Association between gestational diabetes mellitus and allergic diseases in children

Zhi Li[1], Mei Yu[1], Pin Wang[2], Hong Qian[1], Yun Fan[1], Xiuzhu Li[1], Qiaoqiao Xu[1], Xinru Wang[1], Xu Wang[3], and Chuncheng Lu[1]

[1]Nanjing Medical University
[2]Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital
[3]Nanjing Children's Hospital

September 10, 2020

Abstract

Background: Existing knowledge suggests that gestational diabetes mellitus was inconsistently associated with children allergic diseases. The aim of this study was to identify the association between gestational diabetes mellitus (GDM) and the risk of children allergic diseases by systematic review. Methods: We searched and retrieved three databases (PubMed, Web of Science and Cochrane Library) for articles on the association between GDM and children allergic diseases published before December 31, 2019. Stata software version 16.0 was used for statistical analysis. Results: Eight published studies were included in this meta-analysis. The pooled effect estimates showed the association between GDM and allergic outcomes, including asthma (OR:1.13,95%CI:1.01-1.27), wheezing (OR:1.12,95%CI:1.08-1.16), and atopic dermatitis (OR:1.41,95%CI:1.31-1.53). GDM was not associated with the risk of allergic sensitization, with a pooled effect estimate of 1.45 (95%CI: 0.40, 5.23). Conclusion: GDM may increase the risk of allergic diseases in children. However, this finding should be validated with future large-sample epidemiological studies covering a wider spectrum of allergic diseases.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as diabetes that is diagnosed in the second or third trimester of pregnancy and not overt prior to gestation (1). Over the past decade, the prevalence of GDM has been on the rise (2). In 2013, International Diabetes Federation (IDF) conducted a comprehensive survey based on the data from 47 epidemiological studies in 34 countries and regions around the world. The global prevalence of hyperglycemia in pregnant women (20-49 years) was 16.9%, and that of GDM was 14.2% for the same group; about 21.4 million live births showed signs related to maternal hyperglycemia (3). The incidence of GDM varies with countries, and all show an upward trend.

GDM causes adverse events both in women and children , such as maternal type 2 diabetes and obesity in children (4, 5). Previous epidemiological studies have found that GDM may increase the risk of childhood allergic diseases, including asthma and atopic dermatitis (6, 7). Current population-based research results are inconsistent. Delayed pneumocyte differentiation and lung maturation were observed in the offspring in rodent models of diabetes during pregnancy (8-11). The possible mechanism for their pathogenesis is that phosphatidylglycerol production may be inhibited in gestational diabetes, resulting in reduced surfactants and increased susceptibility to respiratory distress syndrome, which may also explain the increased risk of persistent wheezing in human infants born to women with GDM (12).

Food allergy, wheezing, asthma and eczema are the most common allergic disorders in children (13). Four endpoints were set in the present study: asthma, atopic dermatitis, food allergy and wheezing. To date, their association with GDM has not been systematically reviewed, and the results of existing studies on

the association are inconsistent. Thus, we conducted a meta-analysis to evaluate the findings of previous epidemiological studies.

METHODS

Selection criteria

Inclusion criteria

1. Epidemiological studies based on human populations, such as cohort studies, case control studies and cross-sectional studies that identify the association between gestational diabetes mellitus and allergic diseases in the children.

2. Exposure factors relating to GDM.

3. Outcomes relating to allergic diseases in children born to GDM women, including atopic dermatitis, food allergy, asthma, and wheezing.

Exclusion criteria

1. Research articles not published in English.

2. Animal studies, published letters, conference abstracts, editorials or comments, reviews and lecture materials, randomized controlled studies.

3. Studies just about molecular mechanisms.

4. Poor research design and quality, including statistical unavailability.

5. Studies unrelated to GDM and children allergic diseases.

Search strategy

We retrieved appropriate articles published by PubMed, Web of Science and Cochrane library before December 31, 2019 through entering the following terms:

Atopic dermatitis:

#1: (maternal) or (pregnancy) or (pregnant women)

#2: (diabetes) or (diabetes Mellitus) or (endocrine) or (blood glucose)

#3: (hypersensitivity) or (allergy) or (allergy and immunology) or (allergic disease) or (eczema) or (atopic dermatitis)

#4: #1 AND #2 AND #3

Food allergy:

#1: (maternal) or (pregnancy) or (pregnant women)

#2: (diabetes) or (diabetes Mellitus) or (endocrine) or (blood glucose)

#3: (hypersensitivity) or (allergy) or (allergy and immunology) or (allergic disease) or (food hypersensitivity) or (food allergy) or (food allergen sensitization)

#4: #1 AND #2 AND #3

Asthma:

#1: (maternal) or (pregnancy) or (pregnant women)

#2: (diabetes) or (diabetes Mellitus) or (endocrine) or (blood glucose)

#3: (hypersensitivity) or (allergy) or (allergy and immunology) or (allergic disease) or (asthma) or (respiratory allergy)

#4: #1 AND #2 AND #3

All retrieved articles were imported to Endnote version X9 for screening, deduplication, and overall management of the retrieved records.

Study screening and data extraction

Retrieved articles were independently screened according to titles and abstracts by two reviewers. Any discrepancy was resolved by discussion. The same process was employed for full-text screening. The full texts were assured by cross checking by consensus for validation and accuracy. The following data as the characteristics of various studies was extracted from eligible studies: first author's name, publication year, research design, sample size, country, type of allergic diseases in the children, effect estimates (odds ratios, hazard ratios, risk ratios or prevalence ratios) and 95% confidence interval. All data was imported to Excel for analysis.

Quality assessment

The quality of included studies and risk of bias were assessed by two reviewers using Newcastle Ottawa Scale (NOS, a design-specific scale –case–control vs. cohort study) independently (14). Three items were contained in NOS, including selection of study subjects, comparability, exposure assessment and outcome. Eight items were used to identify the quality of study. In exposure/outcome assessment, each item could be given one star, and comparability a maximum of two stars. As such, the total score ranges from zero to nine stars (15). Study inclusion was not affected by quality score, but considered in sensitivity analysis and results interpretation.

Statistical analysis

Meta-analysis was conducted using Stata software 16.0 (Stata, College Station, TX, USA). The outcomes of the dichotomous variables, such as odds ratio (OR) and hazard risk ratio, were included in this study. The included effect estimates (OR, PR, RR and HR) were combined together in subgroup analysis (16, 17). The I^2 statistical test was used to assess the heterogeneity of included studies. The findings with $p < 0.05$ were statistically significant. When the estimated effect was heterogeneous ($I^2 > 50\%$ or $p < 0.05$), the random effect model was applied; otherwise, the fixed effect model was applied. The sensitivity of each study was assessed by omitting one study at one time to reduce heterogeneity of the included studies. We did not assess publication bias because less than ten studies were included (18).

RESULTS

Study search and characteristics overview

We retrieved 2153 articles published before December 31, 2019 about the outcome of asthma from PubMed (613 articles), Web of Science (548 articles) and Cochrane Library (992 articles). Duplicated articles were removed automatically (n=358). After reviewing titles and abstracts from 1795 articles, 1782 studies were excluded, including 575 reviews, lecture materials, and randomized controlled study; 115 animal studies; 1021 studies unrelated to our research objective; 44 molecular mechanism studies; 25 articles duplicates excluded manually and 2 non-English studies. Of the remaining 13 full-text publications, five were further excluded due to various reasons, only abstract, incomplete statistics and irrelevant exposure. Finally, eight articles were included in this meta-analysis. (Figure 1)

We retrieved 1431 articles published before December 31, 2019 about the outcome of atopic dermatitis from PubMed (723 articles), Web of Science (240 articles), and Cochrane Library (468 articles). Duplicated articles were removed automatically (n=133). After reviewing the titles and abstracts of 1,298 articles, 1,291 studies were excluded, including 453 reviews, presentation materials and randomized controlled studies;106 animal studies; 707 studies unrelated to our research objective; 11 molecular mechanism studies; 13 repeated

studies, and 1 non-English study. Of the \soutleft remaining seven full-text articles, one written in an abstract was excluded. In the end, six studies were included for analysis. (Figure 1)

We retrieved 1,374 articles published before December 31, 2019 on the outcome of food allergy from PubMed (697 articles), Web of Science (223 articles) and Cochrane Library (454 articles). Duplicated articles were automatically removed (n = 123). After reviewing the titles and abstracts of 1251 articles, 1243 studies were excluded, including 426 reviews, lecture materials and randomized controlled studies; 102 animal studies; 690 items unrelated to the research objective; 16 molecular mechanism studies; 9 repeated studies. Of the remaining eight full-text publications, one abstract was excluded. Finally, seven articles were included .(Figure 1)

To sum up, a total of eight articles were included. (Table 1)Several of them provided multiple sets of outcomes, with different effect estimates and 95% confidence intervals. Six studies were cohort studies; two were case-control studies. All studies were human population based. In the two case-control studies, the size of case groups ranged from 916 to 14,803, and the size of control groups ranged from 16,527 to 1,386,029; and the size of cohort studies ranged from 131 to 965,224.

Relationship between GDM and children allergic diseases

Overall, GDM was associated with the risk of children allergic diseases, with a pooled effect estimate of 1.17 (95%CI: 1.10, 1.25). Considering the heterogeneity of the included studies (I^2 =65.8%, P=0.000), random effect model was used to show the relationship between GDM and children allergic diseases. The results were shown in Figure 2.

GDM and children asthma

Four studies were included in the subgroup analysis. The study population of one of study was divided into four groups based on preterm or term delivery (Very preterm <32 weeks; Moderate preterm 32+0–33+6 weeks; Late preterm 34+0–36+6 weeks; Term [?]37 weeks)(7). The pooled effect estimate between GDM and children asthma was 1.13 (95% CI: 1.01, 1.27). Due to the heterogeneity of the study (I^2 = 58.3%, P = 0.026), a random effect model was used to show the relationship between GDM and children asthma .(Figure 3(a))

GDM and children wheezing

Three studies about wheezing, though different in types, were included in subgroup analysis. The endpoints were set as transient early wheezing, persistent wheezing and late-onset wheezing (19), or ever wheezing and recurrent wheezing (20). Due to a variety of types of GDM (presentational type 1 diabetes, presentational type 2 diabetes, and gestational diabetes), wheezing (early-onset transient wheezing, early-onset persistent wheezing, late-onset wheezing), 9 sets of data were derived from Liu's study (21). GDM was associated with the risk of wheezing in children, with a pooled effect estimate of 1.12 (95%CI:1.08, 1.16). Due to heterogeneity of the studies with (I^2 =54.6%, P=0.015), a fixed effect model was used to show the relationship between GDM and wheezing. (Figure 3(b))

GDM and children atopic dermatitis

Subgroup analyzes included two studies. The merger effect estimate between GDM and atopic dermatitis was 1.41 (95% CI: 1.31, 1.53). In Rajesh Kumar's study(22), children were divided according to full-term delivery and preterm delivery. The children with atopic dermatitis were divided into four groups (premature delivery <32 weeks; moderate preterm delivery 32 + 0–33 + 6 weeks; premature delivery 34 + 0–36 + 6 weeks; semester [?] 37 weeks) (7). Due to the heterogeneity of the study (I^2 = 35.0%, P = 0.174), a fixed effect model was used to show the relationship between gestational diabetes and atopic dermatitis. (Figure 3(c))

GDM and children allergen sensitization

One study was included in subgroup analysis, with a pooled effect estimate of 1.45 (95%CI:0.40, 5.23).

In this study, the sensitization outcomes included food sensitization, aeroallergen sensitization and total sensitization (22). Allergen sensitization was defined as specific IgE>0.10 kUA/L resulting from at least one of the tested allergens, including food (egg white, milk, peanut, soy, shrimp, wheat, and walnut) and aeroallergens (dermatophygoides pteronyssinus and dermatophygoides farinae, German cockroach, cat, dog, and Alternaria alternata). Similar criterion was used in other studies (23, 24). Due to the heterogeneity of the studies (I^2 =70.5%, P=0.005), a random effect model was used to show the relationship between gestational diabetes and sensitization. (Figure 3(d))

Subgroup analysis

A subgroup analysis was conducted based on the type of epidemiological study, finding showing that the cohort studies were highly heterogeneous (I^2= 67.7%, p = 0.000) while the heterogeneous of case-control studies was reduced to 0 (I^2= 0.0%, p = 0.927). (Figure 4)

Sensitivity analysis

Sensitivity analysis was conducted in clearly-defined GDM patients and not clearly defined GDM patients respectively.The findings were not statistically different, with a pooled effect estimate of 1.10 (95%CI:1.04, 1.17) in clearly-defined GDM patients studies and 1.19(95%CI:1.10, 1.28) in undefined GDM patients studies. It indicated the reliability of the studies included in this meta-analysis. A fixed effect model was uesd in clearly-defined GDM patient studies to show the heterogeneity of the studies with (I^2 =57.2%, P=0.009) and a random effect model in undefined GDM patients studies (I^2=67.4%, P=0.000). (Figure 5)

DISCUSSION

In this study, we examined the effect of GDM on children allergic diseases. Based on eight studies (two case-control studies and six cohort studies), this meta-analysis found that compared to the normal, the children born to GDM women were at a 17% higher risk of allergic diseases (OR:1.17, 95%CI:1.10-1.25). Based on the types of allergic diseases, we conducted a subgroup analysis to reduce heterogeneity (25),providing that the effect estimates of each allergic disease: 1.13 (OR:1.13,95%CI:1.01-1.27) in asthma group, 1.12 (OR:1.12,95%CI:1.08-1.16) in wheezing group, and 1.41 (OR:1.41,95%CI:1.31-1.53) in atopic dermatitis group. GDM may increase the risk of allergen sensitization, but the relationship was not statistically significant (OR:1.45,95%CI:0.40-5.23). We also explored the source of heterogeneity in the study design. No heterogeneity was found in the case-control study, but higher heterogeneity in the cohort study. For sensitivity analysis, we excluded studies in clearly-defined GDM patients and not clearly defined GDM patients respectively, and found that children born to GDM women regardless of whether GDM was clearly defined all confronted an increased risk of developing allergic diseases (OR:1.10,95%CI:1.04-1.17;OR:1.19,95%CI:1.10-1.28)

In previous studies, Rusconi et al. (19) found an association between maternal diabetes during pregnancy and early-onset wheezing in children (OR:1.72, 95%CI:0.99–3.00). Kumar et al. (22) found that GDM increased the risk of atopic dermatitis (OR:7.2, 95%CI:1.5-34.5) and early allergen sensitization in childhood (OR:5.7, 95%CI:1.2-28.0). In a Swedish record linkage study, Aspberg et al. (26) reported that maternal diabetes was associated with a 19% higher risk of having a child who would be prescribed with anti-asthmatic medication (OR: 1.19, 95%CI:1.12–1.28).

In the study of childhood asthma, Paula's findings (7) were inconsistent with ours (OR:1.13, 95%CI: 1.01-1.27), probably because the children of their studies were all born as very preterm (<32 weeks)(OR: 0.96, 95%CI: 0.58-1.69) and late preterm (34+0–36+6weeks) (OR: 0.78, 95%CI: 0.63-1.11). The inconsistency may also be related to sample size, and uncontrolled confounding factors, such as antenatal steroids and early-life feeding, or exclusivity of breastfeeding. In the study of children wheezing, the results of Rusconi et al. (19)(OR: 0.94, 95% CI:0.47-1.86) and Liu et al. (21) (OR: 0.85, 95%CI:0.67-1.09) were inconsistent with ours (OR:1.12, 95% CI:1.08-1.16). Only children with late-onset wheezing were studied in both studies. Liu et al. did not explain the results of late-onset wheezing unassociated with GDM. Rusconi believed that the misclassification of children in the late-onset wheezing group could lead to the inconsistent results. In

the study of atopic dermatitis in children, the results of Kumar et al. (22) (OR: 0.74, 95%CI:0.11-4.91) and Paula et al. (7)(OR: 0.62, 95%CI:0.23-1.69) were inconsistent with ours (OR: 1.41, 95%CI:1.31-1.53). In both studies, only children born as premature (<37 weeks and moderate preterm 32+0–33+6 weeks) were included. The reasons that preterm is not related to GDM have been described above. In the studies about children's allergen sensitization, the three sets of results reported by Kumar et al (OR: 0.37, 95%CI:0.07-1.88) (OR: 0.26, 95%CI:0.04-1.64) (OR: 0.38, 95%CI:0.07-2.19)(22) were inconsistent with ours (OR: 1.45, 95%CI:0.40-5.23). The children studied by Kumar et al. were all born as preterm.

Currently, no mechanisms are revealed to interpret the association between GDM and childhood allergic diseases. We explored the possible mechanisms through this meta-analysis. In GDM, fetal exposure and limited response to high cord blood glucose (27) may cause fetal hyperinsulinemia, hypoxia (28), and ultimate lung immaturation. In addition, the maternal autoantibody may cross the placenta to directly act on the fetal lung development (29). An epidemiological study of human adults in the Netherlands revealed a link between GDM and atopic diseases in early childhood, and the mediatory role of insulin resistance mediates between obesity and allergen sensitization (30). Mothers with GDM have higher levels of TNF-α, leptin and visfatin, and lower levels of adiponectin. Adiponectin can reduce allergic inflammation in mouse models. Therefore, GDM-decreased adiponectin may have a negative impact on the development of infant immunology (31-34). Apart from this, maternal diabetes predisposes mothers to premature births who carry a greater risk of neonatal alveolar surfactant deficiency. In addition, high blood sugar level may significantly inhibit fetal alveolar surfactant synthesis and secretion during late pregnancy (35, 36). Further researches are needed to determine the mechanisms between GDM and children allergic diseases.

Strengths and limitations

There are several strengths in this study. First, the basis for research selection was explicit search strategies and well-defined research inclusion criteria. Grey literature was examined, and articles in different languages were included. Second\soutly, there is currently no systematic review of studies focusing on the impact of gestational diabetes on multiple types of children's allergic diseases. In addition, this study conducted a subgroup analysis on the types of epidemiological studies and explored the research effectiveness of different types of epidemiological studies.

There are also some limitations in our study. All the available evidence was derived from observational studies (cohort, cross-sectional, case–control), which have an inherent bias. In addition, not all studies provided information on preterm/term births, therefore, the confounder may arise from preterm/term status.

Conclusion

GDM is associated with the risk of children allergic diseases, especially asthma, wheezing, and atopic dermatitis. Future epidemiological studies with larger sample size should be conducted to identify this association.

Financial support

This work was funded by the National Key Rearch and Development Program of China(2019YFC1005100); Outstanding young academic leaders of Qing Lan Project of Jiangsu Province;the Priority Academic Program Development of Jiangsu Higher Education Institutions(PAPD).

Conflict of interest statement

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.

REFERENCE:

1. American, Diabetes, Care AJD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. 2019.

2. Melchior H, Kurch-Bek D, Mund M. The Prevalence of Gestational Diabetes: A Population-Based Analysis of a Nationwide Screening Program. Deutsches Arzteblatt International. 2017;114:412-8.

3. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NHJDRCP. Global estimates of the prevalence of hyperglycaemia in pregnancy. 2014;103(2):176-85.

4. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Wong JJDC. Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment. 2015;39(1):75.

5. Pereira TJ, Moyce BL, Kereliuk SM, Dolinsky VJB, Biology C. Influence of Maternal Overnutrition and Gestational Diabetes on the Programming of Metabolic Health Outcomes in the Offspring: Experimental Evidence. 2014;93(5):150113072803006.

6. Azad MB, Becker AB, Kozyrskyj ALJPP. Association of maternal diabetes and child asthma. 2013;48(6).

7. Haataja P, Korhonen PI, Ojala R, Hirvonen M, Paassilta M, Gissler M, et al. Asthma and atopic dermatitis in children born moderately and late preterm. 2016;175(6):799-808.

8. Treviño-Alanis M, Ventura-Juarez J, Hernandez-Pinero J, Nevarez-Garza A, Quintanar-Stephano A, Embryologia AGPJAH. Delayed Lung Maturation of Foetus of Diabetic Mother Rats Develop with a Diminish, but Without Changes in the Proportion of Type I and II Pneumocytes, and Decreased Expression of Protein D-Associated Surfactant Factor. 2009;38.

9. Lawrence, Stewart, Warshaw, Joseph, Nielsen, Heber, et al. Delayed Lung Maturation in the Macrosomic Offspring of Genetically Determined Diabetic (db\\/+) Mice1. 1989.

10. Gewolb IH, Rooney SA, Barrett C, Ingleson LD, Light D, Wilson CM, et al. Delayed Pulmonary Maturation in the Fetus of the Streptozotocin-Diabetic Rat. 1985;8(2-3):141-51.

11. Mulay S, Philip A, Solomon SJJoE. Influence of maternal diabetes on fetal rat development: alteration of insulin receptors in fetal liver and lung. 1983;98(3):401-10.

12. Moore TRJAJoO, Gynecology. A comparison of amniotic fluid fetal pulmonary phospholipids in normal and diabetic pregnancy. 2002;186(4):641-50.

13. Asher I, Pearce NJIJoT, Disease L. Global burden of asthma among children. 2014;18(11):1269-78.

14. Wells GA SB, O'Connell D. The Newcastle-Ottawa Scale(NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019.

15. Andreas S. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. %J European journal of epidemiology. 2010;9(25).

16. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen MJEI. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. 2017;100(MAR.):1-31.

17. Anderson HR, Favarato G, Atkinson RWJAQA, HEALTH. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. 2013.

18. A J S. Empirical assessment of effect of publication bias on meta-analyses. %J BMJ (Clinical research ed.). 2000;7249(320).

19. Rusconi F, Galassi C, Forastiere F, Bellasio M, Pearce NJAJoR, Medicine CC. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. 2007;175(1):16-21.

20. Daniela Z, Claudia G, Isabella AM, Nour B, Henrique B, Mikel B, et al. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. 2015(1):1.

21. Liu X, Esben A, Li J, Dharmage SC, Thomsen RW, J?Rn O, et al. Maternal pregestational or gestational diabetes and childhood wheezing: A population-based cohort study. 2018.

22. Kumar R, Ouyang F, Story RE, Pongracic JA, Hong X, Wang G, et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. 2009;124(5):1031-8.e4.

23. Scichilone N, Sanfilippo A, Sorino C, Giuliano L, Bellia VJEAoA, Immunology C. Allergen sensitizations in southern Italy: A 5-year retrospective study in allergic respiratory patients. 2013;45(3):97-102.

24. Characteristics of allergic sensitization among asthmatic adults older than 55?years: results from the National Health and Nutrition Examination Survey, 2005-2006 %J Annals of Allergy Asthma & Immunology. 2013;110(4):247-52.

25. Althuis MD, Weed DL, Frankenfeld CLJSR. Evidence-based mapping of design heterogeneity prior to meta-analysis: a systematic review and evidence synthesis. 2014;3(1):80.

26. Aspberg S. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma %J Pediatric Allergy & Immunology Official Publication of the European Society of Pediatric Allergy & Immunology. 2010;21(4p2):0-.

27. Fowden AL, Hill DJJBMB. Intra-uterine programming of the endocrine pancreas. 2001(1):1.

28. Taricco E, Radaelli T, Rossi G, Santis MSND, Cetin IJBAIJoO, Gynaecology. Effects of gestational diabetes on fetal oxygen and glucose levels. 2009;116(13):1729-35.

29. Bogna G-G, Natalia R, Micha? R, Mariusz PJR. Antinuclear antibodies in autoimmune and allergic diseases. 2017;55(6):298-304.

30. Husemoen LLN, Glumer C, Lau C, Pisinger C, Linneberg AJA. Association of obesity and insulin resistance with asthma and aeroallergen sensitization. 2008;63(5):575-82.

31. Bao W, Baecker A, Song Y, Kiely M, Liu S, Zhang CJM. Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: A systematic review. 2015;64(6):756-64.

32. Shore, Stephanie A. Obesity and asthma: Possible mechanisms. Journal of Allergy & Clinical Immunology. 2008;121(5):1087-93.

33. Sandra, Radzicka, Marek, Pietryga, Rafal, Iciek, et al. The role of visfatin in pathogenesis of gestational diabetes (GDM). 2018.

34. Bellos I, Fitrou G, Pergialiotis V, Perrea DN, Daskalakis GJJoEI. Serum levels of adipokines in gestational diabetes: a systematic review. 2018.

35. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MKJB. Biological determinants of spontaneous late preterm and early term birth: A retrospective cohort study. 2014;122(4).

36. Weindling AM. Offspring of diabetic pregnancy: Short-term outcomes. Seminars in Fetal & Neonatal Medicine. 2009;14(2):111-8.

Figure legends

Table 1. Characteristics of the retrieved articles

Figure 1. Flow diagram of the retrieved articles of asthma,atopic dermatitis,food allergy

Figure 2. Forest plot for the association between gestational diabetes mellitus and allergic diseases in childhood

Figure 3(a). Forest plot for the association between gestational diabetes and asthma in children

Figure 3(b). Forest plot for the association between gestational diabetes and wheezing in children

Figure 3(c). Forest plot for the association between gestational diabetes and atopic dermatitis in children

Figure 3(d). Forest plot for the association between gestational diabetes and allergen sensitization in children

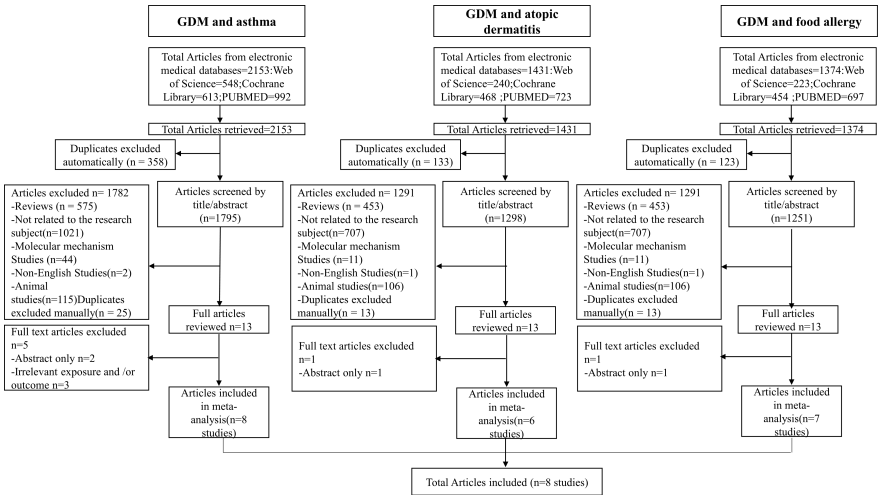
Figure 4. Subgroup analysis by research design

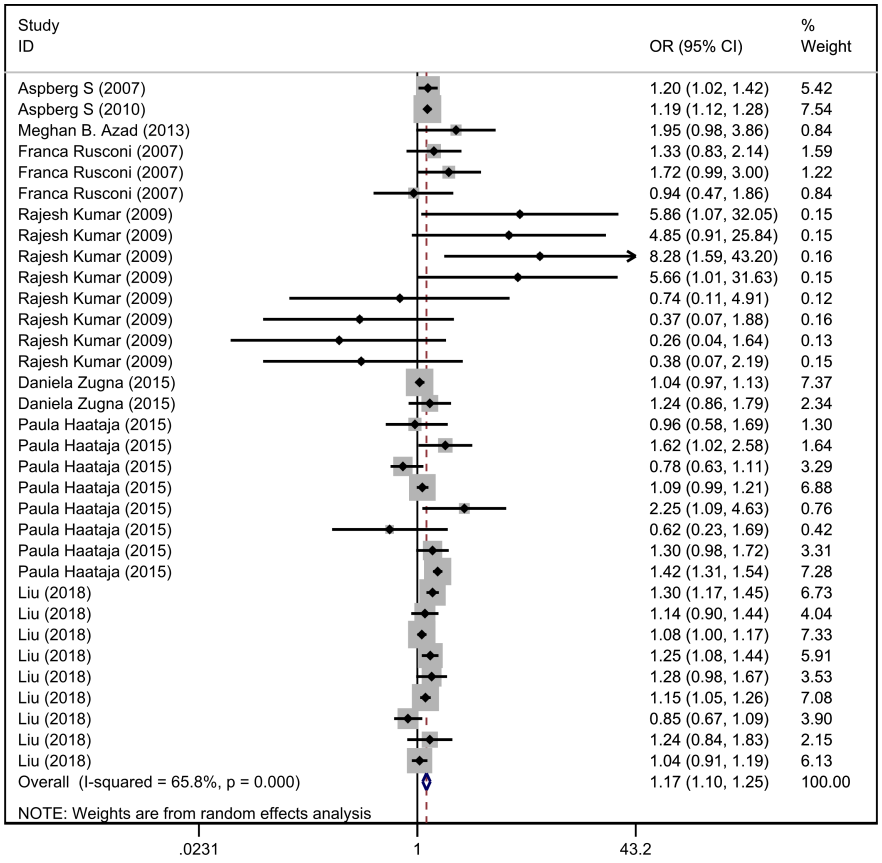
Figure 5(a). Sensitivity analysis for clearly defined GDM

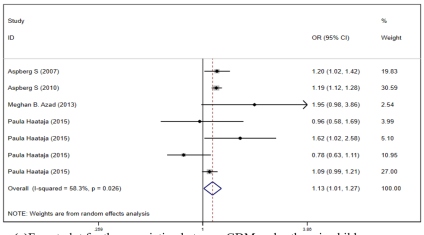
Figure 5(b). Sensitivity analysis for undefined GDM

Hosted file

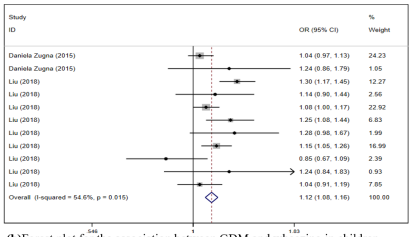
`table1.docx` available at https://authorea.com/users/355112/articles/478479-association-between-gestational-diabetes-mellitus-and-allergic-diseases-in-children



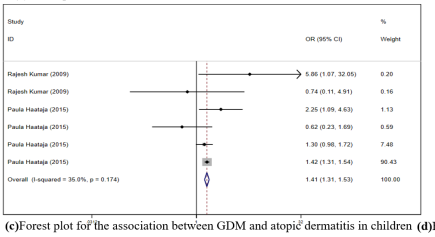




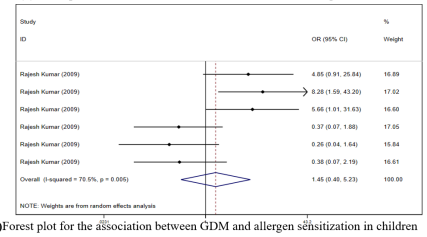
(a) Forest plot for the association between GDM and asthma in children



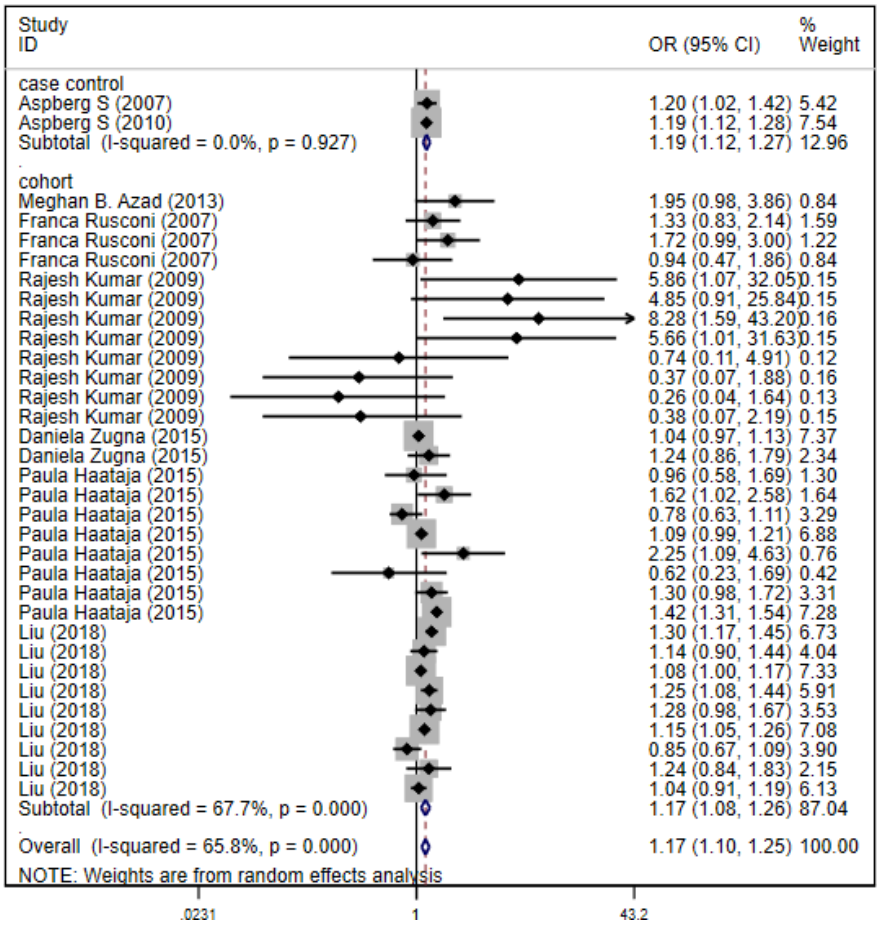
(b) Forest plot for the association between GDM and wheezing in children

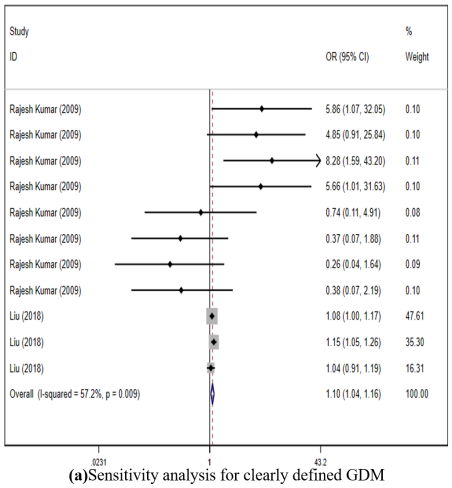


(c) Forest plot for the association between GDM and atopic dermatitis in children

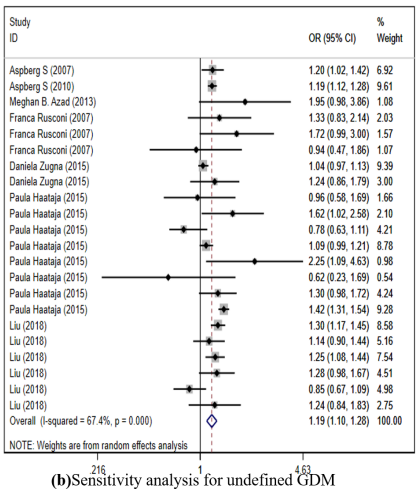


(d) Forest plot for the association between GDM and allergen sensitization in children





(a) Sensitivity analysis for clearly defined GDM



(b) Sensitivity analysis for undefined GDM