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# Significance of cell adhesion molecules profile during pregnancy in gestational diabetes mellitus. A systematic review and meta-analysis

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ABSTRACT

Endothelial dysfunction has been considered as a key etiological factor contributed to the development of vascular disease in diabetes mellitus. Serum level of endothelial cell adhesion molecules (AMs) were reported to be increased in GDM and pregnant women with normal glucose tolerance when compared with nonpregnant women. The literature provides limited evidence of endothelial dysfunction in GDM with heterogeneous and contradictory results respect to their possible involvement in maternal, perinatal and future complications. Our objective is to evaluate current evidence on the role of AMs in maternal and perinatal complications in women with GDM. PubMed, Embase, Web of Science, and Scopus databases were searched. We evaluated the studies' quality using the Newcastle-Ottawa scale. Meta-analyses were conducted, and heterogeneity and publication bias were examined. Nineteen relevant studies were finally included, recruiting 765 GDM and 2368 control pregnant women. AMs levels were generally higher in GDM participants showing statistical significance maternal ICAM-1 levels (SMD = 0.58, 95% CI = 0.25 to 0.91; p = 0.001). Our meta-analysis did not detect significant differences in subgroups or in meta-regression analyses. Future studies are needed to establish the potential role of these biomarkers in GDM and its complications.

## 1. Introduction

Gestational diabetes mellitus (GDM) complicates about 1–14 % of all pregnancies worldwide [1]. Mothers with GDM are at increased risk of preterm birth, preeclampsia, instrumental delivery, type 2 diabetes mellitus (T2DM) and cardiovascular disease in the future [2–4]. In infants, GDM causes macrosomia, shoulder dystocia, prolonged labour, postpartum hypoglycaemia, and metabolic diseases such as obese and impaired glucose tolerance and T2DM in their early adulthood [5,6].

It has been considered that endothelial dysfunction is a key etiological factor contributing to the development of moderate and severe cardiovascular disease (CVD), mediated by adhesion molecules (AMs) in diabetes mellitus (DM), since classical risk factors including hyperlipidemia and hypertension do not completely account for the increased incidence of atherosclerosis in these patients [7]. Similarly, in GDM, hyperglycemia and increased insulin resistance causes endothelial dysfunction and leads to the development of vascular disorders. Abnormal vascular endothelial function in small arteries of women with GDM have been demonstrated, and that could be related to the high incidence of cardiovascular morbidity [8]. Endothelial expression of some markers activates the adhesion of monocyte to the endothelium, an early event in the development of atherosclerosis [9]. Serum level of endothelial AMs were reported to be increased in GDM and pregnant women with normal glucose tolerance when compared with nonpregnant women [10]. Significantly higher plasma concentrations of soluble VCAM-1 and ICAM-1 as well as cord blood VCAM-1 levels were also found in GDM women compared with nondiabetic women [11], and, elevated plasma levels of VCAM-1, ICAM-1 and E-selectin are reported to be independent predictors of T2DM in initially healthy women [12].

The purpose of this systematic review and meta-analysis is to define

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the current evidence on maternal circulating AMs levels during pregnancy in GDM and cord blood, as biochemical mediator associated with its pathophysiology and their potential use as risk markers for GDM development.

## 2. Material and methods

This systematic review and meta-analysis complied with *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) and *Meta-analysis of Observational Studies in Epidemiology* (MOOSE) guidelines [13,14], and closely followed the criteria of *Cochrane Handbook for Systematic Reviews of Interventions* [15].

### 2.1. Protocol

In order to minimize the risk of bias and improve the transparency, precision, and integrity of this study, a protocol on its methodology was *a priori* registered in PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO, registration code CRD42020161141) [16]. The protocol adhered to PRISMA-P statement to ensure a rigorous approach [17].

### 2.2. Search strategy

We searched MEDLINE (through PubMed), Embase, Web of Science and Scopus databases for studies published before the search date (upper limit = November-2021), with no lower date limit. Searches were conducted by combining thesaurus terms used by the databases (i.e., MeSH and EMTREE) with free terms (Table S1), and built to maximize sensitivity. We also manually screened the reference lists of retrieved studies for additional relevant studies. All references were managed using Mendeley Desktop v.1.19.8 (Elsevier. Amsterdam, The Netherlands); duplicate references were eliminated using this software.

### 2.3. Eligibility criteria

Inclusion criteria: 1) Original research from primary-level studies without publication language or date, follow up periods, geographical area or age restrictions; 2) GDM subjects compared to pregnant women without GDM as control group; 3) AMs levels evaluation from maternal/cord plasma or serum; 4) Observational study design, regardless of its cross-sectional/longitudinal study design or prospective/retrospective nature; 5) The names and affiliations of authors, recruitment period and settings were examined to determine whether studies were conducted in the same study population. In such cases, we included the most recent study or that which published more complete data.

Exclusion criteria: 1) Retracted articles, interventional studies, reviews, meta-analyses, case reports, editorials, letters, abstracts of scientific meetings, personal opinions or comments and book chapters; 2) *In vitro* and animal experimental studies; 3) Studies that do not assess the disease of interest (i.e., GDM), do not study AMs levels, or those without a control group; 4) Studies reporting insufficient data to extract or estimate mean ± standard deviation (SD); 5) Data from overlapping populations.

### 2.4. Study selection process

Eligibility criteria were applied independently by two authors (MMRR and CLT). Discrepancies were resolved by consensus with a third author (PRG). Articles were selected in two phases, first screening the titles and abstracts of retrieved articles in an initial selection, and then reading the full text of the selected articles, excluding those that did not meet the review eligibility criteria.

### 2.5. Data extraction

Two authors (MMRR and CLT) independently extracted data from the selected articles, completing a data collection form in a standardized manner using Excel v. Microsoft Office Proffesional Plus 2013 (Microsoft. Redmond, WA). These data were additionally cross-checked in multiples rounds, solving discrepancies by consensus. Data were gathered on the first author, publication year, study country and continent, language, sample size, source of sample (i.e., maternal or umbilical cord plasma/serum), AMs determination -extracting means ± SD, measuring units, technique and properly quantification - in GDM and controls, GDM criteria, control group criteria, family and personal risk of diabetes, gestational age, study design, control of risk factors during pregnancy (maternal age, gestational and pregestational body mass index (BMI), glucose, insulin, homeostatic model assessment (HOMA), glycosylated haemoglobin (A1cHb), maternal and fetal outcomes, follow-up period and patient loss assessment.

### 2.6. Evaluation of quality and risk of bias

We used the Newcastle-Ottawa quality assessment scale (NOS) to assess the risk of bias [18]. Assessment was conducted by two reviewers independently who had content and methodological expertise (MMRR and CLT). The results were compared and conflicts resolved by agreement between the two reviewers, with input of a third reviewer as necessary. Studies that received a star in each domain were considered to be of high quality. The maximum score was 9, the minimum score 0. It was decided a priori that a score of 8 was reflective of high methodological quality (e.g., low risk of bias), a score of 6 or 7 indicated moderate quality and a score of 5 or less indicated low quality (e.g., high risk of bias).

### 2.7. Statistical analysis

Means ± SD values for AMs levels were extracted from primary-level studies to compare among GDM patients and controls. Since methodological heterogeneity was expected, mainly due to variations in laboratory determination methods (see protocol), the standardized mean difference (SMD) was chosen as effect size measure. SMDs jointly with their corresponding 95% confidence intervals (CI) were estimated applying Hedges'g method to account for small sample bias. Data expressed as order statistics (i.e., medians with interquartile range and/or maximum-minimum values) were computed and transformed into means ± SD using the methods proposed by Luo et al. [19] and Wan et al. [20]. If it was desirable to combine two or more different means ± SD from subgroups into a single group, the method provided by Cochrane Handbook was followed [15]. When data were only expressed graphically the extraction was performed using Engauge-Digitizer 4.1. In the meta-analysis, SMDs with 95%CIs were pooled using the inverse-variance method under a random-effects model (based on the DerSimonian and Laird method), which accounts for the possibility that are different underlying results among study subpopulations (i.e., AMs variations, linked to geographical areas, or related to the inherent heterogeneity of the wide range of experimental methods). Forest plots were constructed to graphically represent the overall effect and for subsequent visual inspection analysis ($p < 0.05$ was considered significant). Statistical heterogeneity was evaluated applying the $\chi 2$-based Cochran's Q test (given its low statistical power, $p < 0.10$ was considered significant) and quantified using Higgins $I^2$ statistic (values of 50–75% were interpreted as moderate-to-high degree of inconsistency across the studies), which estimates what proportion of the variance in observed effects reflects variation in true effects, rather than sampling error [21,22]. Preplanned stratifications (by geographical area, trimester, sample source, study design, and risk of bias) and univariable meta-regression analyses (by age, gestational age, gestational and pregestational BMI, glycemia levels, insulin, HbA1c, HOMA) were

conducted to identify potential sources of heterogeneity and to explore the potential variation of AMs levels on these subgroups [23]. For illustrative purposes, weighted bubble plots were also constructed to graphically represent the fitted meta-regression lines. Furthermore, small study effects analysis was performed through the assessment of funnel plots and the Egger regression test ($p < 0.10$ considered significant) [24,25]. Finally, the meta-analysis of some less studied AMs could not be performed due to the low number of primary-level studies identified and a considerable degree of heterogeneity. In order to allow for a better narrative synthesis, by systematically reviewing the non-meta-analyzed parameters, an albatross plot was constructed to graphically represent these findings [26], providing an approximate examination of their underlying magnitudes of effect. Stata version 16.1 (Stata Corp, USA) was employed for all tests, manually typing the commands syntax (PRG) [27].

## 3. Results

### 3.1. Results of the literature search

The flow diagram (Fig. 1) depicts the identification and selection process of studies. We retrieved a total of 663 records published before November-2021: 204 from MEDLINE/PubMed, 205 from Embase, 138 from the Web of Science and 116 from Scopus. After eliminating duplicates, 375 studies were considered potentially eligible (all the studies excluded and their exclusion criteria were listed in Fig. 1). After screening their titles and abstracts, 50 were selected for full-text reading. After excluding studies that did not meet all eligibility criteria, 19 studies were finally included in the review for qualitative evaluation and quantitative meta-analysis.

### 3.2. Study characteristics

Table 1.1. and Table 1.2. summarize the characteristics of the 19 selected studies comparing the changes in AMs blood levels –maternal and cord blood- on a total of 3133 patients (765 GDM and 2368 control

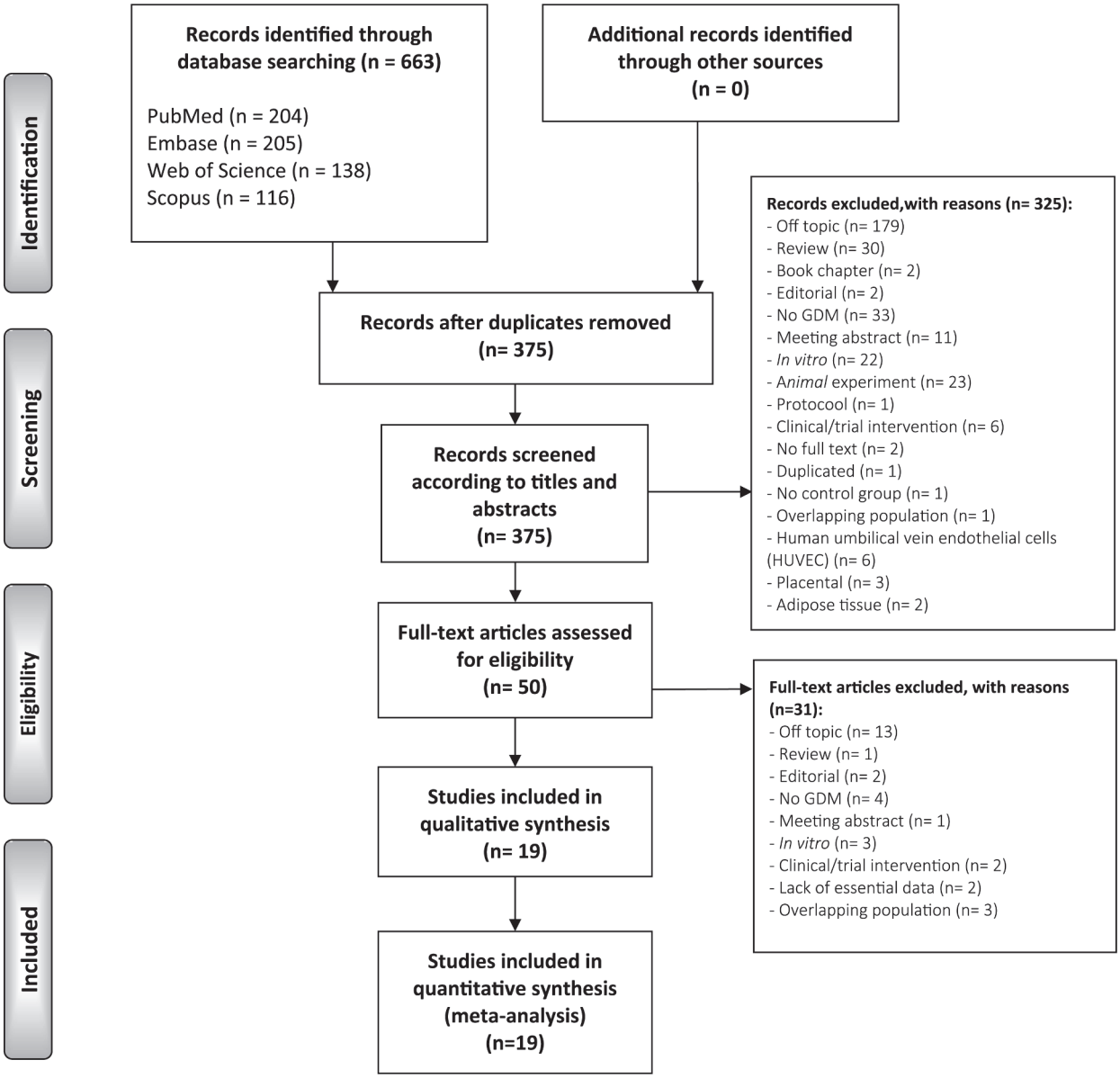


**Fig. 1. Flow diagram.** Identification and selection process of relevant studies comparing AMs levels between GDM patients and controls.

**Table 1.1**
Summarized characteristics of reviewed studies of maternal AMs.

| | VCAM | ICAM | E_Selectin | Syndecam | VAP | CEACAM |
|---|---|---|---|---|---|---|
| Total | 9 studies | 9 studies | 6 studies | 1 study | 1 study | 1 study |
| Year of publication | 1997–2019 | 1997–2019 | 1997–2019 | 2016 | 2019 | 2020 |
| *Number of patients* | | | | | | |
| Total | 1854 patients | 1871 patients | 863 patients | 40 patients | 135 patients | 140 patients |
| GDM | 246 patients | 276 patients | 308 patients | 20 patients | 60 patients | 70 patients |
| Controls | 1608 patients | 1595 patients | 555 patients | 20 patients | 75 patients | 70 patients |
| Sample size, range | 7–1366 patients | 7–1366 patients | 8–248 patients | 20 patients | 60–75 patients | 70 patients |
| *AMs determination* | | | | | | |
| ELISA | 9 studies | 9 studies | 6 studies | 1 study | 1 study | 1 study |
| RIA | 0 studies | 0 studies | 0 studies | 0 studies | 0 studies | 0 studies |
| *Source of samples* | | | | | | |
| Maternal blood serum | 4 studies | 4 studies | 4 studies | 1 studies | 1 study | 1 study |
| Maternal blood plasma | 5 studies | 5 studies | 2 studies | 0 studies | 0 studies | 0 studies |
| Serum or plasma not specified | 0 studies | 0 studies | 0 studies | 0 studies | 0 studies | 0 studies |
| *Geographical region* | | | | | | |
| Europe | 8 studies | 6 studies | 5 studies | 0 studies | 1 study | 0 studies |
| Asia | 1 studies | 2 studies | 1 studies | 0 studies | 0 studies | 1 studies |
| America | 0 studies | 1 studies | 0 studies | 0 studies | 0 studies | 0 studies |
| Oceania | 0 studies | 0 studies | 0 studies | 1 studies | 0 studies | 0 studies |

**Table 1.2**
Summarized characteristics of reviewed studies of cord blood AMs.

| | VCAM | ICAM | E_Selectin |
|---|---|---|---|
| Total | 2 studies | 4 studies | 1 studies |
| Year of publication | 2013–2016 | 2010–2016 | 2016 |
| *Number of patients* | | | |
| Total | 92 patients | 273 patients | 76 patients |
| GDM | 47 patients | 129 patients | 38 patients |
| Controls | 45 patients | 144 patients | 38 patients |
| Sample size, range | 7–38 patients | 7–81 patients | 38 patients |
| *AMs determination* | | | |
| ELISA | 2 studies | 4 studies | 1 studies |
| RIA | 0 studies | 0 studies | 0 studies |
| Source of samples | | | |
| Cord blood serum | 0 studies | 0 studies | 0 studies |
| Cord blood plasma | 1 study | 1 studies | 0 studies |
| Serum or plasma not specified | 1 study | 3 studies | 1 study |
| *Geographical region* | | | |
| Europe | 1 study | 2 studies | 0 studies |
| Australia | Studies | 1 studies | 0 studies |
| America | 1 study | 1 studies | 1 studies |

pregnant women) and Table S2 exhibits in more detail the variables gathered from each study. AMs were quantified by ELISA in both maternal and cord blood. Source of samples in maternal blood were serum in 10 studies and plasma in 6 studies. Source of samples in cord blood were not specified. Sample sizes ranged between 7 and 1366 women. The studies were conducted in all continents except for Antarctica, Africa and South America and comprised the following geographical regions: 12 in Europe, 3 in Asia, 1 in North America, 1 in Central America, 1 in Oceania and 1 in Australia.

### 3.3. Qualitative evaluation

The qualitative analysis was conducted using the Newcastle–Ottawa Scale, which evaluates potential sources of bias in nine domains (Table 2):

In our revision, we only include studies in which the groups of diabetic patients are adequately selected and matched between conditions with their respective controls. Studies without a non-GDM comparator group were excluded. According to the overall Rob the studies were categorized 26.3% as low risk, 63.2% as moderate risk and 10.5% as high risk of potential bias. All studies showed a representativeness of the GDM and control patients (100% and 94.7% defined exactly the diagnostic criteria for GDM and controls, respectively), 100% of studies displayed properly AMs quantification and 94.7% reported an appropriate follow-up period. The analysis revealed that the most frequent biases could be the inadequate description of maternal or fetal outcomes and failure to report on an appropriate follow-up attrition. In this regard, the risk of bias respect to the follow up attrition rate, was elevated in 89.5% of the studies. It is worth highlighting the relevance of declare the lost to the follow-up attrition which are essential data to evaluate any differences on obstetric and perinatal outcomes and on the subsequent follow-up and development of complications in both, the child and the mother.

**Table 2**
Meta-analyses on maternal and cord blood AMs in GDM.

| Meta-analyses | No. of studies | No. of patients | Stat. Model | Wt | Pooled data | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | | | SMD (95% CI) | *P-value* | $P_{het}$ | $I^2$ (%) |
| *Maternal AMs* | | | | | | | | |
| VCAM | 9 | 1854 | REM | D-L | −0.06 (−0.51 to 0.40) | 0.80 | <0.001 | 82.0 |
| ICAM | 9 | 1871 | REM | D-L | 0.58 (0.25 to 0.91) | 0.001 | 0.001 | 68.8 |
| E-selectin | 6 | 863 | REM | D-L | 0.17 (−0.07 to 0.40) | 0.16 | 0.07 | 51.4 |
| Syndecan 1 | 1 | 40 | — | — | 0.34 (−0.28 to 0.97) | 0.28 | — | — |
| VAP1 | 1 | 135 | — | — | 0.99 (0.63 to 1.35) | <0.001 | — | — |
| CEACAM1 | 1 | 140 | — | — | 0.24 (−0.09 to 0.58) | 0.15 | — | — |
| *Cord blood AMs* | | | | | | | | |
| VCAM | 2 | 92 | REM | D-L | 2.19 (−2.17 to 6.55) | 0.33 | <0.001 | 94.2 |
| ICAM | 4 | 273 | REM | D-L | 0.17 (−0.44 to 0.77) | 0.59 | 0.005 | 76.8 |
| E-selectin | 1 | 76 | — | — | 0.16 (−0.29 to 0.61) | 0.48 | — | — |

*Abbreviations*: Stat., statistical; Wt, method of weighting; SMD, standardized mean difference; CI, confidence intervals; REM, random-effects model; D-L, DerSimonian and Laird method; AMs, adhesion molecules; GDM, gestational diabetes mellitus.

### 3.4. Quantitative evaluation

*Meta-analysis on AMs in GDM.* Maternal ICAM levels were significantly higher in GDM participants than in controls showing a relatively medium-large high effect size (SMD = 0.58, 95%CI = 0.25 to 0.91; p = 0.001) (Fig. 2, Table 3) with a moderate degree of heterogeneity (p = 0.001; $I^2$ = 68.8%). The rest of maternal and cord blood AMs meta-analyzed did not show statistically significant differences, although most of them harbored a clear direction of effect (i.e., higher levels in GDM than in controls). Future primary-level studies are needed to confirm if our results of some parameters (e.g., maternal E-selectin or maternal Syndecan1) could be artefactual, due to small underpowered sample sizes presenting type II errors, i.e., false negative results.

*Stratified meta-analyses and univariable meta-regressions.* These analyses were only performed for the maternal AMs, VCAM (Table 3), ICAM (Table 4), and E-selectin (Table 5), which, due to a more competent sample size met better conditions for applicability. Several significant differences were found among subgroups for maternal VCAM (Asian continent: SMD = 0.58, 95% CI = 0.16 to 1.00, p = 0.006; third trimester: SMD = -0.32, 95% CI = −0.57 to −0.07, p = 0.01) and maternal ICAM (European continent: SMD = 0.41, 95% CI = 0.14 to 0.69, p = 0.004; North America: SMD = 2.72, 95% CI = 1.25 to 4.18, p < 0.001; second trimester: SMD = 0.94, 95% CI = 0.41 to 1.47, p = 0.001; third trimester: SMD = 0.29, 95% CI = 0.05 to 0.53, p = 0.02; plasma: SMD = 0.81, 95% CI = 0.22 to 1.39, p = 0.007; serum: SMD = 0.39, 95% CI = 0.12 to 0.66, p = 0.005). On the other hand, significant differences were not found among subgroups and/or study covariates for maternal E-selectin.

*AMs not included in meta-analysis.* Meta-analysis was not performed for maternal Syndecan 1, Maternal VAP1, and for cord blood E-selectin. Results for these AMs were respectively reported by single primary-level studies, and logically could not be pooled with other AMs due to clinical, methodological and statistical heterogeneity. Nevertheless, all AMs analyzed in this systematic review were included in an albatross plot (Fig. 4) and considered separately through visual inspection analysis. Overall these AMs showed heterogeneous magnitudes of effect, and only maternal VAP1 was significantly higher in GDM participants than in controls, showing a large effect size (SMD = 0.99, 95%CI = 0.63 to 1.35; p < 0.001, Fig. 4, Table 2).

*Small-study effects analysis.* The visual inspection analysis of the asymmetry of the funnel plot constructed (Figs. S30-S33, supplementary information) and the statistical tests conducted for the same purpose confirmed the absence of "small-study" effects on the results of this *meta*-analysis (maternal VCAM: $p_{Egger}$ = 0.255; maternal ICAM: $p_{Egger}$ = 0.378; maternal E-selectin: $p_{Egger}$ = 0.803; cord blood ICAM: $p_{Egger}$ = 0.284). Therefore, the presence of biases, singularly publication bias, could be potentially ruled out.

## 4. Discussion

To the best of our knowledge, there are no systematic reviews or meta-analyses in this regard in GDM. This meta-analysis which examined 19 studies and 3133 patients (765 cases and 2368 controls), showed that maternal ICAM-1 levels were significantly higher in GDM

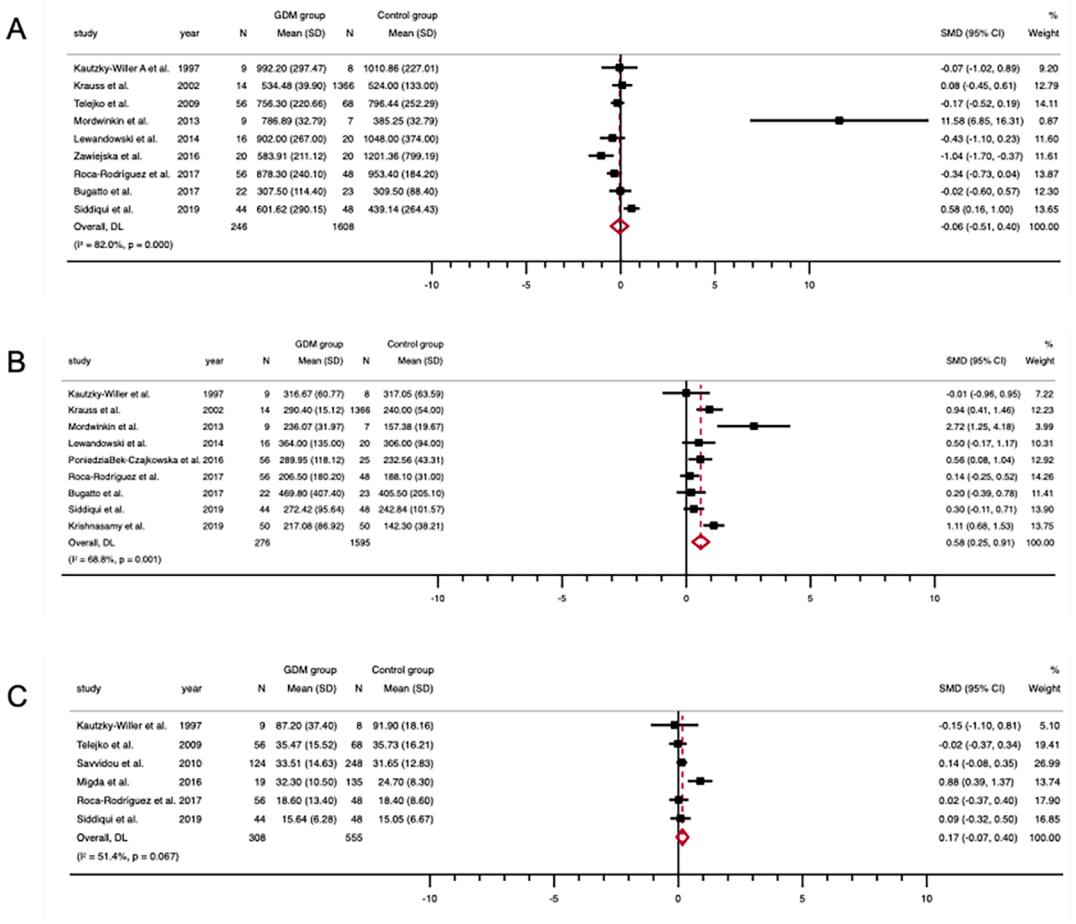


**Fig. 2. Forest plot.** Forest plots graphically representing the *meta*-analysis evaluating the changes in circulating maternal AMs levels (Fig. 2A, maternal VCAM; Fig. 2B, maternal ICAM; Fig. 2C, maternal E-selection) between GDM patients and controls (random-effects model, inverse-variance weighting based on the DerSimonian and Laird method). Standardized mean difference (SMD) was chosen as effect size measure. An SMD > 0 suggests that AMs levels levels are higher in GDM. Diamond indicates the overall pooled SMDs with their corresponding 95% confidence intervals (CI).

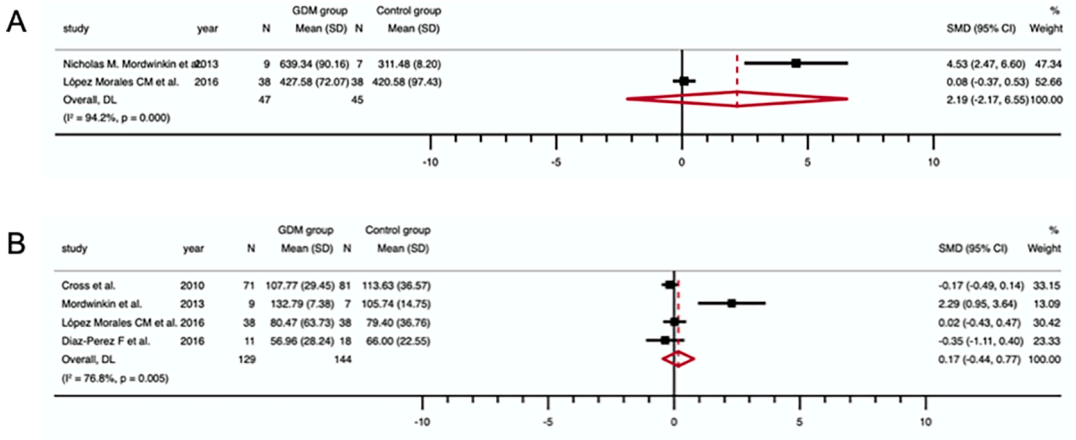


**Fig. 3. Forest plot.** Forest plots graphically representing the meta-analysis evaluating the changes in circulating cord blood AMs levels (Fig. 3A, cord blood VCAM; Fig. 3B, cord blood ICAM) between GDM patients and controls (random-effects model, inverse-variance weighting based on the DerSimonian and Laird method). Standardized mean difference (SMD) was chosen as effect size measure. An SMD > 0 suggests that AMs levels levels are higher in GDM. Diamond indicates the overall pooled SMDs with their corresponding 95% confidence intervals (CI).

**Table 3**
Secondary analyses for Maternal VCAM.

| Meta-analyses | No. of studies | No. of patients | Stat. Model | Wt | Pooled data | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | | | SMD (95% CI) | *P-value* | $P_{het}$ | $I^2$ (%) |
| *Subgroup analysis by Continent*[a] | | | | | | | | |
| Asia | 1 | 92 | —— | —— | 0.58 (0.16 to 1.00) | 0.006 | —— | —— |
| Europe | 8 | 1762 | REM | D-L | −0.17 (−0.64 to 0.29) | 0.47 | <0.001 | 78.4 |
| *Subgroup analysis by trimester*[a] | | | | | | | | |
| Second | 1 | 1380 | —— | —— | 0.08 (−0.45 to 0.61) | 0.77 | —— | —— |
| Third | 6 | 366 | REM | D-L | −0.32 (−0.57 to −0.07) | 0.01 | 0.26 | 23.8 |
| Not reported | 2 | 108 | REM | D-L | 5.82 (−4.95 to 16.59) | 0.29 | <0.001 | 95.2 |
| *Subgroup analysis by sample source*[a] | | | | | | | | |
| Plasma | 5 | 1669 | REM | D-L | 0.08 (−0.56 to 0.72) | 0.81 | <0.001 | 84.3 |
| Serum | 4 | 185 | REM | D-L | −0.22 (−1.02 to 0.58) | 0.59 | <0.001 | 83.7 |
| *Subgroup analysis by study design*[a] | | | | | | | | |
| Prospective | 7 | 1726 | REM | D-L | −0.12 (−0.65 to 0.41) | 0.67 | <0.001 | 81.3 |
| Retrospective | 2 | 128 | REM | D-L | 0.11 (−0.88 to 1.10) | 0.83 | 0.01 | 84.3 |
| *Subgroup analysis by RoB*[a] | | | | | | | | |
| High RoB | 2 | 1396 | REM | D-L | 5.58 (−5.68 to 16.84) | 0.33 | <0.001 | 95.6 |
| Moderate RoB | 6 | 354 | REM | D-L | −0.16 (−0.60 to 0.28) | 0.48 | 0.002 | 73.5 |
| Low RoB | 1 | 104 | —— | —— | −0.34 (−0.73 to 0.04) | 0.08 | —— | —— |
| *Univariable meta-regression*[b] | | | | | | | | |
| Gestational age in GDM (weeks) | 7 | 1,746 | random-effects meta-regression | | Coef = −0.034 (−0.136 to 0.068) | 0.39 ± 0.005[c] | $het_{explained}$= −42.60%[d] | |
| Age in GDM (years) | 6 | 418 | random-effects meta-regression | | Coef = 0.051 (−0.240 to 0.343) | 0.58 ± 0.005[c] | $het_{explained}$= −7.39%[d] | |
| Pregestational BMI in GDM (summary index score) | 6 | 418 | random-effects meta-regression | | Coef = 0.065 (−0.033 to 0.164) | 0.16 ± 0.004[c] | $het_{explained}$= 51.07%[d] | |
| Gestational BMI in GDM (summary index score) | 5 | 326 | random-effects meta-regression | | Coef = 0.035 (−0.204 to 0.274) | 0.58 ± 0.005[c] | $het_{explained}$= 0.00%[d] | |
| Glycemia levels in GDM (mmol/l) | 6 | 418 | random-effects meta-regression | | Coef = 0.299 (0.037 to 0.562) | 0.12 ± 0.003[c] | $het_{explained}$= 100.00%[d] | |
| Insulin in GDM (pmol/l) | 4 | 281 | random-effects meta-regression | | —— | —— | —— | |
| HbA1c in GDM (%) | 5 | 306 | random-effects meta-regression | | Coef = 4.813 (1.553 to 8.073) | 0.10 ± 0.003[c] | $het_{explained}$= 100.00%[d] | |
| HOMA in GDM (summary index score) | 3 | 264 | random-effects meta-regression | | —— | —— | —— | |

*Abbreviations*: Stat., statistical; Wt, method of weighting; SMD, standardized mean difference; CI, confidence intervals; REM, random-effects model; D-L, DerSimonian and Laird method; GDM, gestational diabetes mellitus; AMs, adhesion molecules; NR, not reported.
a- Subgroup meta-analysis.
b- Effect of study covariates on AMs among patients with GDM compared with controls, estimated using SMD as effect size measure.
A meta-regression coefficient > 0 indicates a greater impact of covariates on effect size.
c- P-value ± standard error after 10,000 permutations based on Montecarlo simulation.
d- Proportion of between-study variance explained (adjusted $R^2$ statistic), expressed as percentage, using the residual maximum likelihood (REML) method. A negative proportion reflects no heterogeneity explained.

**Table 4**
Secondary analyses for Maternal ICAM.

| Meta-analyses | No. of studies | No. of patients | Stat. Model | Wt | Pooled data | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | | | SMD (95% CI) | *P-value* | $P_{het}$ | $I^2$ (%) |
| *Subgroup analysis by Continent*[a] | | | | | | | | |
| Asia | 2 | 192 | REM | D-L | 0.70 (−0.09 to 1.49) | 0.08 | 0.007 | 86.2 |
| Europe | 6 | 1663 | REM | D-L | 0.41 (0.14 to 0.69) | 0.004 | 0.19 | 32.8 |
| North America | 1 | 16 | —— | —— | 2.72 (1.25 to 4.18) | <0.001 | —— | —— |
| *Subgroup analysis by trimester*[a] | | | | | | | | |
| Second | 1 | 1380 | —— | —— | 0.94 (0.41 to 1.47) | 0.001 | —— | —— |
| Third | 5 | 283 | REM | D-L | 0.29 (0.05 to 0.53) | 0.02 | 0.62 | 0.0 |
| Not reported | 3 | 208 | REM | D-L | 1.11 (0.20 to 2.02) | 0.02 | 0.001 | 86.0 |
| *Subgroup analysis by sample source*[a] | | | | | | | | |
| Plasma | 5 | 1645 | REM | D-L | 0.81 (0.22 to 1.39) | 0.007 | <0.001 | 82.1 |
| Serum | 4 | 226 | REM | D-L | 0.39 (0.12 to 0.66) | 0.005 | 0.70 | 0.0 |
| *Subgroup analysis by study design*[a] | | | | | | | | |
| Prospective | 7 | 1743 | REM | D-L | 0.66 (0.22 to 1.09) | 0.003 | 0.001 | 75.0 |
| Retrospective | 2 | 128 | REM | D-L | 0.35 (0.002 to 0.70) | 0.05 | 0.62 | 0.0 |
| *Subgroup analysis by RoB*[a] | | | | | | | | |
| High RoB | 2 | 1396 | REM | D-L | 1.69 (−0.03 to 3.41) | 0.06 | 0.03 | 53.8 |
| Moderate RoB | 6 | 371 | REM | D-L | 0.50 (0.18 to 0.83) | 0.003 | 0.06 | 80.0 |
| Low RoB | 1 | 104 | —— | —— | 0.14 (−0.25 to 0.52) | 0.50 | —— | —— |
| *Univariable meta-regression*[b] | | | | | | | | |
| Gestational age in GDM (weeks) | 6 | 1,663 | random-effects meta-regression | | Coef = −0.057 (−0.172 to 0.059) | 0.24 ± 0.004[c] | $het_{explained}$= 42.02%[d] | |
| Age in GDM (years) | 7 | 475 | random-effects meta-regression | | Coef = −0.104 (−0.271 to 0.064) | 0.22 ± 0.004[c] | $het_{explained}$= 66.69%[d] | |
| Pregestational BMI in GDM (summary index score) | 5 | 294 | random-effects meta-regression | | Coef < −0.001 (−0.098 to 0.097) | 0.99 ± 0.003[c] | $het_{explained}$= 0.00%[d] | |
| Gestational BMI in GDM (summary index score) | 6 | 383 | random-effects meta-regression | | Coef = −0.068 (−0.448 to 0.312) | 0.66 ± 0.005[c] | $het_{explained}$= −7.16%[d] | |
| Glycemia levels in GDM (mmol/l) | 7 | 475 | random-effects meta-regression | | Coef = −0.004 (−0.450 to 0.442) | 0.98 ± 0.001[c] | $het_{explained}$= –33.96%[d] | |
| Insulin in GDM (pmol/l) | 3 | 157 | random-effects meta-regression | | —— | —— | —— | |
| HbA1c in GDM (%) | 4 | 182 | random-effects meta-regression | | —— | —— | —— | |
| HOMA in GDM (summary index score) | 2 | 140 | random-effects *meta*-regression | | —— | —— | —— | |

*Abbreviations*: Stat., statistical; Wt, method of weighting; SMD, standardized mean difference; CI, confidence intervals; REM, random-effects model; D-L, DerSimonian and Laird method; GDM, gestational diabetes mellitus; AMs, adhesion molecules; NR, not reported.
a- Subgroup meta-analysis.
b- Effect of study covariates on AMs among patients with GDM compared with controls, estimated using SMD as effect size measure.
A meta-regression coefficient >0 indicates a greater impact of covariates on effect size.
c- P-value ± standard error after 10,000 permutations based on Montecarlo simulation.
d- Proportion of between-study variance explained (adjusted $R^2$ statistic), expressed as percentage, using the residual maximum likelihood (REML) method. A negative proportion reflects no heterogeneity explained.

participants than in controls (SMD = 0.58, 95% CI = 0.25 to 0.91; p = 0.001). Our meta-analysis did not detect significant differences in analysis of subgroups or in meta-regression analyses, in likely relation to the limited number of patients and studies with each molecule.

Siddiqui et al. [28] described that serum VCAM-1 levels were significantly elevated in GDM subjects than controls, but no statistically significant increase in serum levels of ICAM-1 and E-selectin. Serum level of VCAM-1 was significantly higher in greater than equal to one parity categorized GDM group when compared with control. Parity was previously reported to be associated with vascular reactivity in isolated arteries of pregnant women [8]. A positive association of parity and increased risk of cardiovascular disease as well as high prevalence of T2DM among multiparous women has also been reported [29,30].

Other authors found varying results. Mordwinkin et al. [11] found that maternal plasma VCAM-1 and ICAM-1 levels correlated positively with maternal HbA1c, where increased HbA1c was associated with increased VCAM-1 and ICAM-1 levels. In addition, a significant increase in cord blood VCAM-1 levels from patients with GDM with no significant difference in cord ICAM-1 levels was observed. Telejko et al. [31] reported no significant differences in E-selectin and VCAM-1 levels between the groups studied. In the GDM patients VCAM-1 concentrations correlated positively and E-selectin negatively, with gestational age. In the NGT (normal glucose tolerance) group, VCAM-1 concentrations were related to the patient's age, whereas E-selectin levels were not associated with any of the parameters studied. In the control group, E-selectin concentrations correlated significantly with triglycerides values. Multiple regression analysis revealed that VCAM-1 levels were significantly predicted only by the patient's age, whereas none of the parameters studied significantly predicted plasma E-selectin values. Wagner et al. [7] published no differences between the fasting and the stimulated levels of AMs in any group, arguing against an acute effect of hyperglycemia on AMs. ICAM-1 did not differ between groups, while E-selectin and VCAM-1 were elevated in both GDM and NGT versus controls. Whereas fasting and postprandial E-selectin and VCAM-1 decreased in NGT twelve weeks after delivery to the normal range, these AMs remained elevated in GDM postpartum. A high correlation was found between E-selectin and HbA1c or fasting glucose ($r^2 > 0.8$) in GDM both during and after delivery. Thus, women suffering from GDM are characterized by increased E-selectin, VCAM-1 even three months after delivery, when glucose tolerance has normalized. According to Pigott et al. [32] ICAM-I levels do not allow conclusions about endothelial activation or damage, while VCAM-1 expression is more specific

**Table 5**
Secondary analyses for Maternal E-selectin.

| Meta-analyses | No. of studies | No. of patients | Stat. Model | Wt | Pooled data | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | | | SMD (95% CI) | *P-value* | $P_{het}$ | $I^2$ (%) |
| *Subgroup analysis by Continent*[a] | | | | | | | | |
| Asia | 1 | 92 | —— | —— | 0.09 (−0.32 to 0.50) | 0.67 | —— | —— |
| Europe | 5 | 771 | REM | D-L | 0.19 (−0.10 to 0.47) | 0.21 | 0.04 | 60.8 |
| *Subgroup analysis by trimester*[a] | | | | | | | | |
| Third | 3 | 245 | REM | D-L | −0.01 (−0.26 to 0.24) | 0.93 | 0.95 | 0.0 |
| Not reported | 3 | 618 | REM | D-L | 0.33 (−0.09 to 0.75) | 0.12 | 0.02 | 74.7 |
| *Subgroup analysis by sample source*[a] | | | | | | | | |
| Plasma | 2 | 228 | REM | D-L | −0.001 (−0.26 to 0.26) | 0.99 | 0.90 | 0.0 |
| Serum | 4 | 635 | REM | D-L | 0.27 (−0.10 to 0.64) | 0.15 | 0.04 | 64.6 |
| *Subgroup analysis by study design*[a] | | | | | | | | |
| Prospective | 5 | 771 | REM | D-L | 0.19 (−0.10 to 0.47) | 0.21 | 0.04 | 60.8 |
| Retrospective | 1 | 92 | —— | —— | 0.09 (−0.32 to 0.50) | 0.67 | —— | —— |
| *Subgroup analysis by RoB*[a] | | | | | | | | |
| Moderate RoB | 5 | 759 | REM | D-L | 0.20 (−0.08 to 0.49) | 0.16 | 0.04 | 59.1 |
| Low RoB | 1 | 104 | —— | —— | 0.02 (−0.37 to 0.40) | 0.93 | —— | —— |
| *Univariable meta-regression*[b] | | | | | | | | |
| Gestational age in GDM (weeks) | 3 | 245 | random-effects meta-regression | | —— | —— | —— | |
| Age in GDM (years) | 6 | 863 | random-effects meta-regression | | Coef = 0.090 (−0.062 to 0.241) | 0.17 ± 0.004[c] | $het_{explained}$= 35.39%[d] | |
| Pregestational BMI in GDM (summary index score) | 6 | 863 | random-effects meta-regression | | Coef = 0.015 (−0.119 to 0.149) | 0.67 ± 0.005[c] | $het_{explained}$= −66.58%[d] | |
| Gestational BMI in GDM (summary index score) | 4 | 399 | random-effects meta-regression | | —— | —— | —— | |
| Glycemia levels in GDM (mmol/l) | 6 | 863 | random-effects meta-regression | | Coef = 0.058 (−0.440 to 0.555) | 0.71 ± 0.005[c] | $het_{explained}$= −70.06%[d] | |
| Insulin in GDM (pmol/l) | 3 | 245 | random-effects meta-regression | | —— | —— | —— | |
| HbA1c in GDM (%) | 4 | 617 | random-effects meta-regression | | —— | —— | —— | |
| HOMA in GDM (summary index score) | 2 | 228 | random-effects meta-regression | | —— | —— | —— | |

*Abbreviations*: Stat., statistical; Wt, method of weighting; SMD, standardized mean difference; CI, confidence intervals; REM, random-effects model; D-L, DerSimonian and Laird method; GDM, gestational diabetes mellitus; AMs, adhesion molecules; NR, not reported.
a- Subgroup meta-analysis.
b- Effect of study covariates on AMs among patients with GDM compared with controls, estimated using SMD as effect size measure.
A meta-regression coefficient > 0 indicates a greater impact of covariates on effect size.
c- P-value ± standard error after 10,000 permutations based on Montecarlo simulation.
d- Proportion of between-study variance explained (adjusted $R^2$ statistic), expressed as percentage, using the residual maximum likelihood (REML) method. A negative proportion reflects no heterogeneity explained.

for endothelium, and that of E-selectin is completely restricted to endothelial cells. Hence, VCAM-1 and especially E-selectin are good candidates to be included in the rising number of markers for endothelial perturbation. Especially the increase of E-selectin in NIDDM (noninsulin-dependent diabetes mellitus) appears to indicate endothelial activation or turnover, if E-selectin levels reflect its surface expression on endothehal cells, as is suggested by in vitro studies [32]. It has been shown that the soluble forms of E-selectin and VCAM-1 induce angiogenesis. As diabetic vasculopathy, especially its microvascular form, depends on neovascularisation, soluble E-selectin and VCAM-1 may contribute to the development of diabetic vascular disease together with other mediators [33]. On the other hand, Lopez Morales et al. [34] reported statistically significant differences in endothelial dysfunction in cord blood from patients with GDM in IL-6 and ICAM-1, with no difference in VCAM and E-selectin. In contrast to what was observed by Cross et al. [35] who found no significant differences in cord blood ICAM-1, hs-CRP or insulin concentrations between male and female offspring in control or diabetes groups. In the overall control group, mean ICAM-1 concentrations were significantly higher in cord blood samples taken after a normal vaginal delivery compared with those born by caesarean section, and median cord blood insulin concentrations were significantly lower in the normal vaginal delivery group compared with the caesarean section group. In the diabetes groups, there were no significant differences in telomere length, hs-CRP or ICAM-1 concentrations when compared with control subjects matched for delivery method. Díaz-Perez et al. [36] reported that GDM does not induce upregulation of the endothelial dysfunction markers ICAM-1, VCAM-1 and E-selectin in feto-placental endothelium, and we suggest this to be a protective mechanism of GDM placenta. Most recently, Landreth et al. [37] measured AMs in the cord blood serum and conditioned HUVEC (human umbilical vein endothelial cells) media in mothers with GDM or T2DM and women with euglycemia, and found in a fully adjusted model, that VCAM-1 was significantly increased in the cord serum of infants born to mothers with diabetes, with no differences in ICAM-1 and E-selectin levels. ICAM-1 was significantly correlated with maternal HbA1c. From the HUVEC media, the abundance of AMs was not different based on DM or high glucose exposure; however, VCAM-1 abundance in the HUVEC supernatant was significantly correlated with ICAM-1 and cord serum c-peptide. They concluded that alterations in AMs in infants exposed to hyperglycemia during pregnancy may reflect an early alteration in vascular function predicting future cardiovascular disease.

According to our qualitative evaluation -carried out using the Newcastle-Ottawa Scale (NOS)- all primary-level studies systematically reviewed were not conducted with the same rigor, although in general, most of them harbored moderated risk of potential bias across several

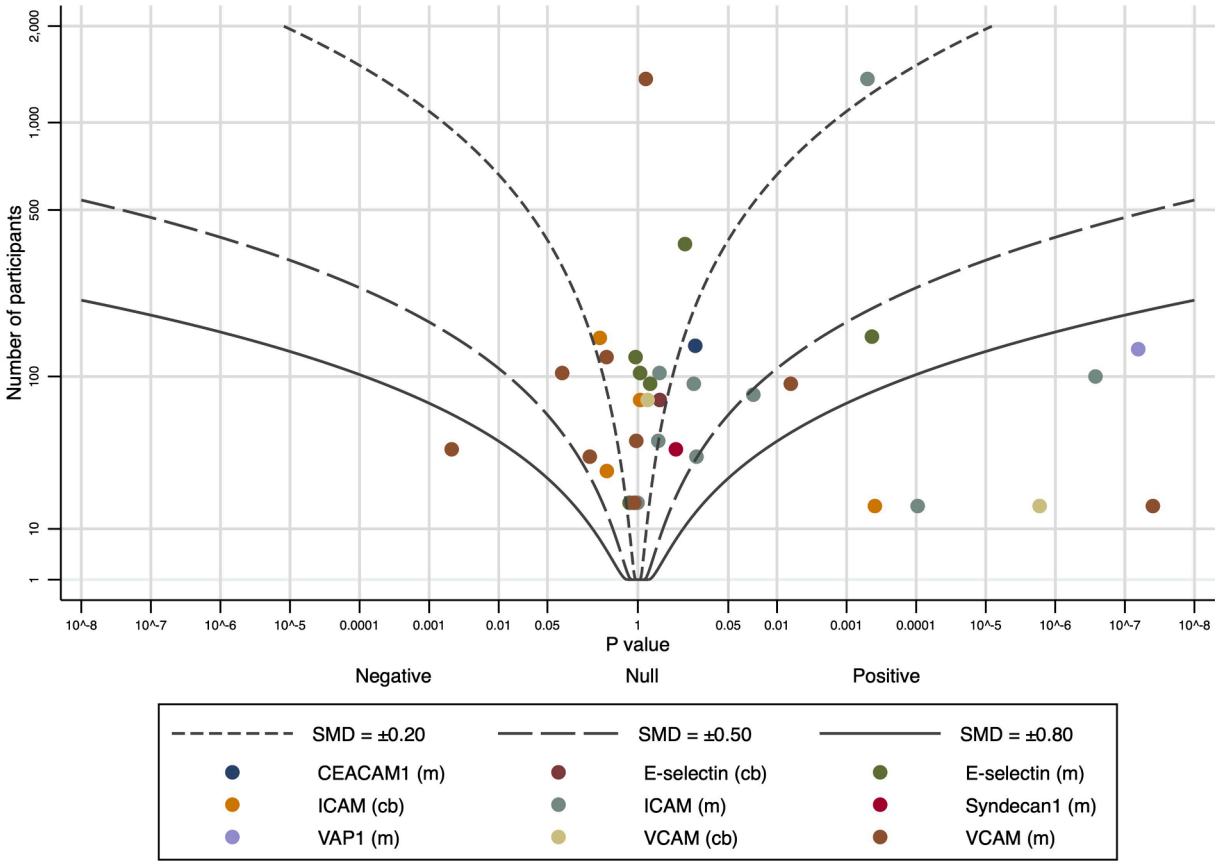


**Fig. 4. Albatross plot.** Albatross plot graphically representing the changing levels of all AMs. (including AMs not meta-analyzed) between GDM patients and controls systematically reviewed in this study. Each single primary-level study is represented by a circle of different color, according to the AMs investigated (see legend). Two-sides p-values (horizontal x-axis) with results separated according to positive/negative differences (i.e. the observed direction of effect) were plotted against the number of participants included within each study (vertical y-axis). The albatross plot allows a better interpretation of p-values from the variables than did not enter in meta-analysis, in the context of the study sample sizes. Small studies lie toward the bottom of the plot and large studies toward the top. Effect contours (black continuous and intermittent lines) were drawn on the plot showing the ranges of the magnitudes of effect, using standardized mean differences (SMD). A p-value $< 0.05$ was considered significant.

domains. Therefore, future studies assessing the relationships between the most relevant AMs levels and GDM women should be more comprehensive in the collection of clinical-analytical variables and consider the potential biases and recommendations reported in this systematic review and *meta*-analysis, to improve and standardize good research practices in the future.

Potential limitations of this study should also be discussed. The published studies on the different AMs are scarce and not all specify the trimester of gestation in which the analysis was performed, which limits reaching conclusive results. This is also an inherent limitation of the primary-level studies included in this study, that reported limited observations for this parameter. Therefore, another relevant recommendation of the present systematic review is the need for future studies to report precise information on the gestational trimester during the study of AMs profile in patients with GDM. On the other hand, another limitation derives from the few primary level studies available, and consequently, from the low number of patients showing results for each molecule. That could justify an unusual result of our meta-analysis in which VCAM-1 was not significantly elevated in women with GDM, which is probably due to the relatively small sample that was able to be analyzed quantitatively (n = 9, 1854 patients). Furthermore, our meta-analysis revealed a considerable degree of heterogeneity with conflicting results. Heterogeneity is a common finding in meta-analyses dealing with biomarkers from serum and plasma measured and expressed as continuous variable [38]. On the other hand, our stratified meta-analysis may have identified potential sources of heterogeneity when assessing the differences among maternal ICAM-1 levels across subgroups. Among the strengths of the study, to the best of our knowledge, this is the first systematic review and meta-analysis respect to AMs in GDM and provides novel promising meta-analytical findings. Our meta-analysis has been conducted under methodological criteria based on high research standards (several databases, no language limitation, assessment of the risk of bias and applying advanced meta-analytical methods).

## 5. Conclusions

Maternal ICAM-1 was significantly higher in women with GDM with higher prognostic capacity in maternal blood. However, VCAM-1 does not appear to be a suitable biomarker of risk with lower levels in women with GDM during the 3rd trimester. AMs emerge as promising biomarkers of GDM, but the low number of primary-level studies published to date may limit the external validity of the results and makes it difficult to analyse the data properly. Due to short and long-lasting health consequences of GDM such as adverse perinatal-obstetric outcomes and increased risk of subsequent metabolic and CVD in mother and child, and the lack of widely-accepted treatment or prevention strategy for GDM (except diet, exercise and insulin therapy), there is a need to discover early predictors of GDM risk that would allow intervention and prevention in high-risk women, and consequently, these biomarkers should be optimally measured in the first trimester. It seems that the identification of disturbances at the molecular level through AMs may -

not only enable the identification of potential new treatments - but also should provide earlier and more specific and sensitive targets for monitoring the effectiveness of current treatments as well as early diagnosis and prevention strategies. Future studies are needed to establish which biomolecules are most accurate in predicting GDM and its complications.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110740.

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