8-31-2021

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Diana Arabiat
Edith Cowan University

Mohammad AL Jabery

Mark Jenkins
Edith Cowan University

Vivien Kemp
Edith Cowan University

Lisa Whitehead
Edith Cowan University

See next page for additional authors

10.1016/j.earlhumdev.2021.105420
This is an author's accepted manuscript of: Arabiat, D., AL Jabery, M., Jenkins, M., Kemp, V., Whitehead, L., & Adams, G. (2021). Language abilities in children born to mothers diagnosed with diabetes: A systematic review and meta-analysis. *Early Human Development, 159*, Article 105420.
https://doi.org/10.1016/j.earlhumdev.2021.105420

Language abilities in children born to mothers diagnosed with diabetes: A systematic review and meta-analysis

Diana Arabiat [a,b,*], Mohammad A.L.Mohammad JAL Jabery[c] , Mark Jenkins[a], Vivien Kemp[a] , Lisa Whitehead[a], Gary Adams[d]

a School of Nursing and Midwifery, Edith Cowan University, Perth 6027, Australia
b Maternal and Child Nursing Department, Faculty of Nursing, The University of Jordan, Amman 11942, Jordan
cCounselling and Special Education Department, Faculty of Educational Sciences, The University of Jordan, Amman 11942, Jordan
d Queen's Medical Centre, School of Health Sciences, The University of Nottingham, Nottingham NG7 2HA, UK
∗Corresponding author at: Edith Cowan University, School of Nursing and Midwifery, 270 Joondalup Drive, Building 21, Joondalup, Perth, WA 6027, Australi

Abstract

Background: This meta-analysis reviewed and synthesized the available evidence on the association between intrauterine exposure to maternal diabetes and language abilities in children.

Method: MEDLINE/PubMed, EMBASE, PsycINFO, Proquest Dissertations and Theses Global, and Google Scholar databases were searched through December 2020. Studies were systematically searched, and effect sizes were calculated using random effects models.

Results: Twelve studies were identified for inclusion in this review, however, only 10 were included in the meta-analysis. Sample size ranged from 9 to 115 participants in the diabetes group and 28 to 8192 in the control and aged around 3 years. The pooled results of the meta-analysis showed a trend of decreased language abilities in receptive (z= , -3.49, df = 10, I^2 = 34, p = 0.001), expressive language development (z = -2.29, df = 11, I^2 = 94%, p =0.022) and general communication (z = -4.12, df= 4, I^2 = 2, p = 0.001) However, results showed a limited effect of maternal diabetes on children's language abilities after excluding high-risk categories such as children born to mothers with other gestational comorbidities, obesity and low socio-economic status.

Conclusion: Our meta-analysis recognises that exposure to maternal diabetes during pregnancy intersects with other factors within the intrauterine environment to create the conditions for reduced language abilities in the child. Multiple factors may contribute to the observed differences between groups in the meta-analysis. A focus on interventions to maintain optimal blood glucose levels during pregnancy and to screen for early developmental delay after birth are recommended.

Keywords: Receptive language, expressive language; intra-uterine life; diabetes; meta-analysis, communication, language development, children.

To cite this paper: Arabiat, D., Jabery, M., Jenkins, M., Kemp, V., Whitehead, L. C., & Adams, G. (2021). Language abilities in children born to mothers diagnosed with diabetes: A systematic review and meta-analysis. Journal of Early Human Development. https://doi.org/10.1016/j.earlhumdev.2021.105420

1. Introduction

Language development refers to the process by which children come to understand what others say (receptive language) and communicate their thoughts (expressive language), while delayed language development relative to other children of the same age is described as language impairment [1]. Children with language delay are often identified on the basis of expressive language delay and typically described as late talkers [2]. Alternatively, children who have mixed expressive/receptive vocabulary delays may have a language disorder or persistent language impairment [3].

Delayed or reduced language abilities in children either may present as a primary condition, without underlying aetiology, or as a secondary condition, related to variety of developmental or neurological conditions, such as autism [4]. It is also often encountered in children who experience biological and environmental risk factors, including prematurity, low birth weight, or maternal conditions [5-9]. The assessment of language abilities in children is evaluated through several screening tests for speech and language disorders, with no single test regarded as a gold standard reference [2]. Early interventions and educational services to improve language abilities are often designed to enhance language development and to reduce the burden of persistent disability on the child's function and ability to communicate [3, 10].

In view of the emerging evidence on the relationship between intrauterine exposure to maternal diabetes and risk for impaired development [11], it is important to understand the evidence related to such risk and then how it can be assessed and managed in clinical practice. The ecological theory of Developmental Origins of Health and Disease (DOHaD)

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presumes that risk for child development and diseases is often influenced by the environmental conditions in early life [12]. Several environmental mediators have been identified in previous meta-analyses reporting developmental outcomes and included multiple factors such as maternal obesity [13], hypertensive disorders during pregnancy [14], and low socio-economic status [15]. At the intrauterine environmental- level, several studies suggest a correlation between intrauterine exposure to hyperglycaemia and risk of delay in language development [16-19]. In other studies, contradicting results have been reported [20-21], or no significant differences between children exposed to maternal diabetes and control groups on language development measures [22] which makes it hard to speculate the true association between maternal diabetes and language abilities in the child. The effect of maternal diabetes on the language abilities of children remains unclear related to inconsistent findings from limited studies. It is unclear also, how exposure to maternal diabetes during pregnancy affects brain development and subsequent psychomotor development in children.

Several studies have linked maternal diabetes, particularly pre-gestational diabetes, with foetal hyperinsulinemia and chronic intrauterine foetal tissue hypoxia [23-24]. Evidence links maternal diabetes with neurodevelopment in the child, proposed mainly to occur either through the teratogenic effect of hyperketonemia [21, 25], or through other intrauterine-related factors such as chronic hypoxia, iron deficiency, and acute changes in glucose level and acidemia [26]. If these studies have correctly predicted the association between intrauterine exposure to hyperglycaemia and psychomotor development, then the future burden of developmental delay among children might be higher than estimated as the incidence of type 2 diabetes and gestational diabetes continues to rise across countries [27].

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Systematically synthesised information on the associations between maternal diabetes during pregnancy and subsequent child development is available only for the cognitive development of the child [25], autism [28] and motor development [29], but not for the child's psychomotor development, particularly the risk of language development. Examining the relationship between maternal diabetes and language abilities in the child represents a critical step for healthcare professionals in understanding the underlying processes through which maternal diabetes may affect children's development and elucidating additional factors associated with language development in children. This in turn may help providing further targets for early interventions aimed at reducing the burden associated with language delays. In the present pooled meta-analysis of published prospective studies, we aim to investigate whether diabetes mellitus impacts language abilities of child, and whether diabetes is differentially related to the main subtypes of language development, that is receptive or expressive language.

2. Methods

A meta-analysis was undertaken involving the synthesis, integration and interpretation from published studies to develop a comprehensive understanding of the association between intrauterine exposure to maternal diabetes and the language development in children.

2.1. Inclusion Criteria

Inclusion criteria are outlined in Table 1. To be included in the present meta-analysis, studies must have been analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies of children born to women who have diabetes during pregnancy (pregestational and gestational

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diabetes), and should have assessed at least one quantitative outcome of child language. Measures that could not be presented by means and SDs or did not report on Odds Ratio, Risk Ratio, Risk Difference, Mean Difference and SD was excluded.

[INSERT TABLE 1. ABOUT HERE]

2.2. Search strategy

A three-step search strategy was applied in this review and aimed at identifying all eligible published studies regardless of publication's year or status. First, MEDLINE/PubMed, EMBASE, PsycINFO, Proquest Dissertations and Theses Global, and Google Scholar databases were searched by one of the research team. An initial limited search was first undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were then used to develop a full search strategy for the report. The search strategy, including all identified keywords and index terms, were adapted for each included information source. Initial keywords used in this review were: Language delay OR language development OR speech delay OR speech development AND maternal diabetes OR pregnancy diabetes OR gestational diabetes AND child OR offspring (Appendix)

Second, following the initial search, all identified citations were collated and uploaded into EndNote version 9 and duplicates removed. Titles and abstracts were then screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies were retrieved in full and their citation details imported into JBI SUMARI [30].

Finally, the full text of selected citations was assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that did not

meet the inclusion criteria was recorded and reported in the systematic review. Disagreements between the reviewers at each stage of the study selection process were all resolved through discussion, and by including a third reviewer. The results of the search were reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

2.3. Assessment of methodological quality

Study quality was assessed and scored independently by two of the reviewers, using standardised critical appraisal instruments from Joanna Briggs institute Meta-analysis of Statistics assessment and Review Instrument (JBI-MAStARI). Any discrepancy in quality assessment between reviewers was resolved through group discussion. Cohort studies were assessed by 11 questions, and case-control studies by 10 questions. An item would be scored 1 if it was answered "yes" and if it was answered "no," or "unclear" then the item scored 0. For this review, studies with poor quality are defined as those that failed to reach a score of 50% on the MAStARI, the predetermined cut off score agreed upon by the authors.

All studies were included in the data extraction and synthesis regardless of their quality of appraisal. This is mainly related to the limited number of published studies on diabetes and language development, in addition to our belief that JBI critical appraisal is claimed to enhance the rigor of the synthesis and not to exclude poor quality studies.

[INSERT PRISMA FIGURE 1 ABOUT HERE]

Data extraction

All data related to speech and language development was extracted and inputted into JBI System for the Unified Management, Assessment and Review of Information (SUMARI) software [30]. Data was extracted from included studies using the standardized data

extraction tools in JBI SUMARI [30] and included specific details about the exposure of interest including different exposure categories when applicable, populations, study methods and outcomes or dependent variables of significance to the review question and specific objectives. Any disagreements that arise between the reviewers was resolved through discussion and with a third reviewer.

2.4. Data synthesis

First, we provided a narrative descriptive synthesis of the findings from the studies included in this review. This narrative summary described and compared major findings within and across studies with respect to the language outcomes in children born to mothers with and without diabetes. It included also a summary of methodological quality, with tabulated JBI critical appraisal scores. The standardized mean differences (SMD), or effect size (ES) was used as a summary measure, which is applicable for interpretation as the ES originally proposed by Cohen [31]. An ES of 0.2 was considered small, 0.5 as moderate, and 0.8 as large. Means, SDs, and sample size for the group of children born to mothers with diabetes and those without diabetes were used to calculate effect sizes (ES), or standardised mean differences (SDM) for each subdomain. Odd ratio was re-expressed as a SMD or ES, so that it can be used in the meta-analysis. Results are presented in a forest plot

Random effect model to compute the summary SDM was applied and used to pool the study results. A random effect model was used since it is assumed that studies were estimating the diabetes effects in different group population with different type of maternal diabetes and measures. Heterogeneity is typically presented through between-study variance in network meta analyses; hence, this was further assessed using the Cochran Q and I^2 statistics; the risk for this analysis was set to a P-value < 0.10 for the Q test, and a value >

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50% for the I^2. In the protocol, subgroup analyses were planned to be conducted according to the child's age at the time of assessment and according to type of maternal diabetes. However, because of the low number of included studies in the review, this was deemed unsuitable and is therefore a deviation from the protocol. All data for the meta-analysis were conducted using JBI SUMARI [30].

3. Results

3.1. Studies Selected

Figure 1 shows the PRISMA flow diagram [32] with the search strategy and results. A total of 12 studies were identified but only 10 studies met the inclusion criteria and contained complete data that could be converted to standardized mean differences (SMD) with 95% confidence intervals [30].

3.2. Sample characteristics

Of the 12 studies included in this review, 6 studies were cohort, and 6 studies were case control. Sample size related to language outcomes ranged from 9 to 115 participants in the diabetes group and 28 to 8192 in the control. The majority of children were approximately aged 3 years at the time of their language screen (Table 2).

[INSERT TABLE 2 ABOUT HERE]

3.3. Synthesis of Results

This systematic review identified several studies that assessed language abilities in children born to mothers with and without diabetes, however there was large variability in the language subdomains and modalities. Heterogeneity analysis and combining studies according to assessment tool left less studies for the 5 meta-analysis groups: 2 studies included measures of general language abilities, 4 included measures of receptive language, 4

included measures of expressive language, 3 included measures of communication speech, and 5 focused on intelligence/cognitive verbal abilities. Ideally, language assessment should include an examination of phonological, lexical, syntactic and pragmatic abilities in both receptive and expressive domains, but in this review only one study was related to semantics and syntax of grammar, and therefore we were not able to determine whether children born to mothers diagnosed with diabetes are impacted in this subdomain.

We performed a second meta-analysis on the same data set, but excluded diabetes samples with predominantly disadvantaged or high risk groups, such as children experienced hypoglycaemia after birth, enrolled before 18 months of age, at high risk for other developmental disabilities such as ASD, and those born to mothers diagnosed with diabetes and in addition were from low socio-economic status or with poor glycaemic control . We found one study with multiple effect sizes from independent cohorts, gestational diabetes, and pre-existing diabetes. Effect sizes were extracted and examined in separate meta-analyses. If a study included more than one measure of same language outcome, we selected the most widely used assessment. In longitudinal studies where language was assessed at multiple points, we selected the latest point to capture the most developed language abilities in the child. If within a study, both adjusted and adjusted effect sizes were provided, we selected the adjusted effect size. We subdivided language outcomes in this meta-analysis to more accurately identify extents of language abilities for children born to mothers diagnosed with diabetes. Results of all effect sizes from included studies for the language subdomains are presented in forest plots in Figures 2 (A), (B), (C) and (D) and Table 2, whereas Table 3 showed the excluded studies.

[INSERT FIGURE 2 (A), (B), (C) and (D) ABOUT HERE]

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[INSERT TABLE 2 ABOUT HERE]

[INSERT TABLE 3 ABOUT HERE]

3.4. Sample heterogeneity

The final heterogeneity of the articles included in the first meta-analysis of the receptive language domain ($I^2 = 34\%$) and the speech communication ($I^2 = 2\%$) was not significant, whereas the heterogeneity of other language categories were all significant ($I^2 > 75\%$, $P < 0.001$). The high heterogenous effect size noticed in our findings may be explained by differences in child's age at time of language assessment, type of maternal diabetes, and type of measure used in exploring child's development. In the second meta-analysis, there was also evidence of considerable heterogeneity between studies for all language subdomains, except the general language domain ($I^2 = 28\%$) and intellectual language abilities for the pre-gestational diabetes group ($I^2 = 0\%$). The elimination of data focused on children with hypoglycaemia [19, 33] in the general language and expressive language domain failed to change the I^2 to an acceptable level, as well as the combination of categories of articles related to gestational diabetes [21, 34] when assessing the intellectual language studies. To overcome some of factors that may have contribute to heterogeneity across studies, breaking down overall verbal intelligence categories into further subdomains according to the measuring tool resulted also in heterogeneous results, and didn't change the final conclusion.

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3.5. Association between maternal diabetes and language subdomains

As shown earlier in Figure 2, the forest plots show the study with which each effect size is associated, and report the standardized mean difference, and 95% confidence intervals. The pooled analysis (Table 4) combining all diabetes groups was reported as having a small effect of maternal diabetes on receptive language development (z= , -3.49, df = 10, I^2 = 34, p = 0.001), expressive language development (z = -2.29, df = 11, I^2 = 94%, p =0.022) and general communication (z = -4.12, df= 4, I^2 = 20, p = 0.001) when compared to controls. However, this effect was limited and insignificant after excluding cohorts with predominantly disadvantaged diabetes groups (Table 4).

[INSERT TABLE 4 ABOUT HERE]

3.5.1. General language skills

Only 2 studies were identified as reporting appropriate data for the general language meta-analysis (See table 4) and focused primarily on children aged between 2 years in Qiao et al. [33] and 3-4 years in Nomura et al. [35]. Those studies produced a non-significant effect size of Z = 0.76 (95% CI, - 3.60 _ 1.58, P = 0.446: Figure 2, Table 4). Thus, maternal diabetes was not associated with decreased general language abilities in children. There was some evidence of effect size heterogeneity (I^2 = 99%). Subgroup analysis of data excluding children exposed to both gestational diabetes and low socio-economic status (SES) [35] and children with low blood sugar after 24 hours of birth [33] resulted also in insignificant effect size of maternal diabetes. Overall, Nomura et al. [35] showed significantly lower language abilities of children born to diabetes mothers, whereas, language abilities were not significantly different among the children born to diabetes mothers and the control group in Qiao et al. [33] study. In Nomura et al. [35], exposure to gestational diabetes in addition to

low SES was associated with lower language abilities in children when compared to children exposed to gestational diabetes alone.

3.5.2. Receptive language

A total of 4 studies produced a significant effect size z = -3.49 (95% CI, - 0.27 - -0.08, P < 0.001; Figure 2). The results of the 4 studies that reported overall receptive language development indicated that children born to diabetes mothers scored lower than the control group (Table 4). However, the sample had a less homogenous age focus; participants ranged across-all ages (6 months -5 years), with the majority of studies focusing on children around 2 years of age. The 4 studies included in this analysis used receptive language as an outcome of interest. Using the inverse variance procedure and excluding children with ASD symptoms in Krakowiak et al. [18] , late entry group of children with lower glycaemic control in Sells et al. [36] (no clear definition was given for the early and late entry group in this study), and other age groups reported in Dionne et al. [16] and Torres-Esinola et al. [37] resulted in insignificant effect of maternal diabetes. While the meta-analysis of these studies revealed maternal diabetes was associated with decreased receptive language abilities in children in the first meta-analysis, the second meta-analysis suggests limited effect after excluding diabetes groups with predominately high-risk population. In this review, three studies [16, 18, 36] found that children born to diabetes mothers scored significantly below controls on receptive language domain. The relationship between maternal diabetes and language abilities was mediated negatively by child's age in Torres-Espinola et al. [37] where children demonstrated accelerated language development at 6 months, this had declined rapidly by 18 months among children born to diabetes mothers.

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3.5.3. Expressive language

In total, 5 studies reported overall expressive language scores in children born to diabetes mothers and their scores were lower than control children (Table 4), with large heterogeneity across the studies. The 5 studies that reported on expressive language indicated a significant pooled effect size of z = -2.29 (95% CI, -0.82_-0.06, P < 0.022, Figure 2). The effect sizes across the studies were also heterogenous (I^2 = 94). Performing the results of the children without including children with hypoglycaemia in Stenninger et al. [19] and other groups with predominately high-risk population listed in the earlier section, the effect size changed to insignificant, with large heterogeneity. Three studies [19, 36-37] reported no significant differences on expressive language scores between children born to diabetes mothers and the control group. On the other hand, children born to diabetes mothers scored significantly below controls on expressive language domain in Krakowiak et al. [18] and Dionne et al. [16]. It was found that expressive delay in children is associated with exposure to maternal diabetes during pregnancy [16], in particular for children less than 5 years.

3.5.4. Language speech communication

Three studies reported on tasks that measure speech communication in children. The meta-analysis revealed a significant difference between groups with a significant effect size z = - 4.12 (95% CI, -0.42_-0.15, P < 0.001: Figure 2, Table 4). Thus, our findings suggest that maternal diabetes was associated with a decrease in language speech abilities in children. Using Vineland Communication subscale (VCS), children born to diabetes mothers scored below controls on speech communication in Krakowiak et al. [18] and Sells et al. [36]. Another study reported also significant lower scores on the oral communication subscale of the Early Development Instrument (EDI) for children born to diabetes mothers at age 6 years

[16]. In Dionne et al. [16], at least 26% of children born to diabetes mothers were identifies as having low language abilities compared with 13% of controls

3.5.5. Verbal intelligence indices

Five studies were identified as reporting overall verbal intelligence indices. The meta-analysis revealed no significant difference between children born to diabetes mothers and control children with a non-significant pooled effects size of z = -1.48 (95% CI, -1.48_ 0.21, P = 0.139: Figure 2, Table 4). While not statistically significant, our result indicates a trend towards a reduction in verbal intelligence abilities in children exposed to maternal diabetes during pregnancy. Performing the results of the children born to mothers with gestational diabetes only [20-21, 34 -35], the effect size remained insignificant, and the individual effect sizes remained largely heterogeneous in all analyses. However, when performing the results for children born to mothers with pre-existing diabetes, the effect size changed to the overall meta-analysis results for gestational diabetes group z = -1.97 (95% CI, -0.42, 0.02), with no heterogeneity. This suggests that pre-existing diabetes had significantly larger effect on verbal intelligence abilities than gestational diabetes.

The Wechsler Preschool and Primary Scale of Intelligence scores (WPPSI) in 2 studies [34, 35] show a greater risk of developing sub-optimal verbal skills abilities in children born to diabetes mothers, while Ornoy et al. [21] reported no significant differences in verbal performance using the same assessment tool.

Veena et al. [20] and Sells et al. [36] also reported no significant relationship between verbal intelligence and maternal diabetes. Notably, Sells et al. [36] found that language abilities are more favourable when diabetes is carefully controlled during pregnancy, while Veena et al. [20] report that children born to diabetes mothers in India scored higher on

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verbal abilities compared to children born to mothers without diabetes. This was the only study to report higher language abilities in children born to diabetes mothers.

3.6. Methodological Quality and Risk of Bias

The methodological quality of most included studies was considered high (score between 8 and 10) (see Table 5 and 6). Only 1 of 12 studies scored low on methodological quality, mostly because it failed to provide sufficient detail on strategies to deal with confounding variables and was unclear in the reporting [33]. The case control studies were of a consistently higher quality than the cohort studies. This was because the response to Q6 (Were the groups/participants free of the outcome at the start of the study or at the moment of exposure?) was not applicable in any of the cohort studies, in addition that not all studies needed to report attrition rates (Q9) or address attrition rates (Q10) due to the study design.

[INSERT TABLE 5 ABOUT HERE]

[INSERT TABLE 6 ABOUT HERE]

4. Discussion

We performed the first meta-analysis for clarification of the association between maternal diabetes and language abilities in the child. Our results suggest that children exposed to maternal diabetes perform less well than control children on overall receptive and expressive language measures and in the general measures of speech communication. Although this pooled analysis suggested a significant reduction in receptive and expressive language abilities in children born to diabetes mothers, the results from the second meta-analysis were non-significant, suggesting that risk for language development is moderated by other factors, such as other gestational comorbidity, obesity and low SES. When considering our results on the overall effect of maternal diabetes on both receptive and expressive

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language abilities, a possible question arises as to whether current literature does not overvalue the diabetes effect when failing to consider the effect of other moderating variables on language development. For example, we found that children born to mothers who did maintain an optimal blood glucose level during pregnancy showed better scores on their language abilities than those born to mother with a poorly managed diabetes [36]. No other studies in this review have accounted for this and a limited number have accounted for other confounding variables. For example, for the four established moderating factors identified in this review, 3 studies included in this meta-analysis provided risk estimates adjusted for maternal weight [20, 34, 37], 3 studies [20 -21, 34] controlled for low SES, while only 1 study controlled for a family history of ASD and ADHD [35], or other comorbidities such as gestational hypertension [16] in their analyses. We generally suggest that inclusion of other high-risk population such as obese diabetes mothers or those exposed to diabetes and low SES or gestational hypertension provide stronger evidence than inclusion of studies limited to maternal diabetes only. Therefore, the evidence from this meta-analysis should be viewed with caution, particularly considering that several studies did not consider the effect of those moderating variables on language outcomes. In this review, only one study presented adjusted extractable data for obesity confirming that both obesity and maternal diabetes were concisely associated with lower language abilities in children born to obese and/or diabetes mothers [37].

Considering the moderating effect of those factors, it seems not surprising that maternal diabetes showed greater effect on language abilities when pooling all effect sizes of diabetes groups regardless of child's age at the time of the assessment or exposure to other mediating factors. This was demonstrated in several primary studies. For instance, in Nomura

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et al. [35], maternal diabetes combined with low SES had a stronger effect on language abilities than did gestational diabetes alone. Similarly, Veena et al. [20] reported maternal diabetes combined with low SES having a stronger effect on verbal intelligence than maternal diabetes alone. Arabiat et al. [29] suggested that poor glycaemic control, low SES, maternal comorbidity as gestational hypertension and/or obesity increase the overall effect and positively mediate the association between child development and exposure to maternal diabetes during pregnancy. The extent to which those moderating factors were controlled differed among studies, which may cause heterogeneity and inaccurate pooled estimates.

Such interrelating relationships between the above-mentioned variables raises the question about what role maternal diabetes play in this process and the pathways through which maternal diabetes may affect children's language development. Unfortunately, we have no enough information to answer this question, so the underlying processes/pathways by which maternal diabetes during pregnancy is associated with the child's language development are unclear. Earlier studies have shown that hyperglycaemia during pregnancy is usually associated with hyperketonemia [21, 25], or chronic hypoxia [26] and that the teratogenic effects will pass to the unborn child and may hinder the brain development in the child. Other complications related to iron deficiency anaemia during pregnancy [26] or gestational comorbidities such as hypertension [29] and obesity [37] are also believed to have detrimental effects on the child neurodevelopment because such response is known to increase the metabolism of the brain and therefore exacerbate neuronal injury in the unborn child. Maternal depression has been identified as another risk factor for language impairment in other studies [39]. However, in our review, a temporal or independent association between maternal depression and diabetes has not been discerned by prior studies that have evaluated

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the effects of diabetes on language outcomes, while considering the effects of other factors associated with poor language development. Accordingly, further studies need to test the effects of maternal depression, to determine if the results will remail the same.

Furthermore, we observed that maternal diabetes was associated with decreased verbal intelligence in studies dominated by pre-existing diabetes (T1DM and T2DM), but no significant association was found in studies limited to gestational diabetes. In this sense, this meta-analysis could provide first conclusive results on the effect of different types of maternal diabetes on verbal intelligence domain. This is congruent with a recent meta-analysis study [29] that children born to mothers with pre-existing diabetes may have a greater risk for poor motor development. Overall, our findings highlight the importance of distinguishing between different types of maternal diabetes, because they may indeed have different effect on language subdomains. Moreover, verbal intelligence abilities based on pre-existing diabetes showed a significant effect more than twice as strong as gestational diabetes based on Fraser et al. [34] and Ornoy et al. [21]. In interpreting this result we need to take into account the sample size in the study of Fraser et al. [34]. This study had relatively smaller sample sizes and significant group size imbalance (26 mothers with pre-existing diabetes, 33 mothers with gestational diabetes, and 264 mothers with glucosuria). The main issue arise from small sample studies is that they tend to result in imprecise effect size estimates and are more likely to produce extreme results in meta-analysis. Several studies included in our review [18, 19 21, 35, 36, 37] had not reach the necessary sample size to provide a conclusive result.

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Our finding contributes to the discussion about the effect of diabetes type on language abilities in children. Earlier evidence has suggested that diabetes type during pregnancy could create a variable effect. For example, in a study that was not included in this review, Hod et al. [38] found that children born to mothers with type 1 diabetes had better psychomotor development than children born to mothers with type 2 diabetes. Pre-existing diabetes may show stronger associations with various language subdomain because they often involve a higher risk for poor glycaemic control and/or gestational hypertension, which are positively associated with negatively interact with brain development and as a result they confoundingly strengthen the relationship between diabetes and low verbal intelligence in the child. For the other language subdomains, we were not able to represent our findings according to the type of diabetes as some studies [19, 33, 36] did not differentiate and consider maternal diabetes as a unique group for all diabetes mothers. Therefore, we cannot discount the possibility that differences in the type of diabetes may have a synergistic effect on language ability in children. Primary studies on different types of diabetes were inconclusive. For example, for the only study that presented adjustable extractable data related to diabetes group (children born to mothers with gestational diabetes and children born to mother with pre-existing diabetes and glycosuria), findings were consistently associated with equal language abilities in children, regardless of type of diabetes. Therefore, more studies are needed to unravel the effect of different types of diabetes and to establish which language subdomain are most affected.

We observed a significant heterogeneity among studies, which was partly explained by the fact that type of maternal diabetes and the type of measures were various and quite

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heterogeneous across studies. Child's age at time of assessment vary across studies, thus providing another explanation for the heterogeneity across studies.

It is suggested that in the event of high heterogeneity, a meta-analysis can be conducted using the random effects model [40-41] and that was used in the current review. As there were significant heterogeneity among the included studies in terms of how studies have defined diabetes in pregnancy and the instruments used for evaluating language development, it would have been impractical to carry out a review focusing on gestational diabetes or the type of the assessment tool or child's age only.

In conclusion, the results of this review recognise that exposure to maternal diabetes during pregnancy interrelate with other factors within the intrauterine environment to increase the risk for reduced language abilities in the child. We posit that several factors will act as moderating factors between diabetes and language outcomes in children, such as maternal obesity, other comorbidities and socio-economic factors. Those multiple moderating factors come to play with what may explain the large magnitude observed in the meta-analysis. Health care professionals and policy makers may focus interventions to keep optimal weight and blood glucose levels during pregnancy and to screen for early developmental delay after birth.

4.1.Limitations

Although the statistical evidence in our meta-analysis was adequate, there are a few shortcomings of the current findings.

First, language development was generally not the main focus of the included studies. Although analysis of total language or speech abilities was based on many studies, results for language subdomain were limited. As such, the pooled estimates were more inclined to the influence from individual studies and should be interpreted with caution.

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Second, the minimal number of studies retrieved meaning that any conclusions drawn from this review must be met with caution.

Thirds, not considering the effects of child's age, gender, and other maternal comorbidities might make our results biased to a large extent.-In this review we included data from three studies [18, 33, 37] which reported on language abilities in children before 3 years of age. Taking into consideration the major differences in language development between children aged 3 years and older it is very likely that our perspectives on the association between diabetes and language development will change as a result of excluding studies limited to children aged 3 years and younger. One of the other factors that needs to be taken into accounts is older sibling presence as it has been suggested that the number of older siblings a child has is negatively correlated with the child's language development.

Fourth, the accuracy of the language classification is still open to discussion, particularly in relation to general language skills and speech communication. The classification of language-subdomain based on the tool used in language assessment is not very clear-cut due to the complicated boundaries between instruments used in evaluating language development achievements, which is why the classification in the review could be somewhat subjective. We could have merged the general language skills with communication speech domain; however, this would have further increased the heterogeneity and added to the problems of generalizability owing to the complexity of language development in this population. In this context, it worth highlighting that we were able to combine numerous measures of language subdomains, ranging from well-established tools to those with lower specificity, but all analysis included studies with similar construct and were within theoretically and clinically relevant subdomains.

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Overall, despite the limitations, our meta-analysis indicated that exposure to maternal diabetes during pregnancy may be an increased factor for reduced language abilities in children. In addition, there are some strengths of this meta-analysis to be acknowledged. First this review was based on a priori protocol which decreases the potential for reviewer bias. Second, we conducted a comprehensive search on multiple databases that was updated through a frequent search with no limitations to time or place of publication. In addition, we had at least 2 independent reviewers screening and extracting relevant papers, with discrepancies between the reviewers discussed and managed by a third reviewer and thus ensuring a meticulous approach in study selection and review. Finally, there was no major methodological flaws of the included studies and which could have impact on the review results or introducing a high risk of bias.

4.2.Implications for research and practice

Our results suggest that maternal diabetes is described as a high-risk factor for reduced language abilities in children. The findings suggest that obesity, type of diabetes and other socio-economic factors and comorbidities moderate the overall effect and mediate this association. Future studies in this field must consider larger sample sizes for the diabetes group to generate a reasonable degree of statistical power and allow for an increase in generalizability. Researchers must also consider including homogeneous groups of maternal diabetes and values of glycaemic control to evaluate whether effects of diabetes maintained regardless of glycaemic level or type of diabetes. Inclusion of other moderating variables, such as mothers age, BMI, Vitamin D level during pregnancy, socio-economic status, and other comorbidities during gestation would be useful in addressing the multifactor aetiology

of risk for poor language abilities. Another potential issue of bias in included studies that should be considered is the lack of gender and age balance among studies. This is important given that males are more likely to have speech problems than females and language abilities are more evident in children below 5 years [43].

As the intrauterine exposure to maternal diabetes initiate negative language outcomes for children, healthcare professionals may want to consider developing and utilising diabetes-management resources to support optimal glycaemic control during pregnancy, especially for mothers with pre-gestational diabetes. Diabetes Australia has already developed improving access to resources and several services for women with diabetes and is aiming to incorporate diabetes services schemes into practice nationwide (https://www.diabetesaustralia.com.au/pregnancy). The inclusion of early developmental screening for children born to mothers with diabetes is likely to be an important consideration for policymakers as well.

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TABLES

Table 1. Inclusion criteria

Types of participants	The child born to diabetes mother, of either gender, and aged 12 years or less. Children born to mothers with other comorbidities such as obesity or hypertension will also be included if they have diabetes.
Phenomena of interest	The impact of intrauterine foetal exposure to maternal diabetes, with no limitation as to the type of maternal diabetes.
Outcomes	Outcomes of language development, and language delay in terms of expressive or receptive language, semantics, syntax of grammar, and/or general language domain. Verbal IQ was included as an outcome measure in the study as they are meaningful to the assessment of overall language development.
Other exclusion criteria	Unclear indicators of maternal diabetes during pregnancy Published in languages other than English Language outcomes related to auditory impairment, such as deafness. Those are excluded because they primarily involve other primary functions and may confound the results.

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Table 2. Studies included in the meta-analysis

Author (Year)	Sample description			Assessment tool and Language domain	Diabetes group			Control group			P-value	Effect size	Controlled variables
	Age at time of assessment	Type of DM	Other characteristics		N	Mean	SD	N	Mean	SD			
Dionne et al. [16]				***McArthur Communicative Development Inventory-SF (MCDI_SF)***									
	1.5 years	GDM	QNTS (n= 861)	Expressive vocabulary	116	-0.25	0.96	745	0.02	0.99	0.01*	-0.28	Adjusted for gestational age, child gender, gestation duration, birth weight, average Apgar score, gestational hypertension, and alcohol
	1.5 years	GDM	QNTS (861)	Receptive vocabulary	116	-0.06	1.00	745	0.00	0.99	0.53	-0.06	
	1.5 years	GDM	QNTS (861)	Receptive grammar	116	-0.10	1.16	745	0.02	0.98	0.46	-0.03	
	2.5 years	GDM	QNTS (764)	Expressive vocabulary	116	-0.33	1.22	648	0.04	0.96	0.01*	-0.34	
	2.5 years	GDM	QNTS (764)	Receptive vocabulary	116	-0.28	1.18	648	0.04	0.96	0.03*	-0.30	
	2.5 years	GDM	QNTS (764)	Receptive grammar	116	0.04	0.97	648	0.01	1.01	0.25	0.03	

	2.5 years	GDM	LSCDQ (955)	Expressive vocabulary	105	-0.28	1.09	850	0.02	0.99	0.03*	-0.29	and cigarette consumption during pregnancy.
	2.5 years	GDM	LSCDQ (955)	Receptive vocabulary	105	-0.18	1.10	850	0.01	0.98	0.14	-0.18	
	2.5 years	GDM	LSCDQ (955)	Receptive grammar	105	-0.38	1.21	850	0.03	0.97	0.003***	-0.37	
				Peabody Picture Vocabulary Test (PPVT)									
	3.5 years	GDM	LSCDQ (1728)	Receptive vocabulary	105	-0.16	0.81	1623	0.02	1.00	0.09**	-0.20	
	5 years	GDM	QNTS (721)	Expressive vocabulary	116	-0.12	0.90	605	0.04	0.99	0.49	-0.17	
	5 years	GDM	QNTS (721)	Receptive vocabulary	116	-0.09	0.86	605	0.01	1.01	0.43	-0.11	
				Early Development Instrument (EDI)									
	6 - 7 years	GDM	QNTS (833)	verbal communication	116	-0.30	1.21	717	0.05	0.96	0.03*	-0.32	
Fraser et al. [34]				***School Entry Assessment (SEA)***									
	4 years	Pre-existing diabetes		General score	26	12.7	4.2	8192	13.1	3.1	0.65	-0.11	Adjusted for sex, maternal age at birth.
	4 years	GDM		General score	33	13.0	2.8	8192	13.1	3.1	0.65	-0.03	
	4 years	Glycosuria		General score	264	12.9	3.1	8192	13.1	3.1	0.65	-0.06	

			Wechsler Intelligence Scale for Children (WISC-III)									pre-pregnancy BMI, maternal smoking in pregnancy, parity, mode of delivery, maternal education and social class, gestational age, birth weight standardized for gestational age, and duration of
	8 years	Pre-existing diabetes	Verbal IQ	26	108.0	19.6	8192	108.2	16.6	0.07**	-0.01	
	8 years	GDM	Verbal IQ	33	101.0	21.2	8192	108.2	16.6	0.07**	-0.38	
	8 years	Glycosuria	Verbal IQ	264	106.1	16.0	8192	108.2	16.6	0.07**	-0.13	

												breast feeding.
Krakowiak et al. [18]				***Mullen Scales of Early Learning (MSEL)***								
	2 - 5 years	T2DM, GDM	ASD	Receptive language	48	22.88	30.35	267	25.98	15.26	0.07**	-0.13	Adjusted for mother's age at delivery, race/ethnicity, education level, delivery payer, calendar time, child's age at enrolment, gender, and catchment area.
	2 - 5 years	T2DM, GDM	ASD	Expressive language	48	36.95	41.00	267	42.36	40.29	0.03*	0.00	
	2 - 5 years	T2DM, GDM	Without ASD	Receptive language	40	21.51	22.59	236	25.19	13.96	0.01*	-0.20	
	2 - 5 years	T2DM, GDM	Without ASD	Expressive language	40	36.99	18.44	236	42.23	18.27	0.03*	0.00	
				Vineland Adaptive Behaviour Scales (NABS)								
	2 - 5 years	T2DM, GDM	ASD	Communication	48	61.74	38.87	267	66.07	22.01	0.05*	-0.14	
	2 - 5 years	T2DM, GDM	Without ASD	Communication	40	87.08	53.99	236	92.53	25.75	0.12	-0.13	
Nomura et al. [35]				***Developmental Neuropsychological Assessment (NEPSY)***								

	3-4 years	GDM and high SES		NEPSY Language score	12	110.5	3.3	97	103.6	1.1	0.001***	2.81	Adjusted for age of mother, mother's alcohol use and smoking during pregnancy, age, sex, race/ethnicity, and birthweight of the child, and maternal ADHD symptoms, paternal ADHD symptoms,
	3-4 years	GDM and low SES		NEPSY Language score	9	95.6	2.9	97	103.6	1.1	0.001***	-3.65	
					21	151.81	8.25	191	158.74	2.72	NS	1.13	
				The Wechsler Preschool and Primary Scale of Intelligence (WPPSI)									
	3-4 years	GDM	GDM but not low SES	Verbal IQ	12	110.5	1.5	97	113.6	4.2	0.001***	-0.98	
	3-4 years	GDM	both GDM and low SES	Verbal IQ	9	92.3	2.7	97	113.6	4.2	0.001***	-6.03	
					21	157.89	9.45	191	155.44	7.50	N/A	-0.29	
	3-4 years	GDM	GDM but not low SES	General Language Composition	12	108.8	1.4	97	112.9	3.9	0.001***	-1.40	
	3-4 years	GDM	Exposed to both mother's GDM and low SES	General Language Composition	9	94.2	2.7	97	112.9	3.9	0.001***	-5.58	

													and risk-group status
					21	159.44	7.76	191	156.37	6.27	N/A	-0.44	
Ornoy et al. [21]				***Wechsler Intelligence Scales for Children (WISC)***									
	Diabetes mothers (T1DM, T2DM)			Verbal IQ	57	112.4	12.0	57	114.4	12.0	N/A	-0.17	Groups were matched for age, SES (based on parental education and occupation), gestational age, birth order and family size.
	GDM			Verbal IQ	32	108.0	11.5	57	114.4	12.0	N/A	-0.54	
Qiao et al. [33]				***Gesell Infant Development Scale (GESELL)***									
	2 years	Diabetes mothers	BGC < 2.6 mM at < 2 h after birth	General language	103	91.7	12.3	144	89.6	11.4	NS	0.18	None

	2 years	Diabetes mothers	BGC < 2.6mM at 2–24 h after birth	General language	38	88.5	10.3	144	89.6	11.4	NS	-0.10	
	2 years	Diabetes mothers	BGC < 2.6mM at > 24 h after birth	General language	16	89.3	8.7	144	89.6	11.4	NS	-0.03	
Sells et al. [36]				***Stanford -Binet Test (S-BT)***									
	3 years	Diabetes mothers	Early entry infants	Verbal reasoning	44	110	10.2	65	114	12.4	NS	-0.35	Adjusted for parents' education
	3 years	Diabetes mothers	Late entry infants	Verbal reasoning	17	105	14.2	65	114	12.4	NS	-0.68	
				Peabody Picture Vocabulary Test (PPVT)									
	3 years	Diabetes mothers	Early entry infants	Receptive language	46	111	10.1	68	114	11.0	NS	-0.28	
	3 years	Diabetes mothers	Late entry infants	Receptive language	23	105	11.4	68	114	11.0	NS	-0.80	
				Mean length of utterance (ML-U)									
	3 years	Diabetes mothers	Early entry infants	Expressive language	46	4.0	0.86	68	4.1	1.0	NS	-0.11	

	3 years	Diabetes mothers	Late entry infants	Expressive language	23	3.7	0.91	68	4.1	1.0	NS	-0.42	
				Vineland Adaptive Behaviour Scales (VABS)									
	3 years	Diabetes mothers	Early entry	Communication	47	110	9.2	67	111	10.2	NS	-0.10	
	3 years	Diabetes mothers	Late entry infants	Communication	22	103	11.5	67	111	10.2	NS	-0.74	
Stenninger et al. [19]				***Griffiths' Mental Developmental Scales (GMDS)***									
	8 years	GDM, T1DM	Hypoglycaemic	Hearing and speech	13	6.4	1.7	28	7.7	1.6	NS	-0.79	None
	8 years	GDM, T1DM	Non hypoglycaemic	Hearing and speech	15	7.0	1.6	28	7.7	1.6	NS	-0.44	
Torres-Espinola et al. [37]				***Bayley Scales of Infant Development, Third Edition (BSID-III)***									
	6 months	GDM		Composite language	58	108.1	8.6	81	104.9	10.1	0.022*	0.34	Adjusted for maternal age, maternal education, placental weight, and
	6 months	GDM		Expressive language	58	10.4	1.7	81	10.0	1.9	0.010*	0.22	
	6 months	GDM		Receptive language	58	12.3	2.1	81	11.6	2.2	0.0351**	0.33	

	1.5 years	GDM		Composite language	50	106.0	6.5	75	107.9	9.3	0.375	-0.24	weight gain during pregnancy
	1.5 years	GDM		Expressive language	50	10.4	1.5	75	10.7	1.9	NS	-0.18	
	1.5 years	GDM		Receptive language	50	11.6	1.4	75	11.9	1.8	NS	-0.19	
Veena et al. [20]				***Kaufman's Assessment Battery for Children—Second Edition***									
	5 years	GDM		Verbal ability – animals (verbal fluency)	32	13.1	3.0	483	12.0	3.3	0.07**	0.35	Adjusted for child's sex, gestation, age, SES, parents' education, rural/urban residence, maternal age, BMI and parity in pregnancy and child's
	5 years	GDM		Verbal ability – names (verbal fluency)	32	18.2	5.2	483	16.0	4.9	0.01*	0.44	

													weight and head circumference at birth

QNTS: The Quebec Newborn Twin Study; LSCDQ: The Quebec Longitudinal Study of Child Development; BCG: Blood glucose concentration; GDM: Gestational Diabetes; T1DM: Type 1diabetes; T2DM: Type 2 diabetes; ASD: Autism spectrum Disorder; SES: socio-economic status

*** P < 0.05; ** Borderline significant (P < 0.09)**

Table 3. Studies not included in the meta-analysis

Author	Main outcome measure	Sample size	Results reported for	Main language findings	Significant p value when compared with controls or other groups
deRegnier et al. [22]	MacArthur Percentile Scores	n=22 diabetes group n = 27 control	Phrases Vocabulary comprehension Vocabulary production	*Percentile ranks* 43±6 44±6 35± 5 37±6	 NS NS NS NS
Taylor et al. [42]	MacArthur Communicative Development Inventories: Words and Sentences (CDI-WS)	n= 946 Twin pair infants) LLE_GDM group n=25 NLE_GDM n=21	Language development	*Bivatiate OR and CI* 9.6 [0.8, 122.2] Adjusted OR and CI 19.5 [1.2, 313.1]	

LLE: Late Language Emergence (LLE); NLE: normal language emergence

Table 4. Meta-analysis results classified by

Language subdomain		Number of studies	Sample size		Effect size (z)	95% CI	I^2
			Diabetes group	control			
General language							
	1st meta-analysis	2	199	820	-0.76	-1.01 [-3.60, 1.58]	99%
	2nd meta-analysis	2	136	432	0.73	-0.34 [-1.27, 2.76]	28%
Receptive language							
	1st meta-analysis	4	832	5267	-3.49**	-0.17 [-0.27, -0.08]	34%
	2nd meta-analysis	4	252	984	1.59	-1.58 [-3.35, 0.37]	98%
Expressive language							
	1st meta-analysis	5	770	3273	-2.29**	-0.44 [-0.42, -0.06]	94%
	2nd meta-analysis	5	265	1012	-1.33	-1.33 [-3.31, 0.65]	99%
Speech communication							
	1st meta-analysis	3	274	1353	-4.12*	-0.28 [-0.42, -0.15]	2.0%
	2nd meta-analysis	3	203	1020	-1.38	-2.37 [-5.74, 1.00]	97%
Verbal intelligence							
	1st meta-analysis	5	631	25980	-1.48	-0.64 [-1.48, 0.21]	99%

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2nd meta-analysis	5	167	9085	0.36	0.66 [-2.91, 4.24]	78%
3rd meta-analysis- GDM	4	102	8829	-0.85	-0.21 [-0.69, 0.27]	80%
4th meta-analysis- Pre-existing	3	127	8314	-1.79*	-0.20 [-0.42, 0.02]	0.0%

Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?

Table 5. Critical Appraisal Results of the Case Control Study

Citation	**Q1** Were the groups comparable other than the presence of disease in cases or the absence of disease in controls	**Q2** Were cases and controls matched appropriately?	**Q3** Were the same criteria used for identification of cases and controls?	**Q4** Was exposure measured in a standard, valid and reliable way?	**Q5** Was exposure measured in the same way for cases and controls?	**Q6** Were confounding factors identified?	**Q7** Were strategies to deal with confounding factors stated?	**Q8** Were outcomes assessed in a standard, valid and reliable way for cases and controls?	**Q9** Was the exposure period of interest long enough to be meaningful?	**Q10** Was appropriate statistical analysis used?
deRegnier et al. [22]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Krakowiak et al. [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ornoy et al. [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Stenninger et al. [19]	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Torres-Espinola et al. [37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
%	100.0	100.0	100.0	100.0	100.0	66.66	50.0	100.0	100.0	100.0

Table 6. Critical Appraisal Results of the Cohort study

Citation	**Q1** Were the two groups similar and recruited from the same population?	**Q2** Were the exposures measured similarly to assign people to both exposed and unexposed groups?	**Q3** Was the exposure measured in a valid and reliable way?	**Q4** Were confounding factors identified?	**Q5** Were strategies to deal with confounding factors stated?	**Q6** Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	**Q7** Were the outcomes measured in a valid and reliable way?	**Q8** Was the follow up time reported and sufficient to be long enough for outcomes to occur?	**Q9** Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	**Q10** Were strategies to address incomplete follow up utilized?	**Q11** Was appropriate statistical analysis used?
Dionne et al. [16]	Y	Y	Y	Y	Y	N/A	Y	Y	N	N	Y
Fraser et al. [34]	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N	Y
Nomura et al. [35]	Y	Y	Y	Y	Y	N/A	Y	Y	Y	N/A	Y
Qiao et al. [33]	Y	Y	U	N	N	N/A	Y	Y	N	N	Y
Sells et al. [36]	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y

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Taylor et al. [42]	Y	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	Y
Veena et al. [20]	Y	Y	Y	Y	Y	N/A	Y	Y	N/A	N/A	Y
%	100.0	100.0	85.71	85.71	85.71	0.0	100.0	100.0	42.85	14.28	100.0

Figures

Figure 1. PRISMA flow diagram. Summary of literature search and selection process (For listing of included full-text articles, see supplemental material Tables 2 and 3).

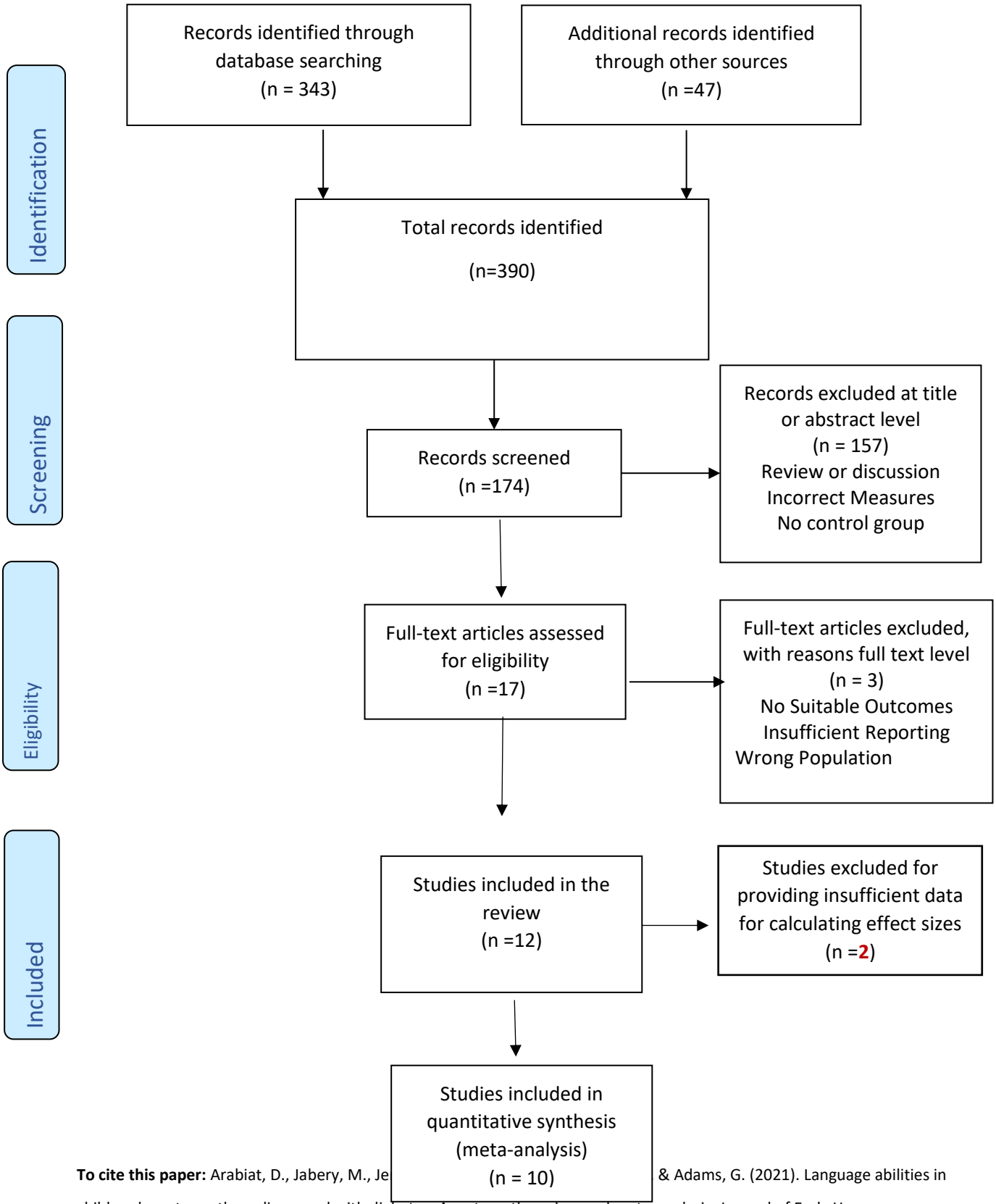

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Figure 2. Forest plots of the effect sizes for each study included in the 1st and following meta-analysis for the following domains: (A) general language domain, (B) receptive language domain, (C) expressive language domain, (D) speech communication, and (E)verbal intelligence.

(A) General language domain

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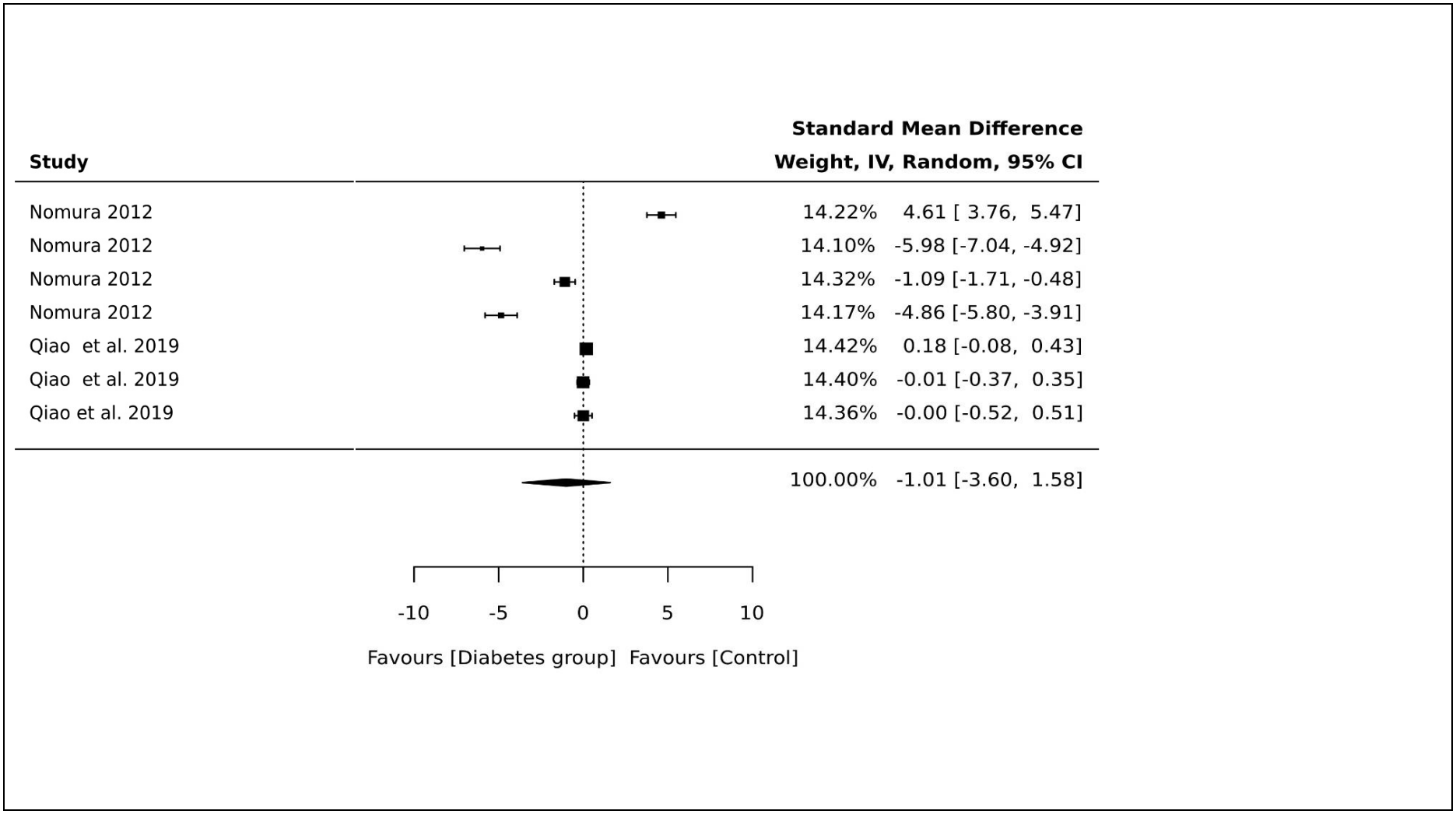

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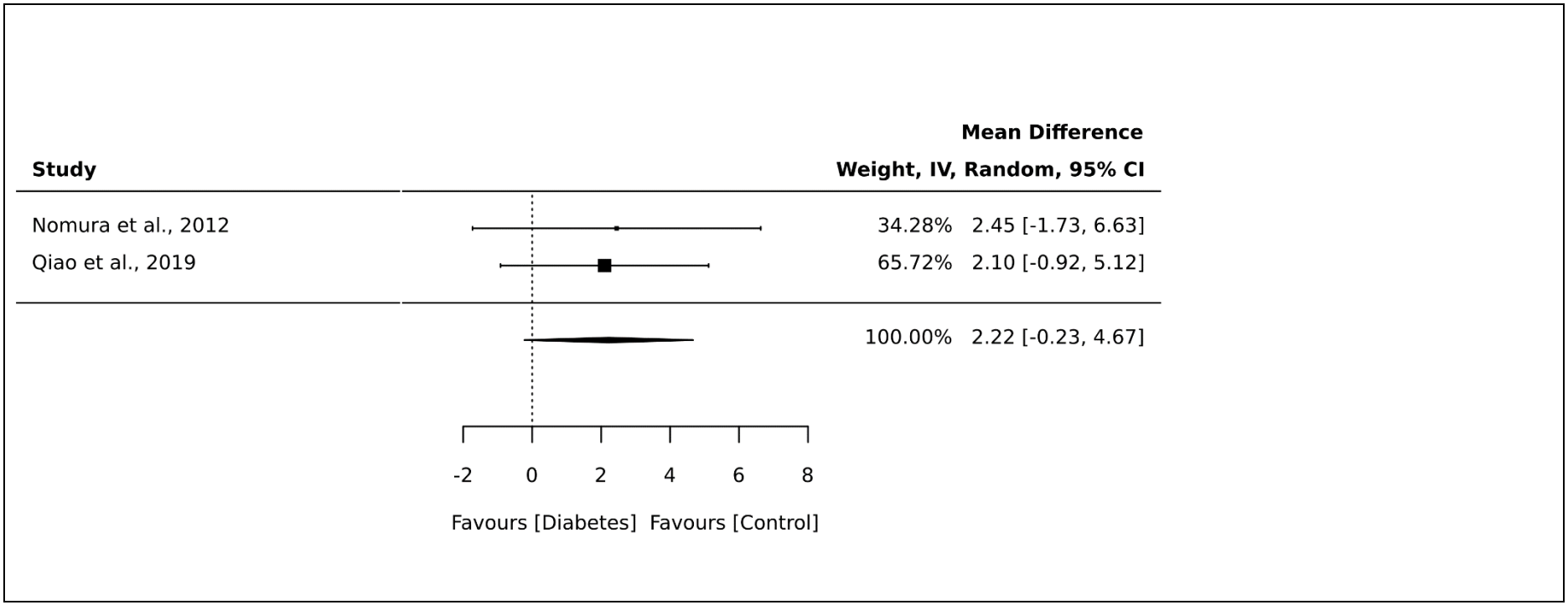

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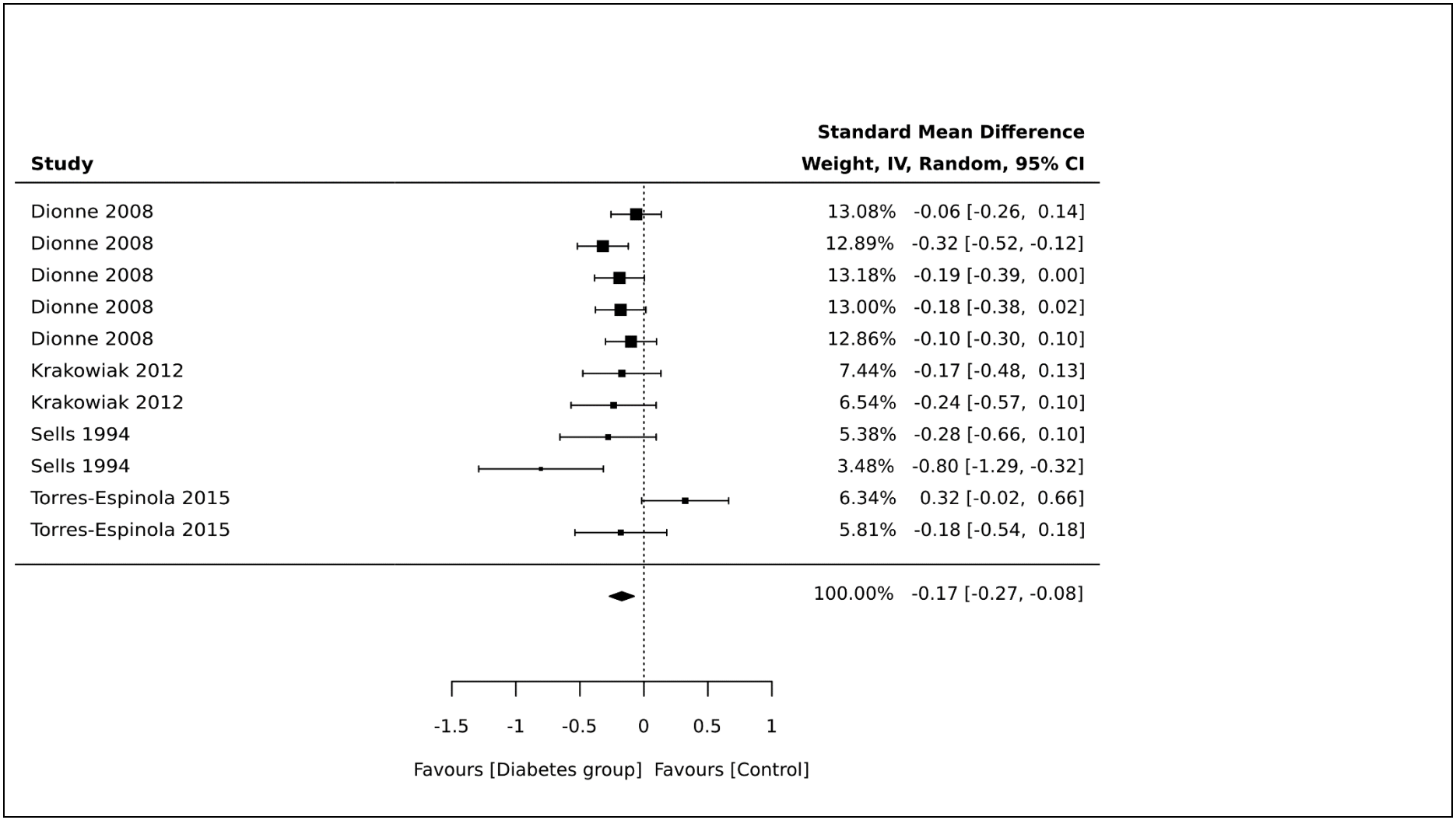
(B) Receptive language



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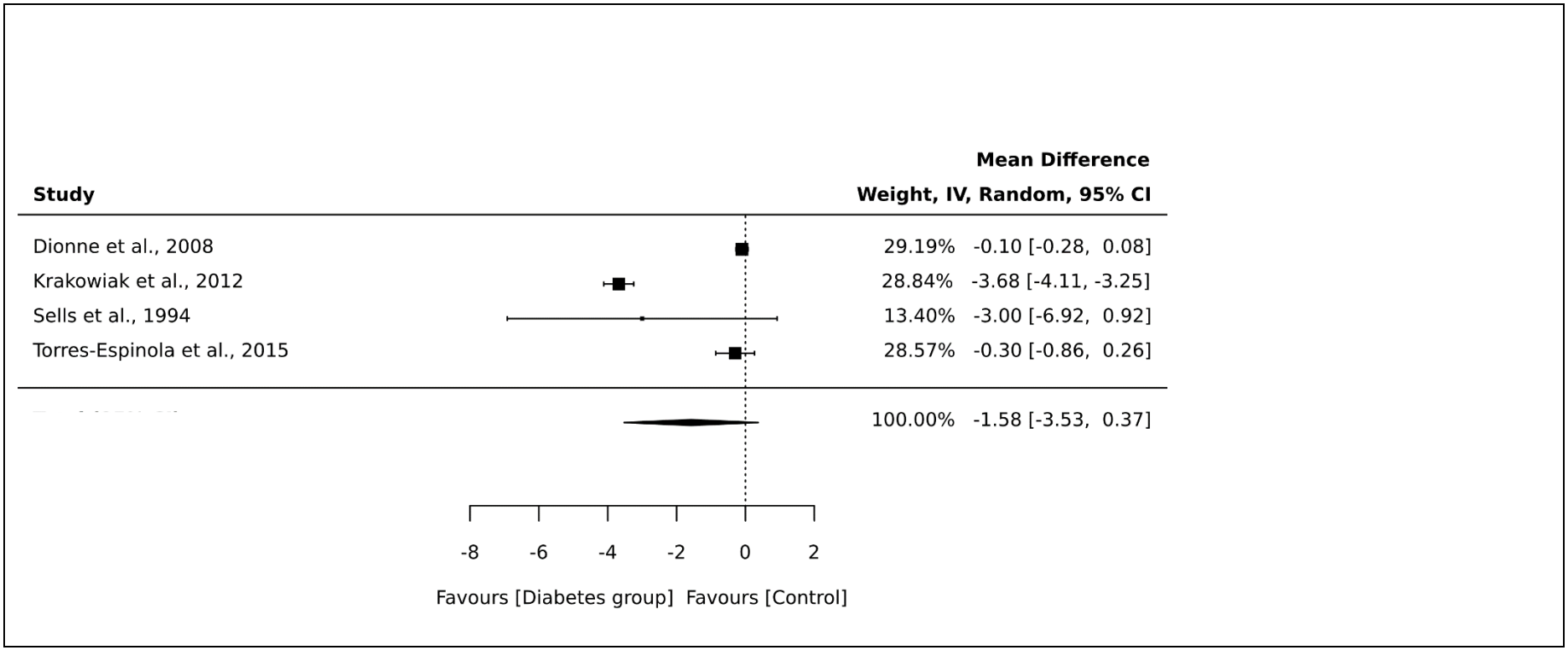

* P < 0.05; ** P < 0.001

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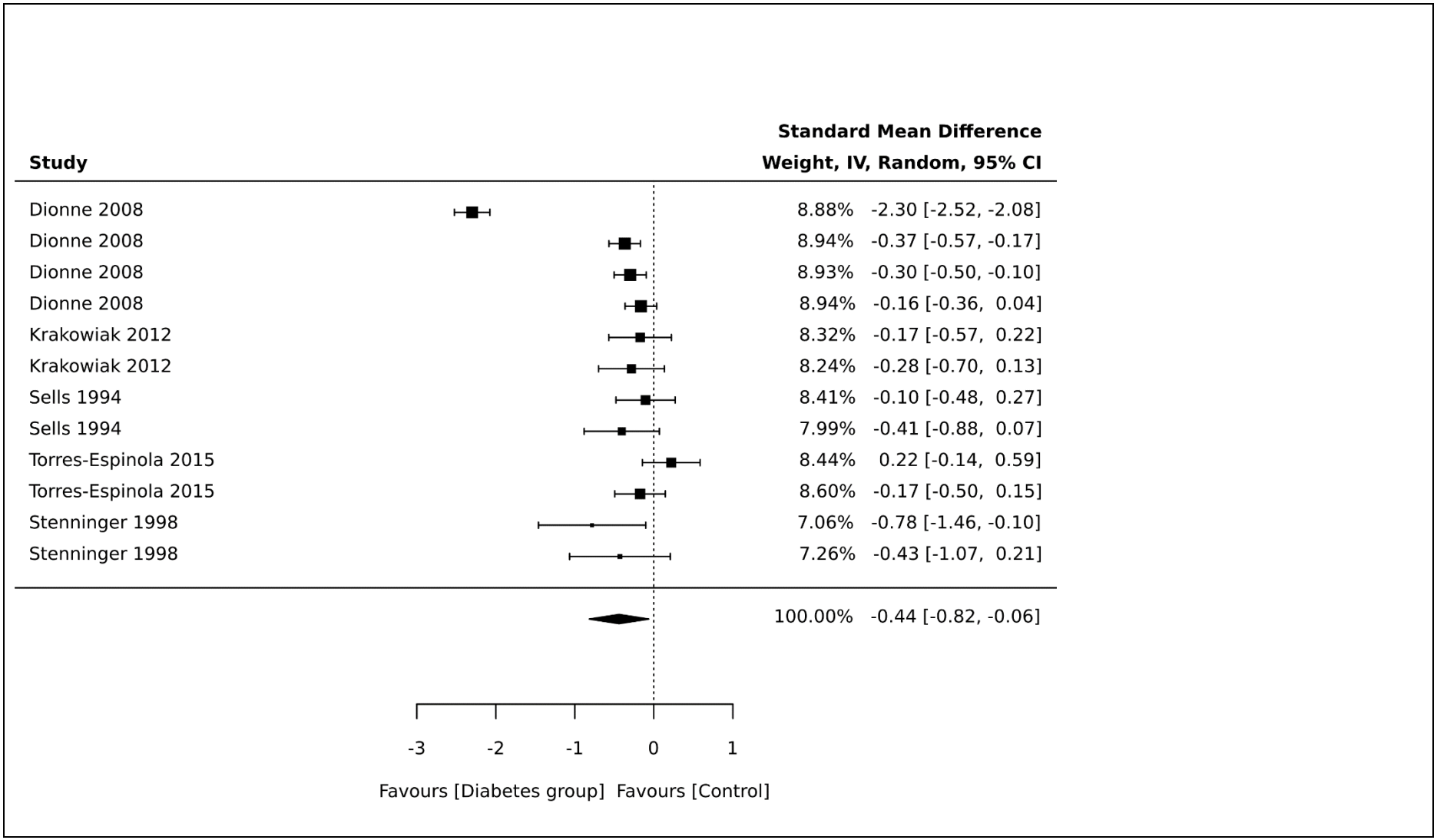
(C) Expressive language



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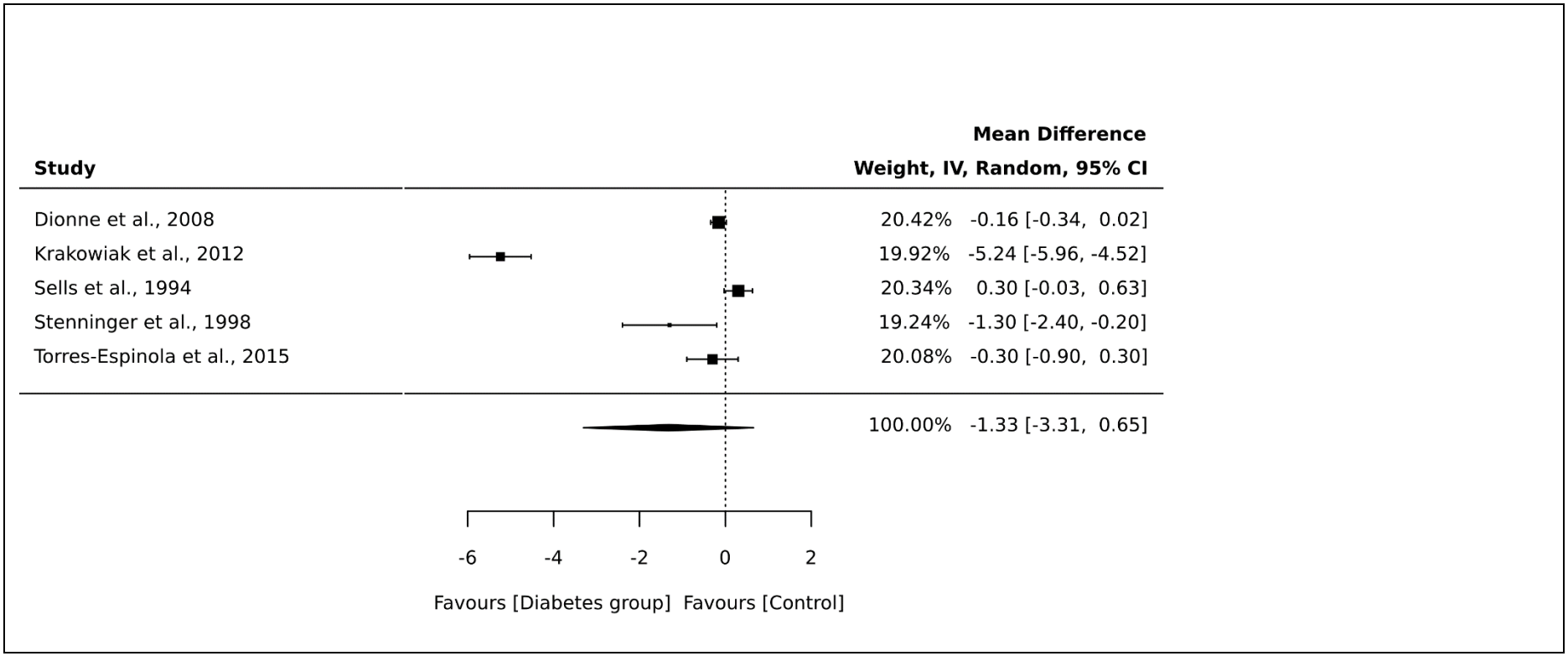

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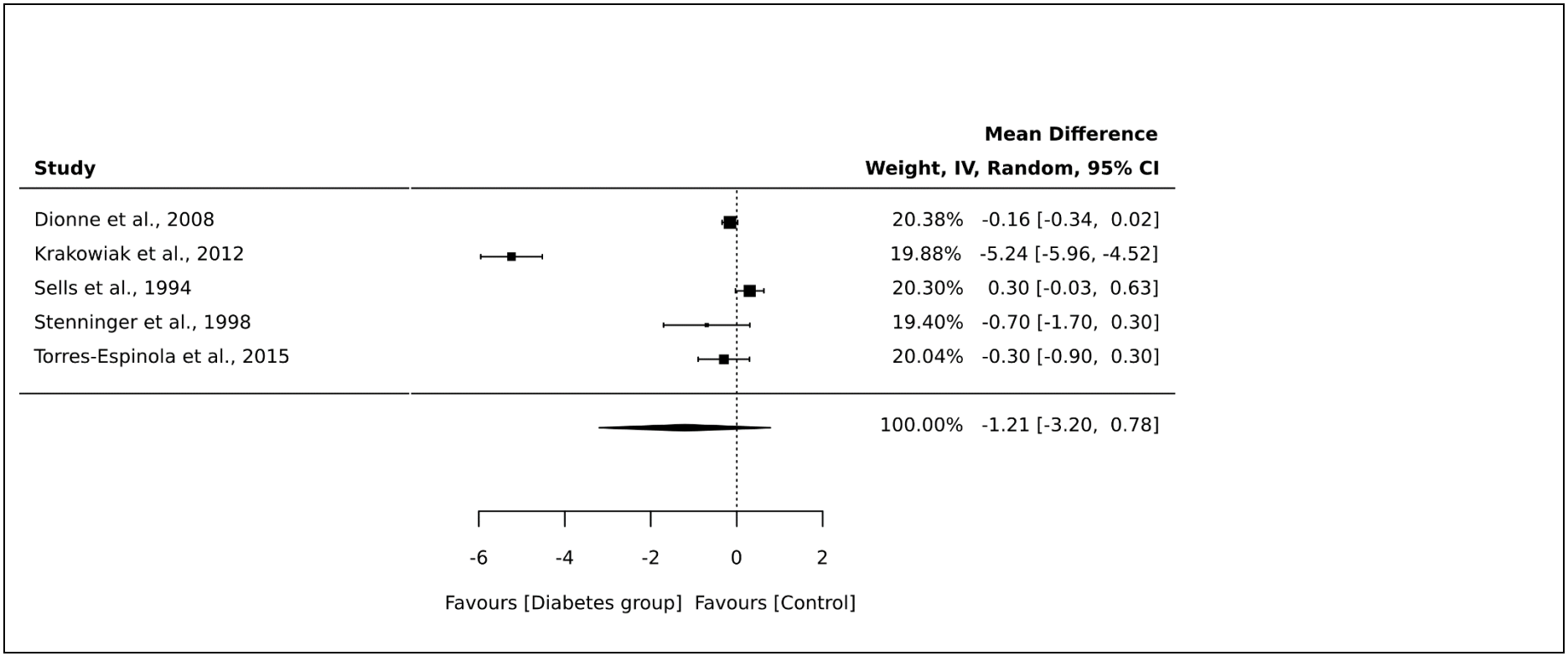

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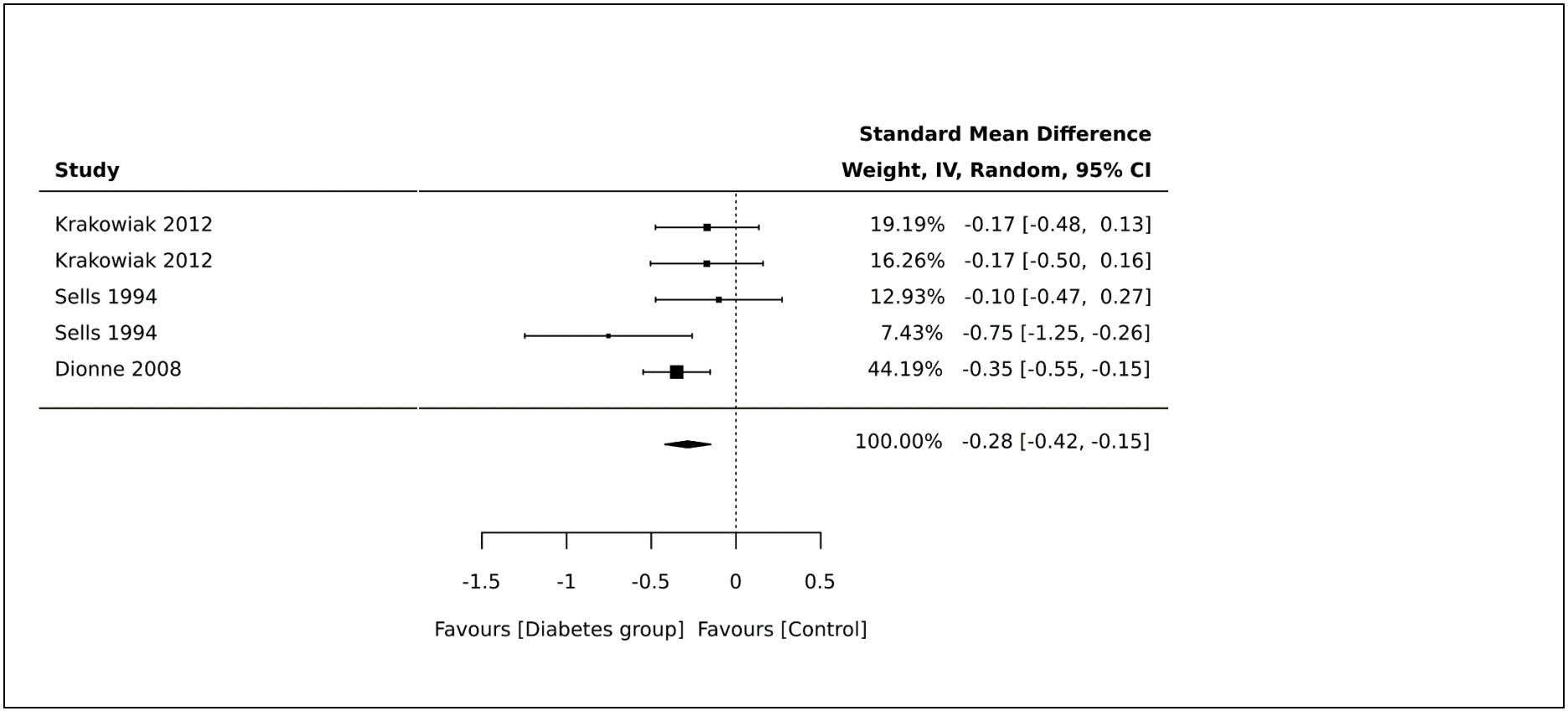
(D) Speech communication



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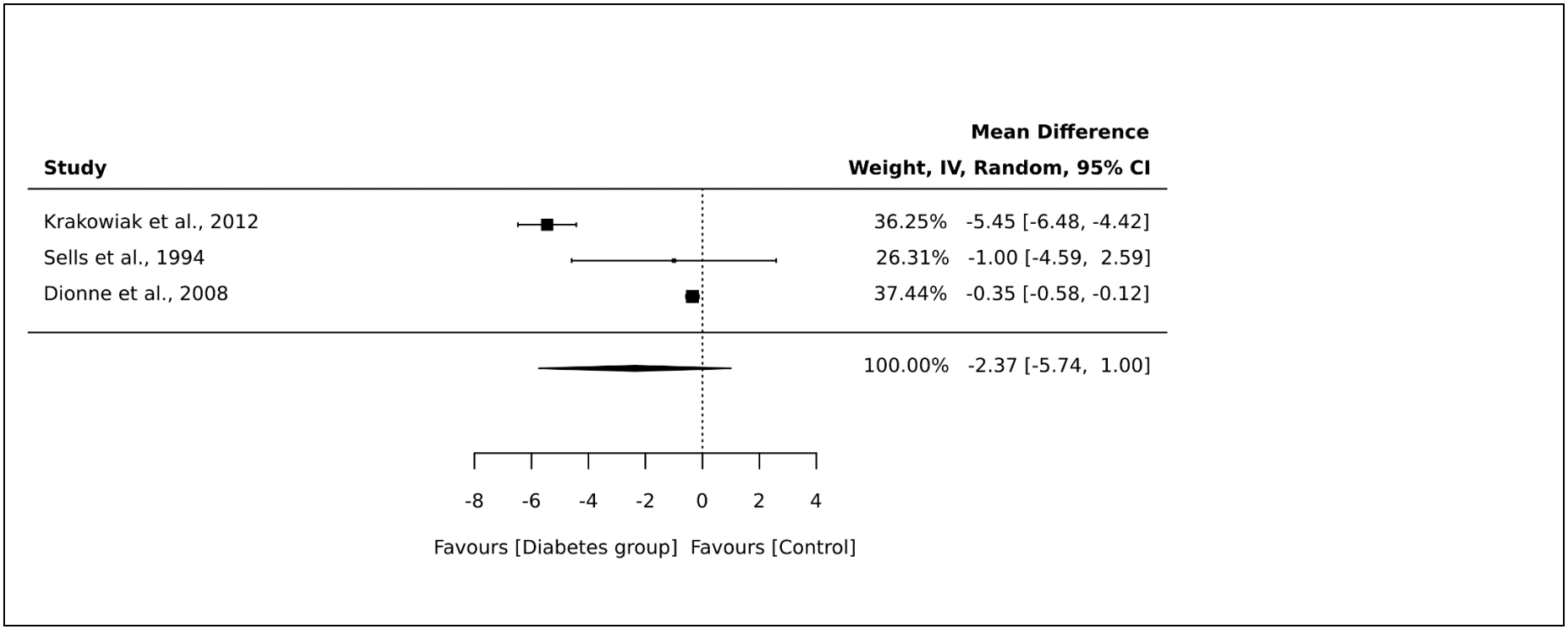

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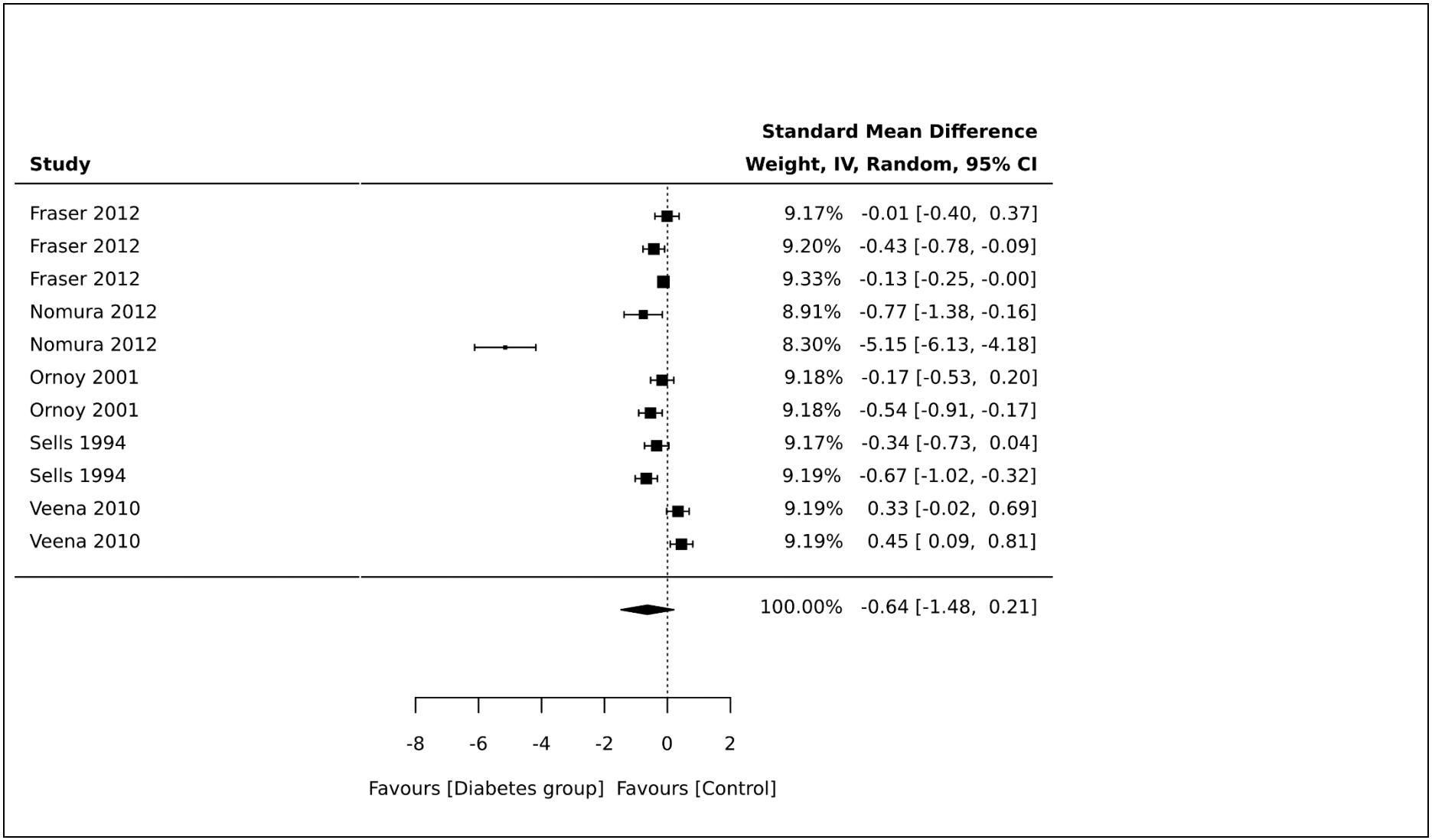
(E) Verbal intelligence



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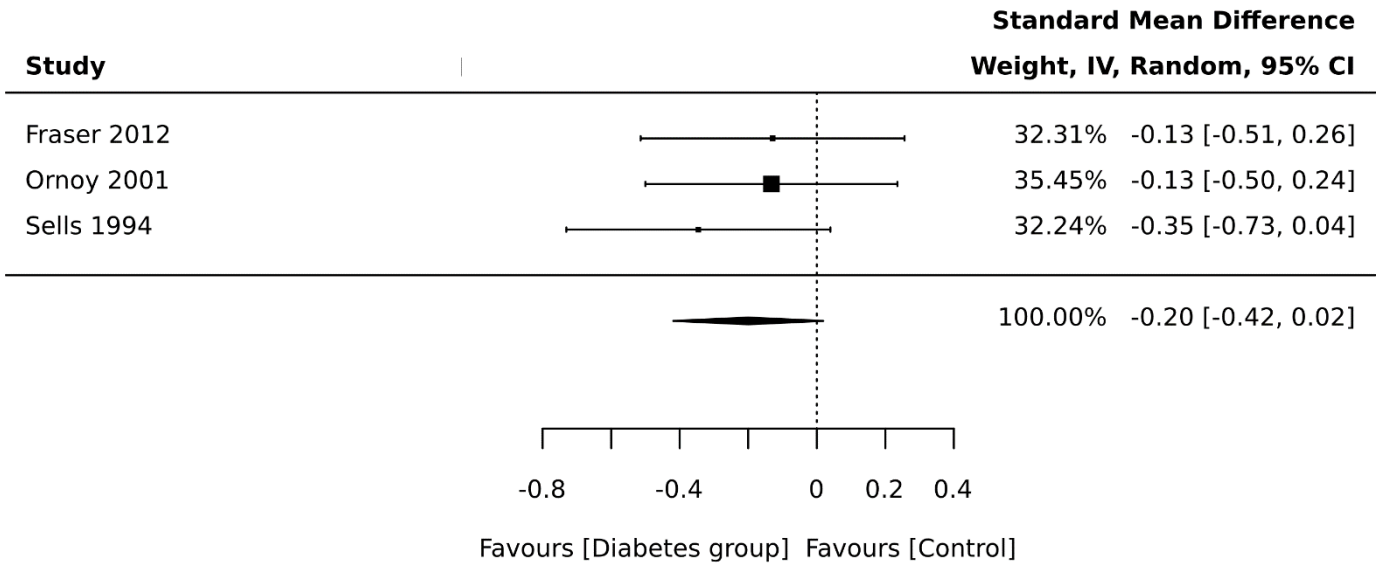
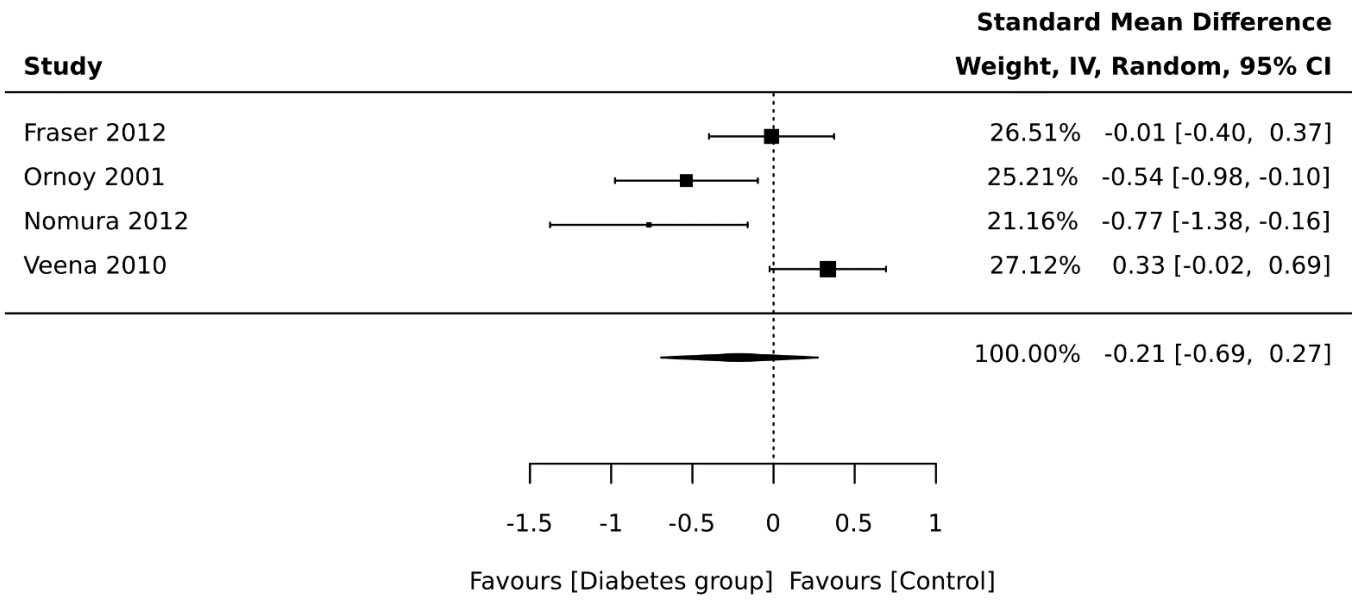
Pre-existing diabetes



Gestational diabetes



Square data markers represent effect size estimates (z), with size of the markers corresponding to 95% CLs and diamond data markers representing the overall effect size based on included studies.

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