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Atopy and asthma in children born to mothers at risk of gestational diabetes mellitus: a follow-up study

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Abstract

Background Gestational diabetes mellitus (GDM) is the most prevalent metabolic disturbance during pregnancy and is associated with adverse outcomes in offspring, including an elevated risk for developing atopic diseases in early childhood. Research is limited regarding only women at risk of GDM among whom some develop GDM while others do not. Information about adverse health outcomes in the offspring of these women is also lacking. The main aim was to assess whether maternal GDM increases the offspring's risk of atopic dermatitis (AD), asthma and allergic rhinitis at 1, 2 and 5 years of age. The second aim was to analyze the association of other maternal health characteristics on the development of these disorders in offspring.

Methods The follow-up study group of the Gestational Diabetes Study (GDS), conducted at Tartu University Hospital, Estonia, between 2014 and 2020, comprised 223 mother–child dyads. All women had at least one risk factor for GDM, of whom only some developed GDM. Information about the diagnoses of interest was obtained from Electronic Health Records. Allergen-specific IgE from children's serum was measured using ImmunoCAP™ Phadiatop™ Infant, with results ≥ 0.35 kU/l considered positive. Statistical analysis was performed using the RStudio software (version 4.3.0).

Results According to our results, only the cases of GDM requiring the use of antidiabetic medications were associated with the development of asthma and/or allergic rhinitis at 2 years of age (aOR 4.68, 95%CI 1.08–20.21, $p = 0.039$). Maternal obesity (BMI > 30) was associated with offspring´s asthma and/or allergic rhinitis diagnosis at 2 years of age (aOR 3.15, 95%CI 1.03–9.63, $p = 0.045$).

Maternal abnormal weight gain during pregnancy was associated with asthma and/or allergic rhinitis at 5 years of age (aOR 2.76, 95%CI 1.04–7.31, $p = 0.041$).

Conclusion Among pregnant women at risk for GDM, maternal weight-related factors significantly influence the development of atopic diseases in their children between 1 and 5 years of age, regardless of the GDM diagnosis. This suggests that, besides women with GDM greater attention should also be paid to women at risk but who do not develop GDM, as their children seem to be at higher risk of atopic diseases.

Keywords Gestational diabetes mellitus, Atopic dermatitis, Asthma, Allergic rhinitis, Maternal obesity, Immune system

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Introduction

Gestational diabetes mellitus (GDM) is the most prevalent metabolic disturbance occurring during pregnancy. It is defined as hyperglycemia which begins during pregnancy and does not meet the criteria of pre-existing diabetes. The pooled global standardized prevalence of GDM is estimated to be 14.0%, with significant regional differences [1]. Obesity, prior macrosomic birth, or previous GDM are common risk factors for GDM. GDM is associated with various maternal and offspring adverse outcomes, both short- and long-term. Babies born to mothers with GDM are at a higher risk for postnatal hypoglycemia, hyperbilirubinemia, macrosomia, neonatal respiratory distress and congenital malformations [2, 3]. Maternal GDM has been related to obesity and abnormal glucose metabolism of the offspring [4, 5]. Other long-term consequences observed in offspring include cardiovascular abnormalities, allergic/respiratory health disturbances and unfavorable neurodevelopmental outcome. It is hypothesized that the effect of GDM on offspring obesity and cardiometabolic health may be partly influenced by maternal obesity [6]. Moreover, children born to mothers with GDM may be at risk of immune dysregulation [7].

Atopic dermatitis, asthma and allergic rhinitis are common health care problems among children, with asthma being one of the most common chronic diseases in childhood.

Asthma is a heterogenous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough [8]. Recurrent wheezing occurs in a large proportion of children under five years of age and it is difficult to establish when this is the initial presentation of asthma. In the past, several different phenotypes of early wheezing have been proposed, with some of them (e.g. persistent early, intermediate and late-onset wheeze) have been associated with atopy, lower lung function, increased airway hyperresponsiveness and an increased risk of asthma diagnosis [9]. The global prevalence for current asthma in children aged 6–7 years is estimated to be 11.7% and rising when children get older (14.1% among 13–14-year age group) [10]. The diagnosis of asthma in preschool children is challenging because objective lung function tests are difficult to perform in this age group, and there are no definitive biomarkers to aid in the diagnosis [9]. Among children 6–7 years of age the prevalence of allergic rhinitis is estimated to be 5.34%. The prevalence of physician-diagnosed allergic rhinitis among pediatric population in general has been rising over the last 10 years, reaching up to almost 20% in the studied population. [11]. According to a recently published international survey, the total prevalence of atopic dermatitis among children under 6 years of age is 12.1% [12].

The association between maternal GDM and offspring allergies, asthma, rhinitis and atopic dermatitis in different studies is contradictory. A recently conducted meta-analysis [13] showed association between maternal diabetes mellitus and offspring asthma, wheezing and atopic dermatitis. Similar relationship between maternal GDM and childhood asthma was found in a cohort study including almost 20,000 children [14]. On the other hand, a study from Singapore showed that male sex, ethnicity and family atopic history were the only consistent risk factors for eczema, rhinitis and wheezing, irrespective of the maternal GDM status [15]. There is also evidence that the need for antidiabetic medications compared to only dietary correction during pregnancy might play a role in childhood asthma development [16].

In some studies it is difficult to differentiate between pre existing hyperglycemia and GDM, leading to non-coherent results in the evaluation of offspring long-term outcomes [17–19]. Furthermore, there is a gap in the research involving only women at risk of GDM among whom some develop GDM while others do not. A recent study highlighted the fact that women with GDM risk factors, but with normal oral glucose tolerance test (OGTT), are at greater risk for excessive weight gain during pregnancy, and giving birth to large for gestational age babies [20]. Information about adverse health outcomes among the offspring in this group of women is also lacking.

Therefore, in order to fill the indicated gap, all pregnant women enrolled in our study had at least one predefined risk factor for developing GDM. To our knowledge, this is the first study to involve only women at risk of GDM and their offspring.

We hypothesized that children born to mothers diagnosed with GDM would have a higher prevalence of allergic diseases. Our second hypothesis was that, in addition to the GDM diagnosis itself, the risk factors considered important for developing GDM could also play a role in the development of allergic diseases in children.

The main aim of our study was to determine if the diagnoses of atopic dermatitis, asthma and allergic rhinitis at 1, 2 and 5 years of age in children were related to maternal GDM. The second aim was to analyse the association of maternal characteristics on the development of the above mentioned respiratory or skin disorders in the offspring.

Materials and methods

Study subjects

The current follow-up study cohort comprised mothers who participated in the Gestational Diabetes Study

(GDS) carried out at Tartu University Hospital, Estonia, between 2014 and 2020. During the first trimester, women at risk for developing GDM were consecutively recruited through regular midwife visits. The risk of GDM was assessed based on the antenatal care guidelines used in Estonia since 2011 and revised in 2018 [21]. The risk factors for GDM were the following: pre-pregnancy overweight/obesity (pre-pregnancy body mass index (BMI) 25–29.9/ > 30 kg/m2), GDM during a previous pregnancy, diabetes in a first-degree relative, previous macrosomic neonate (birthweight > 4500 g), polycystic ovary syndrome, glycosuria during the current pregnancy, polyhydramnios during the current pregnancy, estimated fetal weight at ultrasound greater than at least 2 weeks of the current gestational age, gestational weight gain > 3 kg per month.

All women performed a 2-h 75 g OGTT between gestational weeks 24–28 and GDM was diagnosed if at least one of the following criteria was fulfilled: fasting plasma glucose ≥ 5.1 mmol/l; 1 h plasma glucose ≥ 10.0 mmol/l; 2 h plasma glucose ≥ 8.5 mmol/l. Women with previously diagnosed type 1 or type 2 diabetes, or those having fasting blood glucose > 7.0 mmol/L at the first trimester visit, were excluded from the study.

The study protocol was approved by the Human Research Ethics Committee of the University of Tartu, Estonia (315/M-18 18.05.2020; 350/M-23 20.09.2021). An invitation letter for the current follow-up study, explaining the study goals, the types of blood samples that would be taken, and the clinical information intended to be retrieved from Electronic Health Records, was sent via email and post to all women who participated in the GDS. Participants were informed about how their personal and medical data would be collected and used. Informed written consent was then obtained from all mothers of the participating children, ensuring they fully understood and agreed to the study's procedures and use of their data, and the right to withdraw their consent at any time during the study.

Of the 473 women who participated in the initial GDS, a total of 223 mothers and their children consented to take part in the current follow-up study. Due to several constraints, including participant availability, willingness, and resource limitations, only 100 mother–child dyads could be invited to the pediatrician visit where blood samples for the measurement of allergen-specific IgE were obtained from the children.

Maternal and offspring study variables and outcomes of interest

The maternal variables of interest were as follows: parity, age and mode of delivery, pre-pregnancy BMI, gestational weight gain, GDM diagnosis, results of OGTT and maternal serum folate level (measured on the day of OGTT). Gestational weight gain was classified as normal or abnormal based on the guidelines of optimal weight gain according to maternal pre-pregnancy BMI [22].

The offspring covariates included in the study were sex, gestational age, birthweight, development of postnatal hypoglycemia (diagnosed according to neonatal hypoglycemia monitoring guidelines used in Estonia, and requiring oral, or additionally, parenteral correction) and breastfeeding ever.

The outcomes of interest of the current follow-up study were development of atopic dermatitis, asthma (allergic and non-allergic), and allergic rhinitis at 1, 2, and 5 years of age. Information about the diagnoses was obtained from the Electronic Health Records, with the medical conditions of interest diagnosed by pediatric allergist-pulmonologist or family physician (in cases of atopic dermatitis). Based on the ICD-10, the diagnosis codes of interest were the following: atopic dermatitis- L20.8, L.20.9; asthma- J45; allergic rhinitis- J30.3. Due to the relatively small number of participants, we analyzed the diagnoses in two subgroups: atopic dermatitis and respiratory tract (i.e. asthma and allergic rhinitis) related disorders.

Measurement of allergen-specific IgE

Allergen-specific IgE from the children's serum was measured using ImmunoCAP™ Phadiatop™ Infant test (Thermo Fisher Scientific). The allergens included in the test were: hen's egg, cow's milk, peanut, shrimp, cat epithelium and dander, dog dander, house dust mite, common silver birch, timothy, ragweed, and wall pellitory. Results ≥ 0.35 kU/l were considered positive.

Statistical analysis

Statistical analysis was performed using the RStudio software (version 4.3.0). Comparison of baseline characteristics for the GDM and non-GDM groups was carried out using $\chi 2$- or Fisher's exact test for qualitative variables. The $\chi 2$ test was used when the expected frequencies were at least 5 per cell, while Fisher's exact test was used when any expected cell frequency was less than 5. Student's *t*- or Wilcoxon rank-sum test were used for quantitative variables, for either parametric or non-parametric data, respectively. Multivariate logistic regression analysis was used to evaluate associations of maternal and child variables with the children's diagnoses of respiratory conditions and/or atopic dermatitis. The models were adjusted for sex if not stated otherwise. Additional adjustments included adjusting for maternal gestational weight gain or folate level, and were made as necessary or deemed appropriate, with information provided in the Results section due to their context-dependent nature. In all

statistical analyses, a two-tailed p-value < 0.05 was considered statistically significant.

Results

The 223 mother–child pairs were first divided into two groups based on maternal GDM diagnosis (GDM and non-GDM group, Table S1). Altogether 86 (39%) women had been diagnosed with GDM, of whom 14 (16%) needed antidiabetic medications (metformin, insulin, or both). The mothers of the two groups did not differ in terms of age or delivery mode, but mothers with GDM had given birth to more children ($p = 0.037$). Pre-pregnancy BMI was higher in the GDM group ($p = 0.014$), whereas gestational weight gain was significantly higher in the non-GDM group ($p = 0.006$) (Table S1). We noted that obese mothers had higher odds to deliver via cesarean section, regardless of the GDM status (adjusted (a) OR 2.56, 95%CI 1.10–5.98, $p = 0.030$).

Although the babies of the GDM group were born slightly earlier than in the non-GDM group (39 vs 40 weeks of gestation), their birthweights were similar. Only one child did not get breastmilk ever. Although postnatal hypoglycemia developed twice as frequently in newborns in the GDM group (16%) compared to the non-GDM group (7%), the difference did not reach statistical significance ($p = 0.059$). Using regression modeling we found that postnatal hypoglycemia was associated with higher odds for positive IgE test result at the first visit to the pediatrician, regardless of child´s age (OR 7.86, 95%CI 2.31–26.70, $p = 0.001$). The result remained unchanged after adjustment for sex. The prevalence of the children's diagnoses of interest at 1, 2, and 5 years of age is shown in Table S1. We did not find any significant difference between maternal GDM diagnosis and development of atopic dermatitis, asthma or allergic rhinitis at given time points (Table S1). Overall, as the children got older, the prevalence of respiratory tract-related problems (asthma and/or allergic rhinitis) in the study group increased (from 3% among 1-year-old children to 20% among 5-year-old children, $p < 0.0001$), while the proportion of AD diagnoses remained similar (17% among 1-year-old children versus 13% among 5-year-old children, $p = 0.36$).

Atopic dermatitis at one year of age

At one year of age, a check-up was conducted only for the diagnosis of atopic dermatitis as in the first year of life allergic asthma and rhinitis are not usually diagnosed. Of the 223 children, 37 (17%) had atopic dermatitis (Table S2). Maternal pre-pregnancy BMI did not differ between the groups, but mothers of children with atopic dermatitis had more pronounced weight gain during pregnancy ($p = 0.027$) (Table S2). Also, birthweight was significantly higher in the group of atopic dermatitis ($p = 0.045$) (Table S2). In logistic regression analysis adjusted for maternal gestational weight gain during pregnancy, female sex had an inverse association with odds to have atopic dermatitis diagnosis at one year of age (aOR 0.42, 95%CI 0.19–0.92, $p = 0.031$) (Table 1).

Atopic dermatitis and respiratory tract related diagnoses at two years of age

At 2 years of age, 40 children (18%) had atopic dermatitis and 22 (11%) respiratory tract-related diagnosis (Table S3 and Table S4). In this age group asthma/allergic rhinitis was exclusively diagnosed by a pediatric pulmonologist-allergist. The baseline characteristics among children with or without atopic dermatitis were similar; however a statistically significant difference between the groups was found for delivery via emergency cesarean section ($p = 0.012$) and postnatal hypoglycemia ($p = 0.049$) (Table S3). In crude logistic regression analysis, being born via emergency cesarean section (OR 3.69, 95%CI 1.38–9.84, $p = 0.009$) and postnatal hypoglycemia (OR 2.61, 95%CI 1.03–6.61, $p = 0.043$) raised the odds of having atopic dermatitis diagnosis at 2 years of age. In adjusted logistic regression analysis the significance was maintained for being born via emergency cesarean section (aOR 3.39, 95%CI 1.25- 9.19, $p = 0.016$), whereas the association with postnatal hypoglycemia was lost (Table 1).

The baseline characteristics of the children who were diagnosed with respiratory disorders at two years of age are shown in Table S4. Only birthweight was significantly higher in children who developed asthma and/or allergic rhinitis at two years of age ($p = 0.040$). Both in crude and adjusted regression analysis, maternal obesity (BMI > 30) raised the odds of the child having asthma or allergic rhinitis diagnosis at 2 years of age (aOR 3.15, 95%CI 1.03–9.63, $p = 0.045$) (Table 2). Likewise, the need for antidiabetic drug treatment (metformin and/or insulin) raised the odds to have the above mentioned diagnoses in this age group, both in crude and adjusted models (OR 4.40, 95%CI 1.05–18.37, $p = 0.042$ and aOR 4.68, 95%CI 1.08–20.21, $p = 0.039$, respectively) (Table 2).

Atopic dermatitis and respiratory tract related diagnoses at five years of age

Only 152 (68%) of the 223 children who participated in the study had reached five years of age. In 19 (12.5%) of them the diagnosis of atopic dermatitis had persisted, and no new diagnosis of atopic dermatitis had been made. At five years of age, 32 children (21%) had at least one respiratory tract related diagnosis of interest among whom 19 (12.5%) had allergic asthma or rhinitis. The baseline characteristics of 5-year-old children are presented in

Table 1 Logistic Regression Models Evaluating the Association between Maternal and Child Characteristics and Atopic Dermatitis

Atopic dermatitis		
	OR (univariable)	**OR (multivariable)**
1-YEAR-OLD-CHILD		
Male		
Female	0.52 (0.25–1.08, p = 0.080)	**0.42 (0.19–0.92, p = 0.031)**
Gestational weight gain	1.06 (1.00–1.13, p = 0.049)	1.07 (1.00–1.13, p = 0.038)
2-YEAR-OLD-CHILD		
Male		
Female	0.58 (0.29–1.17, p = 0.129)	0.61 (0.30–1.23, p = 0.167)
Emergency CS	**3.69 (1.38–9.84, p = 0.009)**	**3.39 (1.25–9.19, p = 0.016)**
Postnatal hypoglycemia	**2.61 (1.03–6.61, p = 0.043)**	2.48 (0.97–6.33, p = 0.057)
5-YEAR-OLD-CHILD		
Male		
Female	1.09 (0.42–2.87, p = 0.853)	1.05(0.39–2.81, p = 0.925)
BMI:		
Underweight (BMI < 18.5)	-	-
Normal (BMI 18.5–24.9)		
Overweight (BMI 25.0–29.9)	**0.26 (0.07–0.96, p = 0.043)**	**0.26 (0.07–0.96, p = 0.043)**
Obese (BMI > 30)	0.19 (0.02–1.53, p = 0.119)	0.19 (0.02–1.53, p = 0.119)

Abbreviations: *CS* Cesarean section, *BMI* Body mass index

Table 2 Logistic Regression Models Evaluating the Association between Maternal and Child Characteristics and Asthma/Allergic Rhinitis

Asthma, allergic rhinitis		
	OR (univariable)	**OR (multivariable)**
2-YEAR-OLD-CHILD		
Male		
Female	0.88 (0.36–2.12, p = 0.767)	0.96 (0.38–2.39, p = 0.927)
Antidiabetic treatment	**4.40 (1.05–18.37, p = 0.042)**	**4.68 (1.08–20.21, p = 0.039)**
BMI:		
Underweight (BMI < 18.5)	7.43 (0.60–92.29, p = 0.119)	7.48 (0.60–93.48, p = 0.118)
Normal (BMI 18.5–24.9)		
Overweight (BMI 25.0–29.9)	1.44 (0.46–4.47, p = 0.531)	1.44 (0.46–4.47, p = 0.531)
Obese (BMI > 30)	**3.15 (1.03–9.64, p = 0.044)**	**3.15 (1.03–9.63, p = 0.045)**
5-YEAR-OLD-CHILD		
Male		
Female	0.78 (0.35–1.73,p = 0.542)	0.84 (0.36–1.96, p = 0.681)
Marernal folate 1st trimester	1.02 (0.99–1.05, p = 0.192)	1.02 (0.99–1.06, p = 0.135)
BMI:		
Underweight (BMI < 18.5)	-	-
Normal (BMI 18.5–24.9)		
Overweight (BMI 25.0–29.9)	1.75 (0.77–3.99, p = 0.183)	1.73 (0.75–3.95, p = 0.196)
Obese (BMI > 30)	0.40 (0.08–1.89, p = 0.245)	0.40 (0.08–1.91, p = 0.252)
Gestational abnormal weight gain	2.30 (0.92–5.79, p = 0.076)	**2.76 (1.04–7.31, p = 0.041)**

Abbreviations: *CS* Cesarean section, *BMI* Body mass index

Table S5 and Table S6. When children with or without atopic dermatitis or respiratory disorders were compared, only maternal pre-pregnancy BMI was significantly lower in children with atopic dermatitis compared to children without this diagnosis ($p=0.002$); the same result was obtained when grouping BMI according to the WHO classification ($p=0.038$) (Table S5). In both crude and adjusted analysis, pre-pregnancy BMI ≥ 25.0 (overweight) had the strongest inverse association with odds to have the diagnosis of atopic dermatitis diagnosis at five years of age (aOR 0.26, 95%CI 0.07–0.96, $p=0.043$) (Table 1). In multivariate analysis adjusted for maternal folate level and sex, maternal abnormal weight gain during pregnancy raised the odds for the child to have respiratory diagnoses at five years of age (aOR 2.76, 95%CI 1.04–7.31, $p=0.041$) (Table 2).

Discussion

The main aim of the study was to evaluate the impact of maternal GDM on the offspring diagnoses of atopic dermatitis, asthma and allergic rhinitis at 1, 2, and 5 years of age. The second aim was to find out if maternal risk factors predisposing to GDM could influence the development of atopic dermatitis and asthma in offspring. We hypothesized that as the phenotypes of atopy and asthma are different during childhood, the factors influencing the development of these diseases might also be different in different age groups.

It is important to emphasize that all women participating in our longitudinal study belonged to the GDM risk group according to the pregnancy monitoring guidelines used in Estonia, as they had at least one GDM risk factor. Women with pre-existing diabetes or without GDM risk factors were excluded from the study.

Like Martinez et al. [16], we found an association between maternal GDM and childhood asthma/allergic rhinitis diagnosis only for children whose mothers needed antidiabetic medications. The elevated odds were already evident at two years of age. Consistent with a study by Choa et al. [15], no association was found between maternal GDM and children´s diagnosis of interest among women who managed to control their GDM without antidiabetic medications. Furthermore, based on our results, we hypothesize that offspring of GDM risk group mothers who did not develop GDM, might even be at greater risk for developing atopic dermatitis or asthma/allergic rhinitis during childhood due to inadequate prenatal medical and advisory attention. The outcome of higher gestational weight gain in the non-GDM group can also be explained by the same hypothesis. Recent research indicates that these women experience more pregnancy related complications which also have a negative impact on their offspring [20].

Our results showed that maternal pre-pregnancy obesity (BMI > 30) and abnormal gestational weight gain played an important role in the development of atopic dermatitis and asthma/allergic rhinitis in different age groups in early childhood. Several previous studies have established the link between maternal obesity, pathological weight gain during pregnancy, and childhood asthma [23–25]. We found that maternal obesity (BMI > 30) was associated with increased odds of receiving respiratory diagnosis at two years of age. Additionally, higher gestational weight gain was associated with elevated odds of having atopic dermatitis at one year, and asthma/allergic rhinitis at five years of age. These findings might indicate that dysregulation of the immune system caused by abnormal maternal weight is more important than GDM diagnosis itself. The proinflammatory profile of the immune system is characteristic of both GDM and obesity. In order to balance the immune system, in GDM the overactivated proinflammatory profile is counteracted by the activation of antiinflammatory components [26], while in obese women during pregnancy the disruption of Th1/Th2/Th17 axis has been emphasized [27]. The latter fact might explain why obesity and abnormal weight gain could play a more important role than GDM alone in the development of atopic dermatitis and asthma in childhood, since the development of the fetal immune system is influenced by the status of the maternal immune system [26]. In addition to immune system´s abnormalities, higher BMI and excessive weight gain during pregnancy have been associated with gut dysbiosis, which can be passed on to offspring and increase their risk for developing allergic diseases [28]. During the first year of life, maturation of microbial diversity in the gut is driven by different dietary and environmental factors. The first three months are a critical period of immune development during which environmental exposures can have long-term consequences for immune-mediated diseases like allergies and asthma [29]. Perturbation of microbial colonization, especially during the first weeks of life, is associated with disturbances in stereotypic immune system development early in life [30]. We propose that excessive gestational weight gain, leading also to elevated birthweight, could contribute to the development of atopic dermatitis at one year of age in two possible ways. Firstly, it is known that elevated BMI causes gut dysbiosis and pregnant women pass the dysbalanced microbiota on to their offspring increasing thereby their risk for developing allergic diseases. Secondly, neonates with higher birthweight are at risk of postnatal hypoglycemia which warrants formula feeding during the first days of life. In Estonia, for infants with moderate postnatal hypoglycemia, initial intervention typically involves frequent breastfeeding followed by supplementation with

a cow's milk protein-based formula. However, based on recent findings [31], the European Academy of Allergy and Clinical Immunology (EAACI) suggests avoiding regular supplementation of the cow's milk formula in breastfed infants during the first week of life as it can increase the risk of developing cow's milk allergy in early childhood [32]. Considering this, our result of a positive association between postnatal hypoglycemia and IgE positivity, detected with the Phadiatop Infant panel—which includes cow's milk as an allergen—is reasonable.

Regarding the mode of delivery, cesarean section has been associated with changes in the offspring microbiota, as well as with development of atopy and allergic rhinitis [33, 34]. Moreover, newborns born by cesarean section are more likely to be fed formula milk, in addition to breast milk, during the first days of life compared to children born vaginally. Therefore, postnatal hypoglycemia and being born via cesarean section carry somewhat similar risks to the newborn regarding possible consequences of formula feeding on gut microbiota development and possible immune mediated disease outcome later in childhood. Unexpectedly, the association of postnatal hypoglycemia and delivery by cesarean section with atopic dermatitis diagnosis was only found at 2 years of age. It is possible that some children with gut dysbiosis manage to surpass the delayed microbiota maturation and thus follow a typical pathway of immune system development [30]. Others, however, fail to do so for unknown reasons, leading to the development of immune-mediated disease. Breast milk feeding has a major impact on normalizing the gut environment as it contains distinct bioactive molecules that contribute to immune maturation, organ development, and healthy microbial gut colonization. It also secures a proper immunological response that protects against infection and inflammation in the newborn [35]. Although we know that all but one of the children in our study group were breastfed to some extent, we were unable to analyse the impact of breastfeeding because of the unavailability of detailed data for all study participants.

Attempts have been made to distinguish between different phenotypes of childhood atopic dermatitis according to age at the onset and progression of the disease [36]. In our study group children with atopic dermatitis diagnosis at 5 years of age most probably represent the early persistent phenotype of the disease as no new diagnosis was recorded in this age group. Surprisingly, the offspring of women with higher BMI had fewer diagnoses of atopic dermatitis. The reason for this might be the composition of the study group, but also family history or different atopic dermatitis phenotypes in early childhood (i.e. early transient, early persistent, or late phenotype) [36] manifesting in different age groups and having different contributing factors to it.

Strengths and weaknesses of the study

Despite 473 women participating in the GDS, we managed to recruit only 223 women in the follow-up study. Women who did not develop GDM during the index pregnancy were less interested in participating in the follow-up study despite repeated invitations. Although a family history of atopic dermatitis and asthma is important in the analysis of variables, we were unable to include these data in our study due to the inconsistent quality of the information retrieved. Therefore, our results might be different from the studies that have adjusted for this factor. As stated above, the extent and duration of breastfeeding is also an aspect that we could not cover due to the lack of information. Nonetheless, we included information about breastfeeding ever as a covariate in our analysis.

As a strength, we can be confident that the women who took part in the study were all at risk of GDM and also, importantly, without pre-existing diabetes. Additionally, the documentation of the medical history of the children was available from the national online platform where every visit to any doctor is registered. Thus all information about the diagnoses of interest for the children was documented, with the possibility that only some very mild cases were not registered because the parents had not seeked medical advice.

Conclusion

Our results indicate that apart from women diagnosed with GDM who need antidiabetic medications, maternal weight related factors significantly influence the development of atopic and allergic diseases in the offspring of pregnant women at risk for GDM, regardless of GDM diagnosis. Therefore, besides GDM mothers, greater attention should be paid to women who are at risk of GDM but do not develop it, because their children appear to be even at greater risk of allergic diseases.

Abbreviations

AD	Atopic dermatitis
BMI	Body mass index
CS	Cesarean section
GDM	Gestational diabetes mellitus
OGTT	Oral glucose tolerance test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-024-06819-y.

Supplementary Material 1.

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Authors' contributions
A.B. contributed to the design of the study, collected the data of the participants, performed the statistical analysis, interpreted the data, and wrote the manuscript. A.T. contributed to the design of the study, the statistical analysis, data interpretation, and revision of the manuscript. H.V. contributed to the design of the study and revision of the manuscript. R.U. contributed to the design of the study and revision of the manuscript.

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Availability of data and materials
Individual participants' data that underlie the results reported in this article and a data dictionary defining each field in the set are available to investigators whose proposed use of the data has been approved by an independent review committee for work. Proposals should be directed to weima@sdu.edu.cn to gain access, data requestors will need to sign a data access agreement. Such requests are decided on a case by case basis.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Human Research Ethics Committee of the University of Tartu (315/M-18 18.05.2020; 350/M-23 20.09.2021) and was conducted according to the guidelines of the World Medical Association (WMA) Declaration of Helsinki. Before participating in the study, all participants (parents of or guardians for children) signed a written consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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