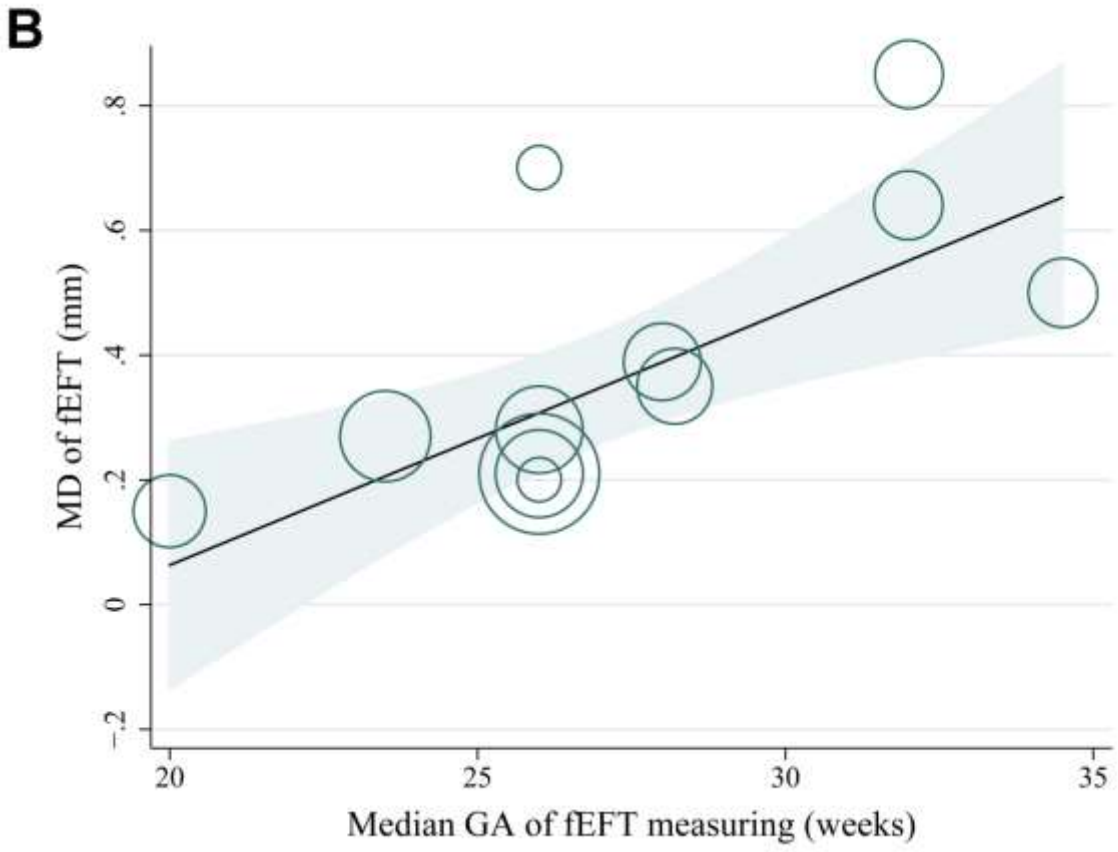


Figure 2. Forest plots for the meta-analysis comparing fEFT between women with and without DM in pregnancy and plots of the meta-regression analysis for the influence of GA of fEFT assessment; A, forest plots for the overall meta-analysis; and B, meta-regression for the influence of GA of fEFT assessment on the results;

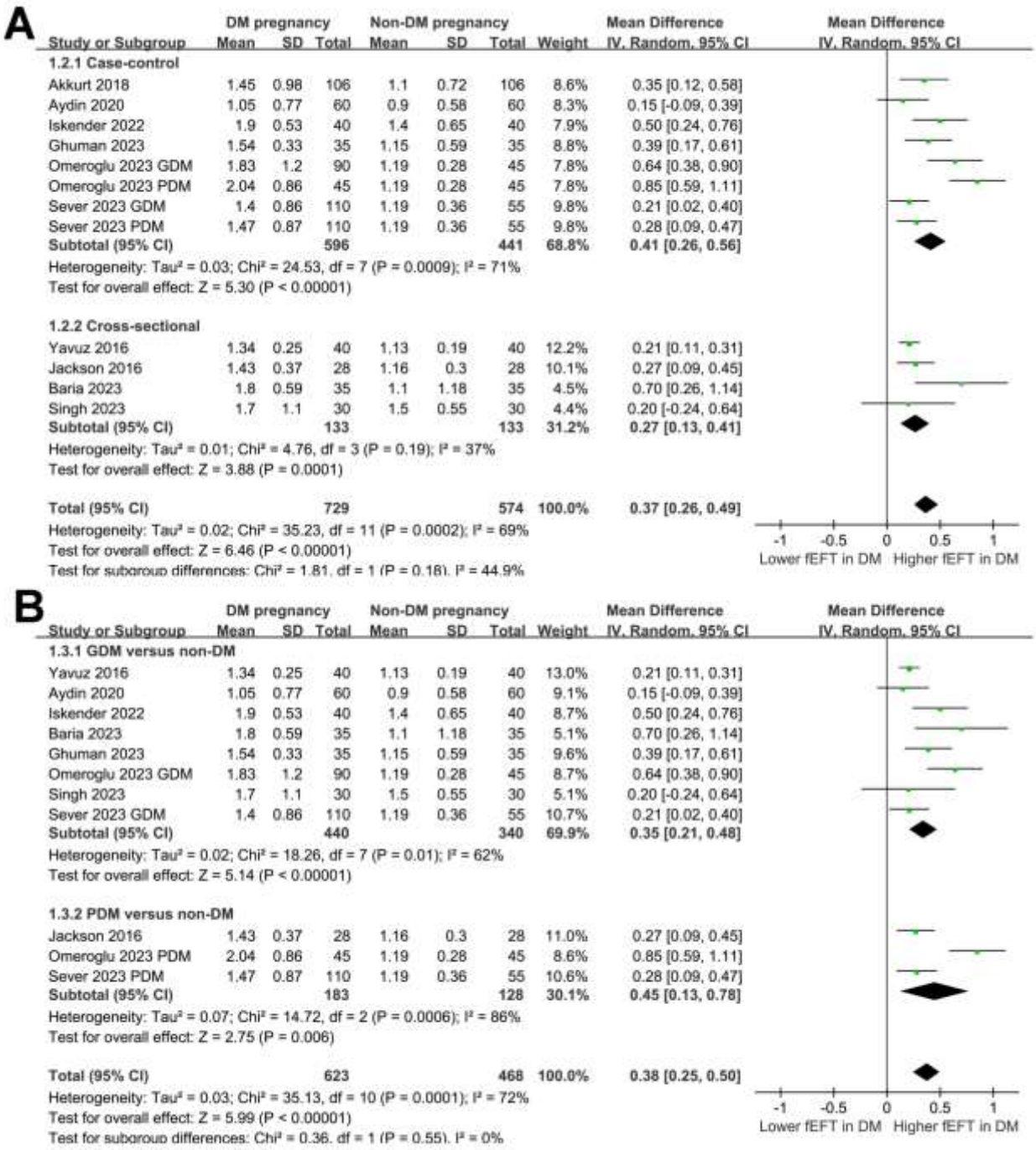


Figure 3. Forest plots for the subgroup analyses comparing fEFT between women with and without DM in pregnancy; A, subgroup analysis according to study design; and B, subgroup analysis according to the type of DM in pregnancy;

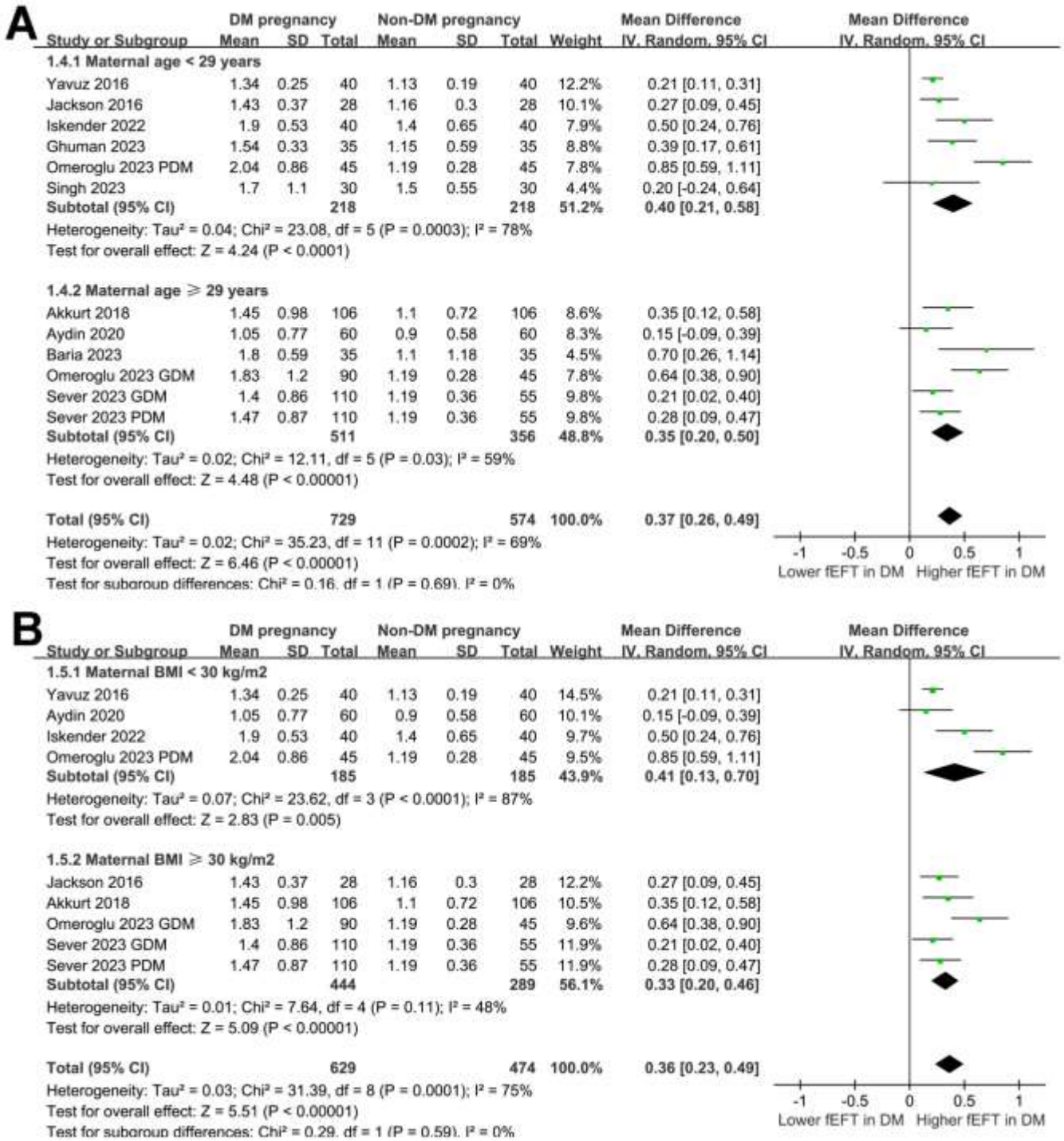


Figure 4. Forest plots for the subgroup analyses comparing fEFT between women with and without DM in pregnancy; A, subgroup analysis according to the mean maternal age; and B, subgroup analysis according to the mean maternal BMI;

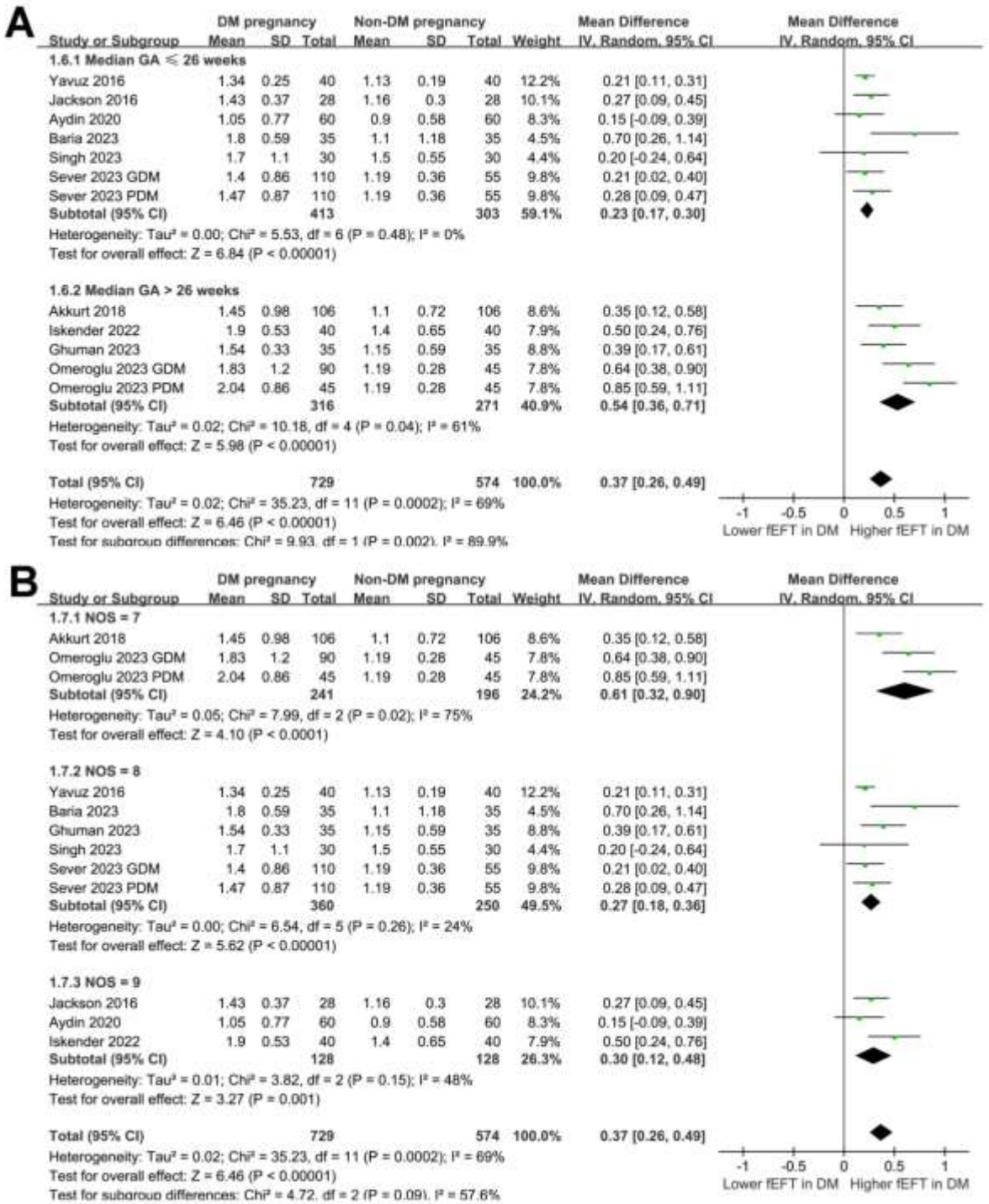


Figure 5. **Forest plots for the subgroup analyses comparing fEFT between women with and without DM in pregnancy**; A, subgroup analysis according to the median GA of fEFT measurement; and B, subgroup analysis according to the NOS scores;

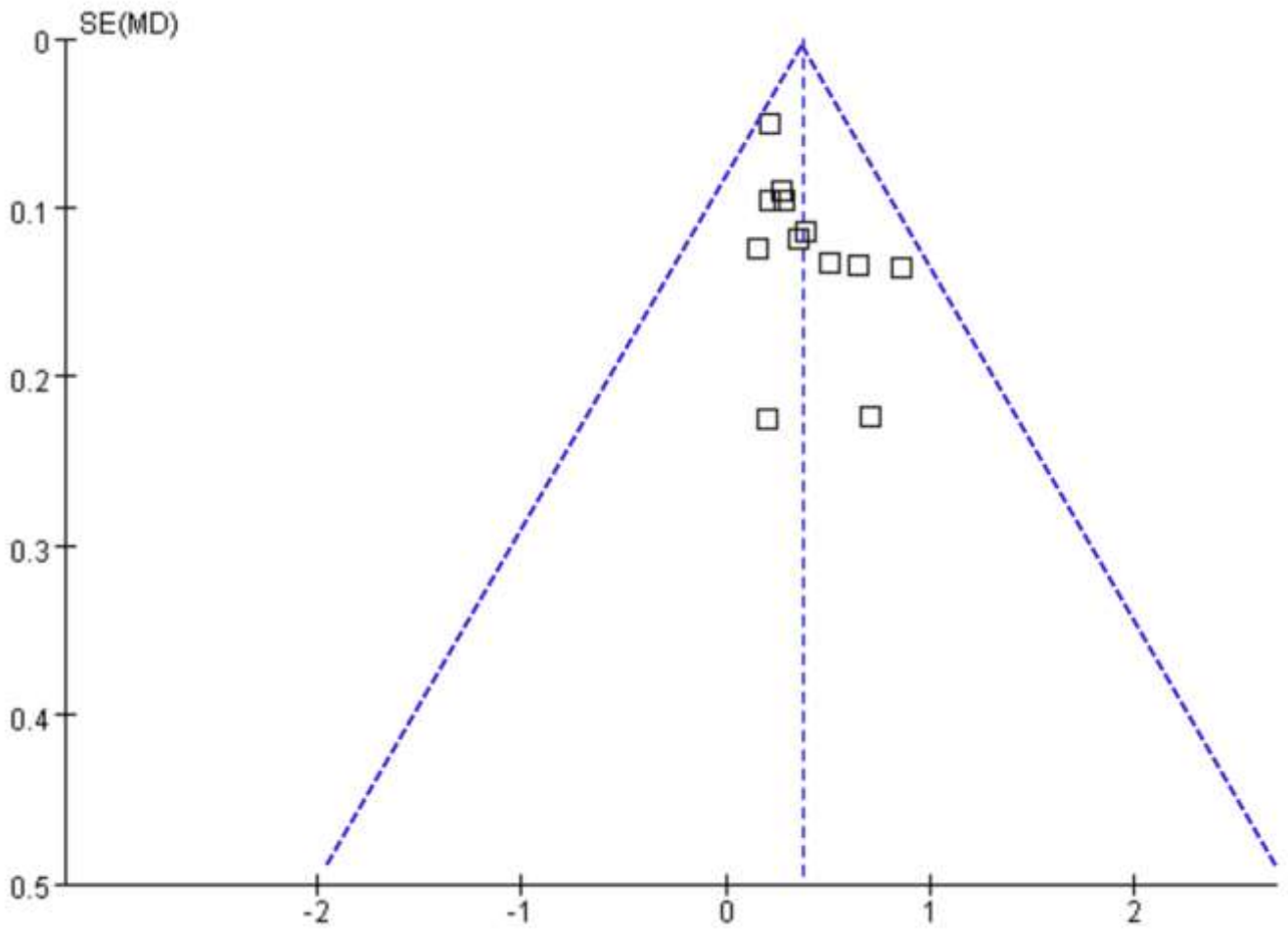


Figure 6. Funnel plots for evaluating the possible publication bias of the meta-analysis comparing fEFT between women with and without DM in pregnancy.

SUPPLEMENTAL DATA

PubMed from inception to November 12, 2024

#	Searches	Results
1	"epicardial adipose tissue"[MeSH] OR "epicardial adipose tissue" OR "epicardial fat" OR "pericardial adipose tissue" OR "pericardial fat" OR "cardiac adipose tissue" OR "cardiac fat" OR "subepicardial adipose tissue" OR "subepicardial fat" OR "heart fat" OR "heart adipose tissue"	**1553**
2	("gestational diabetes"[MeSH] OR "gestational diabetes" OR "GDM" OR "pregestational diabetes" OR (("gestational" OR "pregnancy"[MeSH] OR "pregnant" OR "pregestational") AND ("diabetes"[MeSH] OR "diabetic" OR "hyperglycemia"[MeSH]))	**3736**
3	1 and 2	**88**

Embase from inception to November 12, 2024

#	Searches	Results
1	'epicardial adipose tissue'/exp OR 'epicardial adipose tissue' OR 'epicardial fat' OR 'pericardial adipose tissue' OR 'pericardial fat' OR 'cardiac adipose tissue' OR 'cardiac fat' OR 'subepicardial adipose tissue' OR 'subepicardial fat' OR 'heart fat' OR 'heart adipose tissue'	**7542**
2	'gestational diabetes mellitus'/exp OR 'gestational diabetes' OR 'GDM' OR 'pregestational diabetes' OR ('gestational' OR 'pregnancy'/exp OR 'pregnant' OR 'pregestational') AND ('diabetes'/exp OR 'diabetic' OR	**31262**

	'hyperglycemia'/exp)	
3	1 and 2	**68**
4	Limit 3 to human	**62**
5	Limit 4 to clinical study	**60**
6	Limit 5 to Embase	**52**

Web of Science from inception to November 12, 2024

#	**Searches**	**Results**
1	TS="epicardial adipose tissue" OR "epicardial fat" OR "pericardial adipose tissue" OR "pericardial fat" OR "cardiac adipose tissue" OR "cardiac fat" OR "subepicardial adipose tissue" OR "subepicardial fat" OR "heart fat" OR "heart adipose tissue"	**5714**
2	TS="gestational diabetes" OR "GDM" OR "pregestational diabetes" OR ("gestational" OR "pregnancy" OR "pregnant" OR "pregestational") AND ("diabetes" OR "diabetic" OR "hyperglycemia")	**11312**
3	1 and 2	**28**