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ORIGINAL RESEARCH

Gestational diabetes mellitus and offspring health: A 12-year register-based analysis of specialized health care utilization in Finland

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is associated with various health risks in offspring. We investigated the effect of GDM exposure on offspring morbidity in a population-based cohort, assessed by the utilization of specialized health care services up to 12 years of age.

Material and Methods: This register-based study, part of the Finnish Gestational Diabetes (FinnGeDi) study, included all singleton children born in Finland in 2009, captured from the Medical Birth Registry. Mothers of children in the study cohort underwent comprehensive screening for GDM. The study cohort included 6235 (11.1%) GDM-exposed children and 49 484 unexposed children. Utilization of

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; FCR, Finnish Care Register for Health Care; GDM, gestational diabetes mellitus; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; IRR, incidence rate ratio; MBR, Medical Birth Registry; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

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specialized health care services was measured as the number of outpatient visits and inpatient treatment episodes (including duration in days). Data were obtained from the Finnish Care Register for Health Care up to 12 years of age and were analyzed separately for early childhood (0–2 years), preschool age (3–6 years), and school age (7–12 years) also. Maternal, birth, and child-related factors were considered, including maternal age, pre-pregnancy body mass index (BMI), parity, maternal hypertensive disorders, socioeconomic status (SES), smoking status, mode of delivery, preterm birth, small for gestational age, and child sex in the adjustment model.
Results: Children exposed to maternal GDM had a higher incidence of outpatient visits than unexposed children (adjusted incidence rate ratio [IRR] 1.10, 95% confidence interval [CI] 1.07–1.13). Among children with multiple outpatient care visits (the highest quartile), GDM-exposed children were overrepresented in early childhood (adjusted odds ratio [aOR] 1.08, 95% CI: 1.00–1.15), preschool age (aOR 1.12, 95% CI: 1.05–1.19), and school age (aOR 1.11, 95% CI: 1.04–1.19). Children exposed to GDM were also more likely to require inpatient treatment than unexposed children (adjusted IRR 1.14, 95% CI: 1.10–1.19). The difference was not explained by shorter episodes (adjusted IRR 1.20, 95% CI: 1.16–1.24 for inpatient treatment days).
Conclusions: Children exposed to maternal GDM required more specialized health care services than unexposed children, with increased utilization of specialized health care observed across all age categories up to 12 years of age.

KEYWORDS
gestational diabetes, health care utilization, hospitalization, maternal exposure, morbidity, offspring

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a glucose metabolism disorder first diagnosed during pregnancy that does not meet the criteria for type 1 or type 2 diabetes.[1] The prevalence of GDM has risen in recent decades, driven by increasing rates of overweight and obesity and older maternal age. On average, every fifth newborn is exposed to GDM, and GDM covers nearly 90% of diabetes during pregnancy.[1–3] Current practices favor comprehensive GDM screening, improving diagnostic accuracy and reflecting in the prevalence of GDM.[4–6] Exposure to GDM is associated with multiple long-term health risks in offspring, including cardiovascular risks, metabolic syndrome, and neurodevelopmental disorders.[7–9] Although these associations have been convincingly demonstrated, the use of specialized health care services, a proxy of overall morbidity, in the group of GDM-exposed children remains underexplored.[10,11] This study investigated whether specialized health care utilization differs between children exposed to maternal GDM and those not exposed to any maternal diabetes up to 12 years of age using a population-based register cohort. Additionally, we explored whether the difference in specialized health care utilization prevailed throughout childhood. Studying the overall morbidity—such as specialized health care utilization—offers a more comprehensive understanding of the long-term burden and impact of prenatal exposures, such as GDM.

Key message

Gestational diabetes exposure is associated with increased morbidity in offspring, evidenced by increased utilization of specialized health care services up to 12 years of age. This study demonstrated this association in a population-based cohort comprehensively screened for gestational diabetes.

2 | MATERIAL AND METHODS

2.1 | Study design

This study was part of the register-based arm of the Finnish Gestational Diabetes Study (FinnGeDi), which includes all singleton pregnancies in Finland in 2009 ($n = 59\,057$). This cohort has been previously described in detail.[12] The cohort population was identified from the Finnish Medical Birth Registry (MBR). After excluding children of mothers with preexisting diabetes ($n = 451$), pregnancies of women with two deliveries in 2009 (the second excluded, $n = 19$), children deceased during the monitoring period (perinatal deaths, $n = 257$, and other deaths before the age of 12, $n = 112$), and children diagnosed with a major congenital anomaly ($n=2499$), 55 719 children were included in the study. Of these children, 6235 were exposed to maternal GDM and 49 484 unexposed children served as controls (Figure 1).

2.2 | Research methods

Specialized health care utilization was retrieved from the Finnish Care Register for Health Care (FCR), including data on specialized care outpatient visits, inpatient treatment periods, and inpatient treatment days. Outpatient visits or treatment periods in primary health care are not covered in the FCR and were thus not included in the current study.

The MBR covers all live births and stillbirths in Finland with a gestational age of at least 22 gestational weeks or a birthweight ≥ 500 g. It also includes maternal background information and data related to pregnancy, delivery, and perinatal period. The FCR includes all inpatient care periods (since 1969) and outpatient care visits (since 1998) in hospitals, including diagnoses and the length of hospitalization. Diagnoses are recorded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes since 1996. The MBR and the FCR are comprehensive, validated registers maintained by the Finnish Institute of Health and Welfare (THL).[13,14] As a registry operator, the THL has given permission to use the register data for this study. No specific permissions were required from the participants according to Finnish legislation, as no participants were contacted for the study. Mother–child data pairs were matched using personal identity codes, and unique study numbers were generated by a person who did not participate in the study. The FinnGeDi research protocol was approved by the Northern Ostrobothnia Hospital District Regional Ethics Committee and the THL.[12]

Comprehensive screening for GDM has been in use in Finland since 2008: An oral glucose tolerance test (OGTT) is recommended at 24–28 gestational weeks for all pregnant women except those at low risk. Low-risk women are defined as those with a BMI <25.0 kg/m^2 and nulliparous women aged <25 years with no family history of type 2 diabetes or parous women <40 years of age with no history of GDM or a child born large for gestational age (LGA, birthweight ≥ 2 standard deviations [SD] above the sex- and gestational age-specific mean).[15] For women with GDM risk factors, an OGTT is recommended at 12–16 weeks of gestation. In 2009, risk factors included BMI ≥35.0 kg/m^2, glucosuria in the first trimester, family history of type 2 diabetes, use of systemic corticosteroid medication or diagnosis of polycystic ovary syndrome. If the OGTT at 12–16 weeks of gestation is normal, another test is recommended at 24–28 weeks. Additional testing is advised at any gestational age if diabetes is clinically suspected. The OGTT involves a 2-h test with a 75 g glucose load after overnight fasting. Diagnostic thresholds for venous plasma glucose are ≥5.3 mmol/L fasting, ≥10.0 mmol/L 1 h and ≥8.6 mmol/L 2 h after the glucose load. The diagnosis of GDM is based upon one or more abnormal values. All mothers diagnosed with GDM receive dietary and lifestyle counseling, as well as guidance on self-monitoring blood glucose. Target values for self-monitoring are fasting <5.5 mmol/L and <7.8 mmol/L 1 h postprandial. If self-monitored glucose levels are repeatedly exceeded, medication is initiated, typically insulin or metformin.[16,17] In this study, GDM was identified based on MBR data indicating at least one of the following: abnormal OGTT during pregnancy, initiation of insulin therapy during pregnancy, or a GDM diagnosis (ICD-10: O24.4 or O24.9). The MBR is validated to cover GDM pregnancies with 94.2% accuracy.[12]

We obtained background data on mothers and children from the MBR and the FCR. Covariates known to be associated with child morbidity were considered: maternal age, pre-pregnancy BMI,

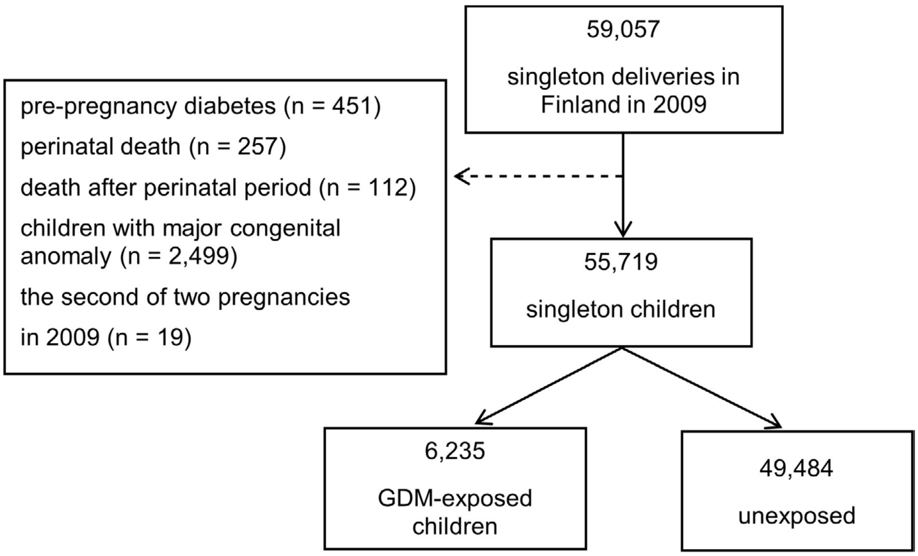

FIGURE 1 Flow chart of the study population, perinatal death: Intrauterine death ≥22 weeks of gestation or death during the first week of life. GDM, gestational diabetes mellitus.

parity, hypertensive disorders, smoking status, socioeconomic status (SES), mode of delivery, preterm birth (<37+0 weeks), small for gestational age (SGA, more than 2 SDs below the sex- and gestational age-specific mean), and sex of the child.[15] Continuous variables were categorized for the analysis. The categories of maternal age were as follows: <20, 20–24, 25–29 (reference), 30–34, 35–39, 40–44, ≥45 years. The categories of maternal pre-pregnancy BMI were as follows: <18.5 kg/m^2, 18.5–24.9 kg/m^2 (reference), 25–29.9 kg/m^2, 30.0–34.9 kg/m^2 and ≥ 35.0 kg/m^2. The categories of parity were as follows: first (reference), second or third, and fourth or more. The categories of maternal smoking status were as follows: no smoking during pregnancy (reference), smoking cessation during the first trimester, or continued smoking after the first trimester. SES was categorized based on maternal occupation: higher official (reference), lower official, manual worker, other (including self-employees, stay-at-home mothers, students, pensioners), and missing information as its own group. Mode of delivery was categorized as vaginal birth (including vacuum- and forceps-assisted deliveries) or cesarean delivery. Maternal hypertensive disorders (yes/no) were determined as ICD-10 codes I10, O10, O13, O14, and O15. Preterm birth and SGA were grouped into a variable of perinatal adverse outcome (yes/no). Sex of the child was categorized as girl or boy. Childhood mental, behavioral, and neurodevelopmental disorders (ICD-10 codes F00–F99) were obtained from the FCR up to 12 years of age for the subanalysis to explore specialized health care utilization in somatic morbidity.

2.3 | Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics 29.0 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp). Differences in background characteristics were analyzed using a Student's *t*-test in the case of continuous variables and a Chi-square test in the case of categorical variables. Because of overdispersion assumptions for Poisson regression, we used negative binomial regression to compare the prevalence of children's specialized health care use between the study groups.[18] For the comparison of categorized numbers of visits, we used logistic regression. The adjustment model considered presented confounders and mediators. Sensitivity analyses were performed by excluding children born SGA and preterm, and those with missing maternal occupational data.

3 | RESULTS

Mothers with GDM were older, more often overweight or obese, and had higher parity and lower SES than mothers without GDM. Their children were more often born preterm or by cesarean delivery, and they were less often SGA and more often LGA. Background characteristics of the children and mothers are presented in Table 1.

3.1 | Outpatient care visits

Of all children, 90.4% (n = 50 351) had at least one outpatient care visit in specialized health care up to the age of 12 years, with a mean of 15.8 (SD 29.3) visits. The median of visits for GDM-exposed children was 7.0 (interquartile range [IQR] 2.0–17.0) and 6.0 (IQR 2.0–14.0) for unexposed children, and the mean of visits was 16.5 (SD 33.6) for GDM-exposed children and 14.1 (SD 27.5) for the ones without exposure ($p < 0.001$). Children exposed to GDM had a higher incidence of specialized care outpatient visits than unexposed children (incidence rate ratio [IRR] 1.18, 95% CI 1.15–1.22, $p < 0.001$), and exposure to GDM remained a risk factor in the adjusted analysis (adjusted IRR 1.10, 95% CI: 1.07–1.13, $p < 0.001$). Similar findings were also observed in the sensitivity analysis after excluding children born SGA and preterm, and those with missing maternal occupational data. Differences in the number of outpatient care visits between groups are presented in Figure 2.

We analyzed outpatient care visits across different age categories: early childhood (0–2 years), preschool age (3–6 years), and school age (7–12 years). Children exposed to GDM had a higher incidence of outpatient care visits in all age categories: early childhood IRR 1.11 (95% CI: 1.08–1.15, $p < 0.001$) and adjusted IRR 1.06 (95% CI: 1.02–1.10, $p < 0.001$), preschool age IRR 1.26 (95% CI: 1.23–1.30, $p < 0.001$) and adjusted IRR 1.18 (95% CI: 1.14–1.21, $p < 0.001$), and school age IRR 1.17 (95% CI: 1.14–1.20, $p < 0.001$) and adjusted IRR 1.07 (95% CI: 1.04–1.10, $p < 0.001$). To investigate whether GDM-exposed children are more likely to have multiple outpatient care visits across childhood, we defined thresholds for high visit frequency using the higher quartile of visits in each age category (early childhood: ≥4 visits, preschool: ≥3 visits, and school age: ≥6 visits). Children exposed to GDM had a higher risk of multiple visits in all age ranges. These results are presented in Figure 3.

3.2 | Inpatient treatment

Of all children, 39.5% had at least one inpatient treatment period until the age of 12 years, with the periods being more prevalent among GDM-exposed children (45.8% vs. 38.6% in unexposed children, OR 1.34, 95% CI: 1.27–1.41, $p < 0.001$, and aOR 1.24, 95% CI 1.17–1.31, $p < 0.001$). Overall, children exposed to GDM had a higher incidence of inpatient treatment episodes (IRR 1.21, 95% CI: 1.16–1.25, $p < 0.001$) and a higher number of inpatient treatment days (IRR for the inpatient treatment days 1.25, 95% CI: 1.21–1.29, $p < 0.001$) compared with unexposed children. These differences between groups were also present after adjustments (adjusted IRR for episodes 1.14, 95% CI: 1.10–1.20, $p < 0.001$ and adjusted IRR for days 1.20, 95% CI: 1.16–1.24, $p < 0.001$). In the sensitivity analysis, where children born SGA and preterm, and children with missing maternal occupational data were excluded, findings were in line with the primary analyses. The mean of the inpatient treatment episodes was 0.9 (SD 2.4) in GDM-exposed children and 0.8 (SD 2.0) in unexposed children, and the means

TABLE 1 Background characteristics of the study population.

	GDM (*n* = 6235)		Unexposure (*n* = 49 484)		
	Mean (SD)	%	Mean (SD)	%	*p*-value
Maternal age at delivery, years					
<20	31.1 (5.6)	1.6	29.3 (5.3)	2.5	<0.001
20–24		10.8		16.4	
25–29		27.4		32.6	
30–34		32.3		32.2	
35–39		20.2		13.2	
40–44		7.4		3.0	
≥45		0.3		0.1	
Maternal pre-pregnancy BMI, kg/m^2					
<18.5	28.4 (6.0)	1.3	23.7 (4.3)	4.0	<0.001
18.5–24.9		30.6		65.3	
25.0–29.9		32.2		20.1	
30.0–34.9		21.5		6.2	
≥35.0		13.7		2.4	
Missing		2.2		3.1	
Parity					
1	1.24 (1.6)	36.5	1.01 (1.4)	43.0	<0.001
2–3		50.4		47.8	
≥4		13.1		9.3	
Socioeconomic status					
Higher official		14.9		16.7	<0.001
Lower official		34.6		31.7	
Manual worker		15.3		12.4	
Other		14.7		16.6	
Missing		19.7		21.8	
Smoking					
No		80.1		82.5	<0.001
Cessation at 1st trimester		6.5		4.9	
Continued		11.3		10.0	
Missing		2.1		2.6	
Maternal hypertensive disorder		10.2		5.1	<0.001
Mode of delivery					
Vaginal		78.7		86.0	<0.001
Cesarean		21.3		14.0	
Perinatal outcomes					
Gestational weeks at delivery	39.6 (1.6)		39.9 (1.6)		<0.001
Preterm birth <37 weeks		4.6		3.6	<0.001
Term birth ≥37 to <42 weeks		91.3		90.8	0.158
Post-term birth ≥42 weeks		4.0		5.5	<0.001
Missing		0.1		0.1	0.327
Birth weight, g	3615 (533)		3514 (513)		<0.001
SGA		2.1		3.0	<0.001
LGA		4.5		1.7	<0.001
Perinatal adverse outcome[a]		6.3		6.2	0.677
Offspring's sex (%, female/male)		48.8 / 51.2		49.1/50.9	0.738

Abbreviations: GDM, gestational diabetes mellitus; LGA, large for gestational age ≥2 SDs above the sex- and gestational age-specific mean; SD, standard deviation; SGA, small for gestational age ≤−2 SDs below the sex- and gestational age-specific mean.

[a]Perinatal adverse outcome = Preterm birth or SGA. *P*-values based on a Student's *t*-test in the case of continuous variables and a Chi-square test in the case of categorical variables.

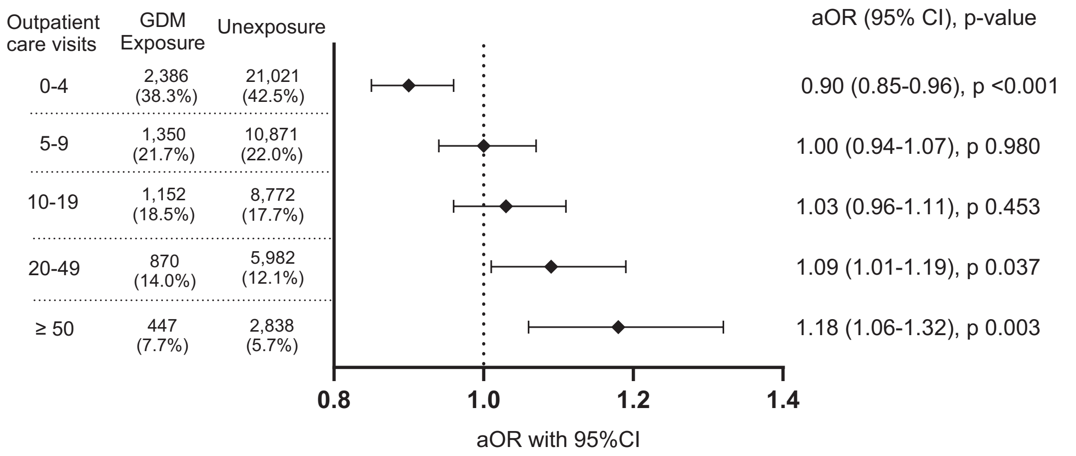

FIGURE 2 Proportions of children exposed and nonexposed to gestational diabetes mellitus (GDM) according to categorized outpatient care visit, adjusted odds ratios (aOR) with 95% confidence intervals (CI). Adjusted for maternal age, pre-pregnancy BMI, parity, mode of delivery, smoking, socioeconomical status (SES), hypertensive disorders, perinatal adverse outcomes, and offspring sex.

of inpatient treatment days were 3.8 (SD 13.2) and 3.1 (SD 11.9), respectively ($p < 0.001$ for both). Categorized numbers of inpatient treatment episodes among the study groups are presented in Figure 4.

3.3 | Specialized health care utilization in somatic morbidity

We explored specialized health care utilization focusing on somatic morbidity by excluding children with mental, behavioral, and neurodevelopmental diagnoses (ICD-10 codes F00–F99) from the analyses. In the cohort, 18.2% ($n = 1134$) of the GDM-exposed children and 14.1% ($n = 6980$) of the unexposed children had at least one of these diagnoses ($p < 0.001$). The difference in specialized health care utilization between groups remained even after children with mental, behavioral, and neurodevelopmental disorders were excluded. Results are presented in Figure 5.

4 | DISCUSSION

According to this population-based study, exposure to maternal GDM is associated with increased utilization of specialized health care up to 12 years of age, likely reflecting increased morbidity in these children. This difference between the study groups was observed in all studied age ranges up to 12 years of age.

A few previous studies have investigated the morbidity of children exposed to GDM by examining their need for hospitalization.[10,11,19] Åberg et al. investigated this topic by examining a Swedish register-based data set from 1987 to 1997. In their study, GDM exposure increased the risk of hospitalization when maternal age, parity, and smoking were considered (aOR 1.27), although pre-pregnancy diabetes appeared to be a more significant risk factor (aOR 1.76). However, the prevalence of GDM in their data was low, and the diagnosis of GDM was based on a glucose value of ≥9.0 mmol/L 2 h after a 75 g glucose load, reflecting a more severe end of the GDM spectrum. Åberg and colleagues reported that exposure to maternal GDM was a risk factor for increased hospitalization in offspring from the neonatal period up to 10 years of age. This is consistent with the findings of our study. In contrast, a large Danish register-based study found that increased morbidity in GDM-exposed children was restricted to the first 2 years of life.[11] The study assessed the risk for hospitalization by calculating the percentage of days spent in a hospital. The prevalence of GDM in their data was very low, which may be related to the wide study period (1976–2003) and the screening practices and diagnostic criteria used at that time.[11]

Potential reasons for the increased hospitalization rate among children exposed to GDM have also been investigated. Åberg et al. showed that congenital malformations, mental and behavioral disorders, infections, and accidents were the most prevalent causes for increased hospitalization, although mental and behavioral diagnoses were rare in the data.[10] Abokaf et al. reported that endocrine disorders also account for a greater utilization of health care services among children exposed to GDM compared with unexposed children.[19] Previously, we reported that GDM-exposed children were at higher risk for congenital anomalies than unexposed children.[20] In the present study, we excluded children with major congenital anomalies from the data, as they are associated with significant comorbidity.[21] A higher prevalence of mental, behavioral, and neurodevelopmental disorders in GDM-exposed children is reported in the literature and was also observed in our study.[22] This finding is notable since a small proportion of the population utilizes a significant proportion of the resources in specialized health care services, and the risk of being a high-utilizer (top 15% according to the number of visits) has been found to be 10 times higher in child psychiatry than in pediatrics.[23] This phenomenon was also seen in our data: 74% of the children with the most specialized care outpatient visits (≥50 visits) had a mental,

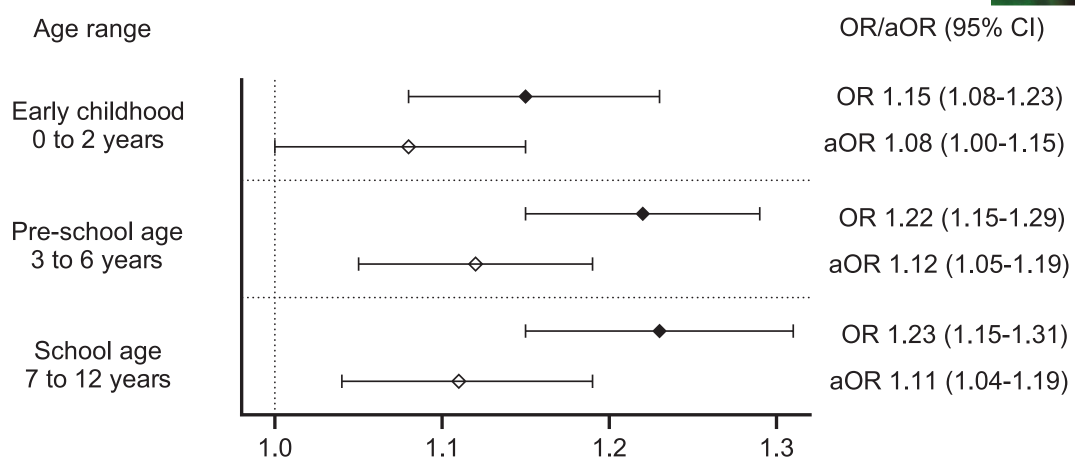

FIGURE 3 The risk of gestational diabetes exposed children to have multiple outpatient care visits (highest quartile) in early childhood (0–2 years), preschool age (3–6 years), and school age (7–12 years), adjusted odds ratios (aOR) with 95% confidence intervals (CI). Adjusted for maternal age, pre-pregnancy BMI, parity, mode of delivery, smoking, socioeconomic status (SES), hypertensive disorders, perinatal adverse outcome, and offspring sex.

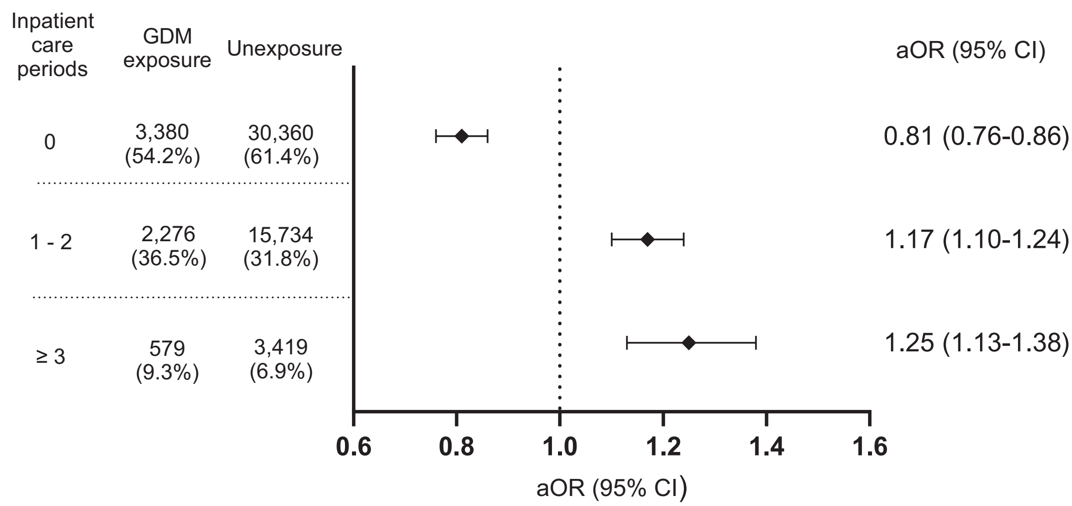

FIGURE 4 Categorized number of inpatient treatment periods in children exposed and unexposed to gestational diabetes mellitus (GDM). Adjusted odds ratios (aOR) with 95% confidence intervals (CI). Adjusted for maternal age, pre-pregnancy BMI, parity, mode of delivery, smoking, socioeconomic status (SES), hypertensive disorders, perinatal adverse outcome, and offspring sex.

behavioral, or neurodevelopmental disorder diagnosis in the FCR (ICD-10 codes F00–F99). To explore whether increased specialized health care utilization was linked to somatic morbidity in our data, we conducted an analysis that excluded these children. Among children without mental, behavioral, and neurodevelopmental disorders, those exposed to GDM had a higher incidence of outpatient visits and inpatient treatments compared with unexposed children.

Although research on the overall morbidity of children exposed to maternal GDM in childhood remains limited, several mechanisms have been proposed to explain how GDM exposure may affect the health of offspring.[24,25] Maternal hyperglycemia, for instance, leads to fetal hyperinsulinemia, which further leads to increased fetal growth, risk of fetal hypoxemia and adaptation challenges in the neonatal period. In addition to hyperglycemia, other metabolic imbalances, such as higher maternal lipid levels, leading to lipotoxity, and free oxygen radicals, leading to oxidative stress, might induce an inflammatory response.[26–28] This antenatal environment may adversely impact fetal development and have implications for the long-term health of offspring. The theory of developmental origins of health and disease also includes the idea of epigenetic modification, whereby environmental factors can induce changes in gene expression in the fetus. The effects of these changes on the subsequent health of the offspring can thus be transmitted epigenetically and increase the overall morbidity of the offspring.[24,29]

The most important strengths of our study were its population-based setting and the high-quality register-based data.[13] Exposure to GDM was defined with a validated method.[12] The proportion of GDM-exposed children was comparable to the overall prevalence

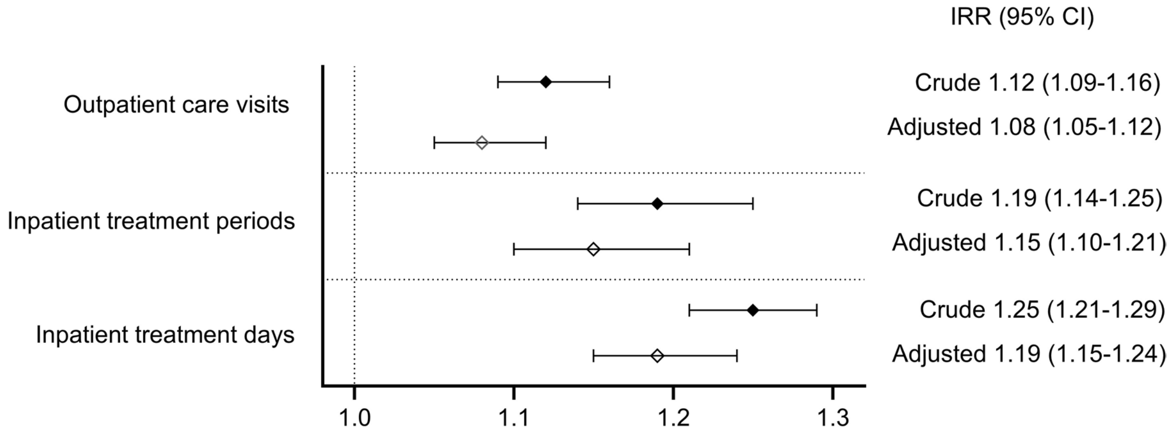

FIGURE 5 Specialized health care utilization in somatic morbidity in gestational diabetes exposed children compared with unexposed children, incidence rate ratios (IRRs) and adjusted IRRs with 95% confidence intervals (CI).

of GDM at that time, although this prevalence has increased during the last decade, being 20.6% in 2019 in Finland.[3,13,30] The guideline of GDM screening had only recently been introduced (in 2008), and the proportion of women undergoing OGTT has increased thereafter.[16] The findings of this study are highly applicable to clinical practice, as the screening methods and diagnostic criteria used have remained largely consistent and closely align with American Diabetes Association recommendations while also conforming to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[1,6,16,31] We focused on the use of specialized care, of which the FCR provides comprehensive information. The number of outpatient visits and inpatient treatment periods provides a comprehensive overview of specialized health care utilization and overall morbidity of children.[32] The Finnish health care system provides equal services for all people. Private health services can be used alongside those offered publicly, although they rarely substitute for hospital-based specialized health care and do not affect the use of public services for children.[33] We were able to adjust the analyses widely since many factors related to GDM may also reflect the child's health, especially maternal age, obesity, smoking, and SES disparities.[34–37] Children with major congenital anomalies that would more likely lead to increased specialized health care utilization were excluded from the study.

One limitation of this study was that we could only observe the association between GDM exposure and the use of specialized health care services, not the cause–effect relationship between them. Although the majority of health care services in Finland are provided in primary health care, the most significant health care costs arise from specialized health care.[38] While the study did not cover the use of primary health care services, it is likely that morbidity is higher among children with increased use of specialized health care. Although we considered many potential confounding and mediating factors, we were not able to capture maternal weight gain during pregnancy or body size or body composition of the children, which can mediate specialized health care utilization in children. In addition, we had no data on lifestyle factors, such as alcohol intake among parents. As we defined SES according to maternal occupation during pregnancy, it was not possible to consider subsequent changes in maternal and/or paternal educational attainment or family income during childhood.[37]

5 | CONCLUSION

Exposure to GDM is associated with increased morbidity in children up to 12 years of age, defined by specialized health care utilization. The difference in morbidity between exposed and unexposed children was not limited to a certain age period but was, in fact, present from early childhood to school age.

AUTHOR CONTRIBUTIONS

Conduction of the FinnGeDi study: MV, MG, HL, JGE, and EKa. Design of the particular study: JK, HN, and MV. Statistical analysis, visualization, manuscript writing, and editing: JK. Supervision: HN and MV. All authors revised the article and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The use of registry data requires permission from the registry authorities, and the data used for the present study is not publicly available without permission. The registers used in this study are maintained by the THL, and researchers can apply for similar register data from Findata, Finnish Social and Health Data Permit Authority: https://findata.fi/en/.

ETHICS STATEMENT

The entire FinnGeDi study protocol was approved by the Regional Ethics Committee in Northern Ostrobothnia Hospital District (reference number 33/2008) on June 19, 2008, and the permission of the register holder THL (reference number THL/270/6.02.00/2019) on March 20, 2019. The FinnGeDi study included two study arms; the register-based arm used in this study was based on registers administered by the THL, with the register administrator approving the use of the data. According to Finnish legislation, no specific permission is required in the case of register studies, as participants are not contacted for the study. We confirm that all methods were carried out in accordance with relevant regulations.

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