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ORIGINAL RESEARCH ARTICLE

Neonatal outcome following metformin-treated gestational diabetes mellitus: A population-based cohort study

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Abstract

Introduction: Neonatal hypoglycemia is a common complication associated with gestational diabetes and therefore relevant to consider in evaluations of maternal treatment. We aimed to investigate the risk of neonatal hypoglycemia in offspring exposed to metformin treatment alone (MT) or combined with insulin (MIT) in comparison with nutrition therapy alone (NT), and insulin treatment alone (IT). In addition, we investigated MT in comparison with MIT. Secondary outcomes included neonatal anthropometrics, respiratory morbidity, hyperbilirubinemia, 5-min Apgar score, and preterm birth.

Material and methods: This Swedish population-based cohort included 16 181 women diagnosed with gestational diabetes, and their singleton offspring born in 2019–2021. We estimated risk as adjusted odds ratio (aOR) with 95% confidence interval (CI), using individual-level, linkage register-data in multivariable logistic regression models.

Results: In the main analysis, MT was associated with a lower risk of neonatal hypoglycemia vs NT (aOR 0.85, 95% CI: 0.74–0.96), vs MIT (0.74 [0.64–0.87]), and vs IT (0.47 [0.40–0.55]), whereas MIT was associated with a similar risk of neonatal hypoglycemia vs NT (1.14 [0.99–1.30]) and with lower risk vs IT (0.63 [0.53–0.75]). However, supplemental feeding rates were lower for NT vs pharmacological treatments ($p < 0.001$). In post hoc subgroup analyses including only exclusively breastfed offspring, the risk of neonatal hypoglycemia was modified and similar among MT and NT, and higher in MIT vs NT. Insulin exposure, alone or combined with metformin, was associated with increased risk of being large for gestational age. Compared with NT, exposure to any pharmacological treatment was associated with significantly lower risk of 5-min Apgar score < 4. All other secondary outcomes were comparable among the treatment categories.

Conclusions: The risk of neonatal hypoglycemia appears to be comparable among offspring exposed to single metformin treatment and nutrition therapy alone, and

Abbreviations: ATC, Anatomical Therapeutic Chemical; aOR, adjusted odds ratio; CI, confidence interval; GDM, gestational diabetes mellitus; ICD-10, International Classification of Disease, version 10; IADPSG, International Association of Diabetes in Pregnancy Study Group; LGA/SGA, large/small for gestational age; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test; SPR, Swedish Pregnancy Register; SNQ, Swedish Neonatal Quality Register; WHO, World Health Organization.

the lower risk that we observed in favor of metformin is probably explained by a difference in supplemental feeding practices rather than metformin per se. By contrast, the lower risk favoring metformin exposure over insulin exposure was not explained by supplemental feeding. However, further investigations are required to determine whether the difference is an effect of metformin per se or mediated by other external factors.

KEYWORDS
gestational diabetes mellitus, metformin, neonatal hypoglycemia, neonatal outcome, population-based, register-based

1 | INTRODUCTION

Identifying gestational diabetes mellitus (GDM) is an important aim in maternal health care as maternal hyperglycemia is associated with accelerated fetal growth and adverse pregnancy outcome.[1] Neonatal hypoglycemia is strongly associated with GDM,[2,3] and therefore relevant to consider in evaluations of benefits and harms of GDM treatments. Neonatal hypoglycemia can become a serious condition and is associated with cerebral damage and neurodevelopmental impairment if unrecognized, and left untreated.[4] However, current evidence for the benefit of GDM treatment regarding neonatal hypoglycemia is inconclusive.[5] Nutrition therapy combined with physical activity and self-monitoring of blood glucose levels are cornerstones when treating GDM.[6] Metformin is increasingly used as adjunctive treatment when nutrition therapy alone is insufficient to achieve normoglycemia.[7,8] Metformin treatment exposes the fetus to serum concentrations comparable to maternal levels.[9] Randomized controlled trials have confirmed that short-term neonatal outcome following metformin treatment is noninferior to insulin treatment,[8] but long-term safety data are still limited.[2,10,11] However, only a few studies have investigated neonatal outcome following metformin treatment in comparison with nutrition therapy,[11–16] and most studies evaluating neonatal outcome following GDM have not distinguished metformin alone from combined metformin-insulin treatment, which makes it difficult to draw conclusions regarding metformin treatment per se.

Our primary aim was to investigate the risk of neonatal hypoglycemia in offspring exposed to metformin in comparison with nutrition therapy alone and insulin treatment, by evaluating metformin as single adjunctive treatment separately from combined metformin-insulin treatment. In addition, metformin alone was evaluated against combined metformin-insulin treatment. Neonatal anthropometrics, and other morbidities associated with fetal hyperinsulinemia were investigated as secondary outcomes, including neonatal respiratory disorders, hyperbilirubinemia, low Apgar score, preterm birth, and neonatal intensive care unit (NICU) admissions.[17] Our hypothesis was that metformin as single adjunctive treatment would be associated with similar risk of neonatal hypoglycemia as nutrition therapy alone, based on the assumption that maternal glycemic targets are met in the absence of concomitant insulin treatment, and that requirement of supplemental insulin is a marker of more severe maternal hyperglycemia and therefore associated with higher risk of neonatal hypoglycemia in the offspring.

Key message

Offspring exposed to metformin as single adjunctive treatment for gestational diabetes appear to have similar short-term neonatal outcome as offspring exposed to nutrition therapy alone, and more favorable outcome compared with offspring exposed to combined metformin-insulin treatment or insulin alone.

2 | MATERIAL AND METHODS

This study was conducted in Sweden, where screening policies and diagnostic criteria for GDM vary among 21 independent health care regions. The study coincided with the Covid pandemic, but diagnostic approaches and clinical practice remained unaffected, as Sweden had no lockdown. In summary, random capillary glucose is analyzed five times during the pregnancy as a general screening for GDM. Additional screening with a 75 g oral glucose tolerance test (OGTT) is either universal (two regions) or selective based on risk factors, and the sampling medium is either venous or capillary (Table S1). Eight of the 21 regions, comprising 42% of Sweden's deliveries, apply the IADPSG/WHO 2013 diagnostic thresholds[18] for fasting (≥5.1 mmol/L) and 2-h post load glucose levels (≥8.5 mmol/L), whereof seven also apply the 1-h post load glucose threshold (≥10.0 mmol/L). The remaining regions apply higher thresholds for GDM diagnosis (Table S1). Women with GDM are advised to engage in physical activity at moderate intensity for at least 150 min/week. Nutrition therapy is first-line treatment, except when criteria for manifest diabetes are fulfilled and pharmacotherapy deemed necessary. Glucose self-monitoring by capillary measurements is recommended 4–7 times/day, 2–7 days/week depending on mode of treatment and regional variations. Glucose target levels are in most regions <5.3 mmol/L fasting, <6.0 mmol/L preprandial, <8.0 or

<7.0 mmol/L 1-h or 2-h post-prandial, and <7.0 mmol/L at bedtime (Table S1). Adjunctive pharmacological treatment is initiated when glycemic control is not met by nutrition therapy alone, defined as >3–5 measurements above target within in the same week, and the Swedish National Board of Health and Welfare endorse both metformin and insulin as pharmacological adjunctive treatments during pregnancy.[19] For prevention and screening of neonatal hypoglycemia, the Swedish Neonatology Society recommends early establishment of uninterrupted skin-to-skin contact; initiation of breastfeeding as soon as possible after delivery, and thereafter at least every second to third hour; supplementary feeding with breastmilk or infant formula within the first hour of life to infants at risk, such as maternal GDM; consideration of delaying supplementary feeding when satisfactory breastfeeding is established in appropriate for gestational age offspring of mothers treated with nutrition therapy alone if blood glucose is normal; screening of infants at risk by plasma glucose measurement, initially before the second feeding and thereafter before feeding until glucose levels stabilize above 3.0 mmol/L.[20]

We performed a register-based cohort study on individual-level linkage data collected from Swedish national registers and health quality registers (Figure 1). Swedish residents are assigned a unique personal identity number at birth, or when immigrating and receiving resident status, which enables linkage of register data.[21] Participation is compulsory in Swedish government-administered national registers, but individuals can opt out from quality registers. The Swedish Pregnancy Register (SPR) is a national quality register that retrieves prospectively collected maternal and neonatal pregnancy, delivery, and neonatal period data by automated processes directly from the medical records.[22] In addition, maternal health

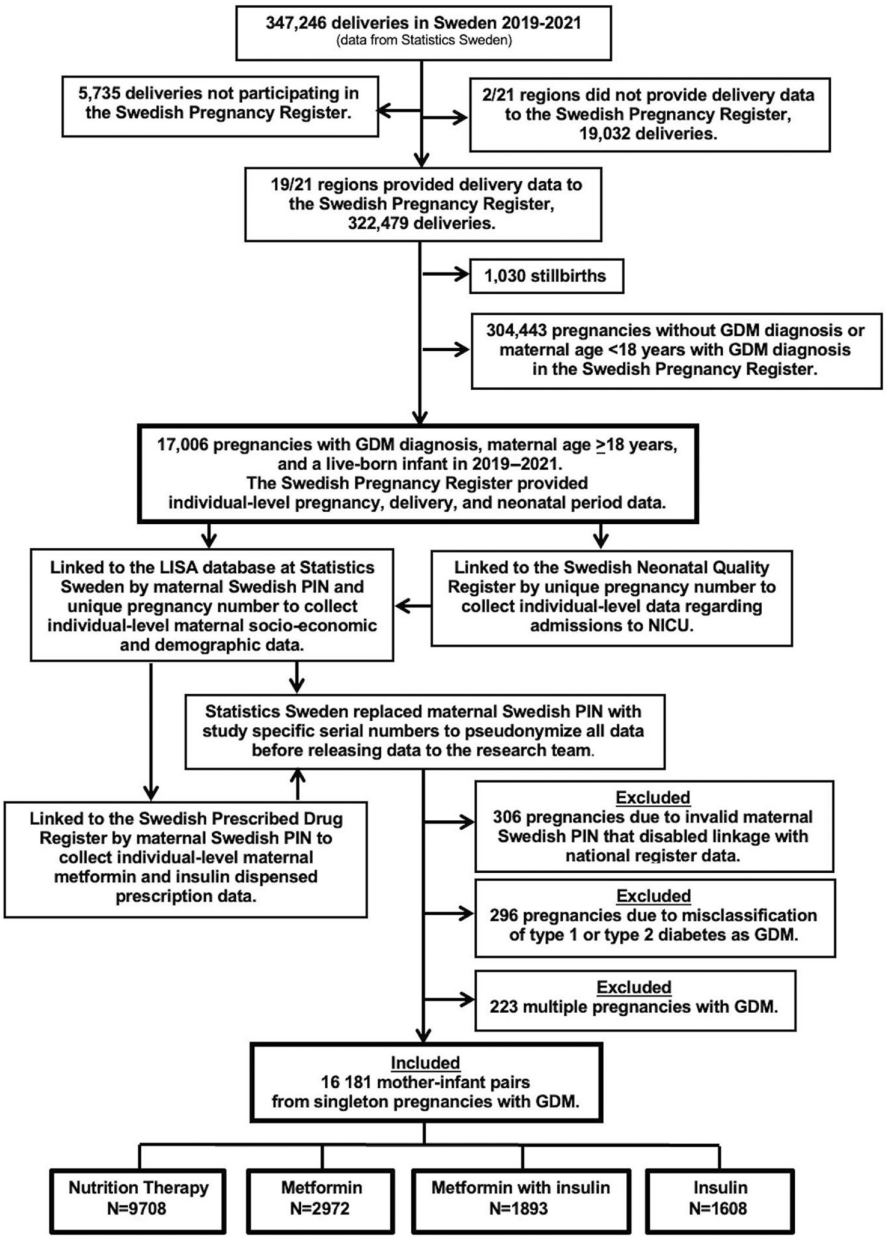

FIGURE 1 Flow chart illustrating study design and selection of the study population. Aggregated data were obtained from the Swedish Pregnancy Register and Statistics Sweden. GDM, gestational diabetes mellitus; LISA, longitudinal integrated data base for health insurance and labor market studies; NICU, neonatal intensive care unit; PIN, personal identity number.

care providers manually enter data that are not documented in a structured way in the medical records. The annual coverage rate was 97.9% to 98.4%, but delivery data was lacking from two of 21 regions (comprising 5.5% of Swedish births in 2019–2021) due to technical issues. The Swedish Neonatal Quality Register (SNQ) is a national quality register that collects neonatal data from all Swedish NICU.[23] The coverage rate is 98% for gestational ages <35 weeks.[23] Statistics Sweden is a government agency that provides official population-based aggregated statistics, and their longitudinal integrated database for health insurance and labor market studies, the LISA-database, provides individual-level data for research.[24] The Swedish Prescribed Drug Register collects individual-level dispensing dates and Anatomic Therapeutic Chemical (ATC) codes for all dispensed drugs on a daily basis from Swedish pharmacies by automated processes, which is compulsory and ensures reliable and nearly complete data.[25]

Inclusion criteria for the study were GDM diagnosed during the pregnancy, maternal age ≥ 18 years, singleton pregnancy, and live offspring born beyond gestational week 21 + 6 days in 2019 to 2021. Exclusion criteria were pre-existing type 1 or type 2 diabetes, and stillbirth. GDM diagnosis was identified by the International Classification of Disease (Swedish) version 10 (ICD-10) code O24.4, and/or if a checkbox variable for GDM diagnosis was ticked yes in SPR by the maternal health care provider. The GDM diagnosis was further validated by metformin and insulin prescriptions in pharmacologically treated participants, and by OGTT glucose values available from 75.6% of the participants treated with nutrition therapy alone. Pregnancies with additional ICD-10 codes indicating pregestational diabetes (O24.0, O24.1, O24.3, E10–E11), and/or if a checkbox variable "diabetes prior to the pregnancy (not GDM)" was ticked yes, were assumed to have pregestational diabetes and therefore excluded from the cohort when pharmacological treatment prior to the pregnancy was verified by ATC-codes and dispensation dates, and/or OGTT was negated or this information was lacking. Pregnancies with invalid maternal personal identity number were also excluded. In all, 16 181 mother-infant pairs were included and stratified into four treatment categories (Figure 1).

Exposure was mode of treatment at the time of delivery. Metformin exposure was identified if at least one metformin (ATC A10BA02) prescription was dispensed during the pregnancy. Prepregnancy treatment with metformin for other conditions, for example, polycystic ovary syndrome, was assumed discontinued once pregnancy was confirmed, which is customary in Sweden. Any redispensation during pregnancy was assumed to be for GDM. Single treatment was assumed if metformin, but no insulin (ATC A10A) prescription was dispensed. Combined treatment was assumed if both insulin and metformin prescriptions were dispensed, and insulin as single treatment was assumed if at least one insulin but no metformin prescription was dispensed during the pregnancy. Nutrition therapy was assumed if neither metformin, nor insulin were dispensed during the pregnancy.

Primary outcome was neonatal hypoglycemia, clinically defined by at least one plasma glucose <2.6 mmol/L (47 mg/dL) detected by screening or clinically indicated measurement up until discharge from the hospital. To verify which ICD-10 codes that were used to document the primary outcome, we reviewed 260 medical records, after random sampling by SPR among deliveries at five units derived from different health care regions. Three different ICD-10 codes

TABLE 1 Measures used for identification of primary and secondary outcomes, the data sources, and descriptions of the outcomes.

Outcome	ICD-10 codes	Other measures	Source	Description
Neonatal hypoglycemia	P70.0 P70.1 P70.4	Checkbox for diagnosis in SNQ Plasma glucose <2.6 mmol/L documented in SNQ	SPR, SNQ	The Swedish Neonatal Society recommends screening of infants at risk, and advocates treatment if glucose is <2.6 mmol/L
Neonatal respiratory morbidity	P22.0 P22.1 P22.8 P22.9		SPR, SNQ	Documentation of a treatment code for CPAP without a concomitant ICD-10 code P22.0–9 was not considered as neonatal respiratory morbidity
Neonatal hyperbilirubinemia	P59	Treatment code phototherapy	SPR, SNQ	Screening is by transcutaneous measurements of all infants. Diagnosis is based on serum concentrations above the age-corrected upper limit, warranting phototherapy or other treatment
LGA +2 SD		Birthweight z-score > +2.0	SPR	INTERGROWTH 21st was the reference population
SGA −2 SD		Birthweight z-score < −2.0	SPR	INTERGROWTH 21st was the reference population
Low Apgar score at 5 min		Apgar score at 5 min <7 Apgar score at 5 min <4	SPR	Assessed by the delivery staff at 5 min of age
Preterm birth		Gestational age at delivery <37 weeks	SPR	Based on date of embryo transfer when applicable, first or second trimester scan, or date of LMP if no scan was performed before gestational week 22 + 3
NICU admittance			SNQ	Based on registration in SNQ

Abbreviations: CPAP, continuous positive airway pressure; ICD-10, International Classification of Disease 10th (Swedish) version; LGA, large for gestational age; LMP, last menstrual period; NICU, neonatal intensive care unit; SD, standard deviation; SGA, small for gestational age; SNQ, Swedish Neonatal Quality Register; SPR, Swedish Pregnancy Register.

representing neonatal hypoglycemia (O70.0, O70.1, O70.4) were identified among cases with neonatal hypoglycemia according to the medical records. Primary outcome data were identical between SPR and 82% of the reviewed medical records. The proportion of nonidentical data, introducing over- or underestimation of neonatal hypoglycemia in the SPR data, was similar among treatment groups, as verified by a chi-square test. In addition to ICD-10 codes, plasma glucose values entered in SNQ for infants cared for at NICU and a checkbox variable for neonatal hypoglycemia in SNQ were used to identify offspring with neonatal hypoglycemia.

Secondary outcomes were small, and large for gestational age (SGA/LGA) relative to the INTERGROWTH-21st reference population,[26,27] neonatal respiratory morbidity, neonatal hyperbilirubinemia, low Apgar score at 5 min defined as <7 and <4, preterm birth, and NICU admissions (Table 1).

Covariates identified as confounders were selected a priori to the analysis, and based on determinants for the exposure, and known risk factors for the outcomes (Table 2).[17,20] Directed acyclic graphs were constructed using the DAGitty.net version 3.1 to identify biasing pathways between exposure and outcomes (Figure 2).[28]

2.1 | Statistical analyses

Analysis of maternal and neonatal baseline characteristics according to treatment group was done by Kruskal Wallis test for continuous data and chi-square test for categorical data, and regarded as statistically significant when the *p*-value was <0.05. Risk of the primary and secondary outcomes were estimated as odds ratio (OR) relative to the reference treatment. Crude OR was estimated by univariate logistic regression models and confounder adjusted OR by multivariable logistic regression models. Only covariates affecting both the exposure and the outcome were controlled for in the adjusted models, and all covariates were entered simultaneously. Minimal sufficient adjustment to control for all biasing pathways was applied to avoid overadjustment bias due to adjustment for

TABLE 2 Covariates identified as confounders and adjusted for in the multivariable logistic regression models.

Covariate	Description	Source
Maternal age at delivery	Continuous variable	SPR
Maternal BMI in the first trimester	Continuous variable	SPR
Parity	Continuous variable	SPR
Country of birth	Categorical variable: • Sweden • European country other than Sweden • African country • Asian country • Other country	Statistics Sweden (LISA) SPR
Annual year-specific prevalence of GDM in region of care	Continuous variable representing region of care to account for difference among regions in factors that determine GDM diagnosis and thereby selection for the study (population characteristics, screening policy, and diagnostic criteria for GDM)	SPR
Year of delivery	Categorical variable to account for difference in screening policies, diagnostic criteria, and treatment policies over time: • 2019 • 2020 • 2021	SPR
Gestational age at diagnosis (date for OGTT)	Continuous variable	SPR
Mode of initial treatment of GDM	Categorical variable: • Nonpharmacological (nutrition therapy) • Pharmacological To account for difference in severeness of maternal hyperglycemia at the time of GDM diagnosis, and to account for that mode of treatment at delivery may be different from treatment initiated at diagnosis. Pharmacological treatment initiated within 2 weeks from diagnosis was considered as the initial treatment	SPR, SPDR
Maternal care for suspected fetal growth restriction during pregnancy	Categorical variable: • Yes (identified by ICD-10 O36.5) • No (identified by absence of ICD-10 O36.5) To account for that metformin is advised against in case of suspected fetal growth restriction	SPR

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; ICD-10, International Classification of Disease 10th (Swedish) version; LISA, longitudinal integrated database for health insurance and labor market studies; OGTT, oral glucose tolerance test; SPDR, Swedish Prescribed Drug Register; SPR, Swedish Pregnancy Register.

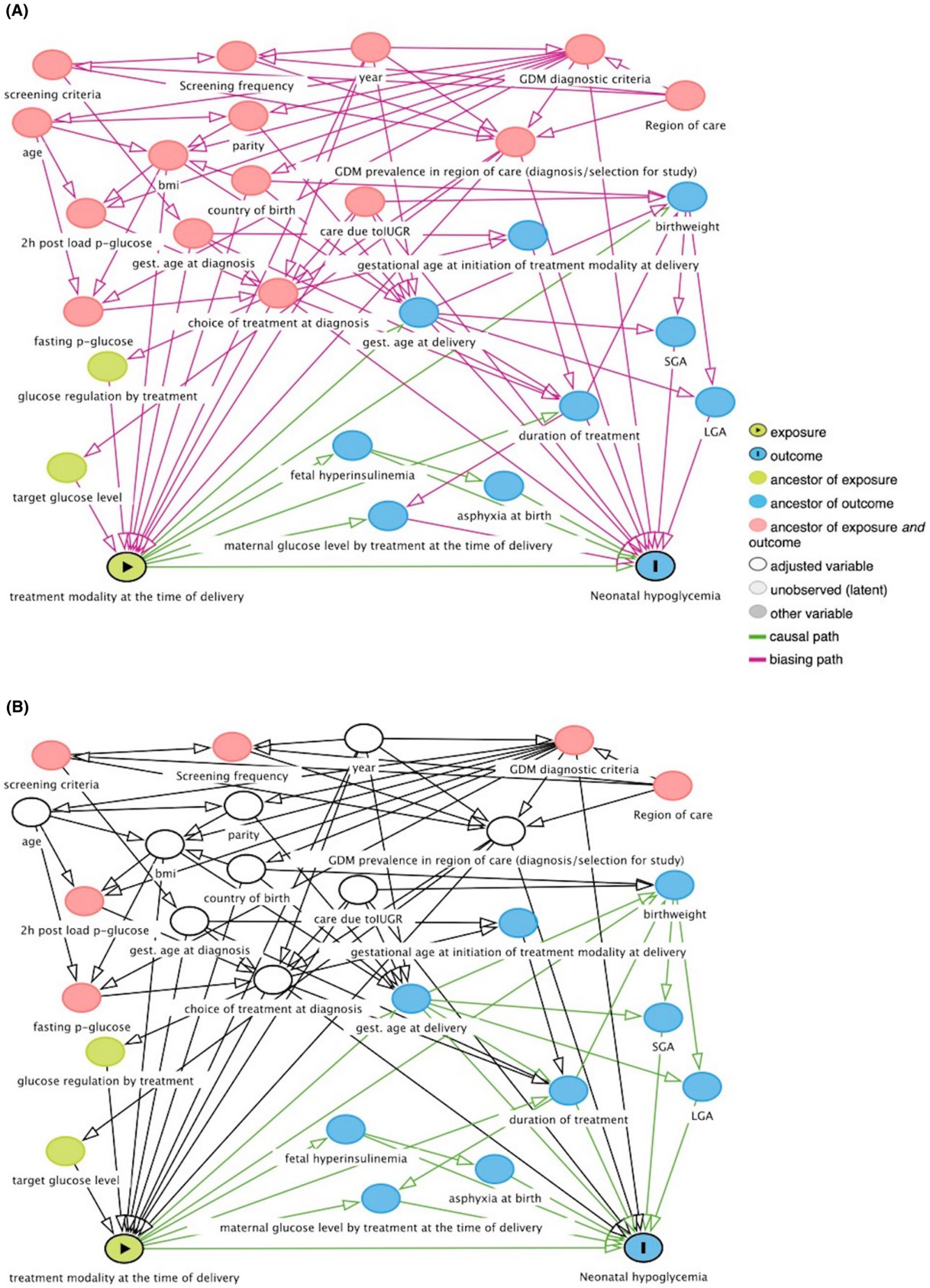

FIGURE 2 Directed acyclic graphs (DAG) of (A) the biasing pathways between mode of treatment for maternal gestational diabetes mellitus and neonatal hypoglycemia in the offspring, as indicated by pink arrows, and (B) minimal sufficient adjustment to control for all the biasing pathways, as indicated by black arrows, without introducing overadjustment bias from mediating pathways, as indicated by green arrows. The DAGs were constructed using DAGitty.net, version 3.1.

mediators (Table 2, and Figure 2).[29] To obtain unbiased estimates and reduce the risk of selection bias, missing covariate data points were assumed as missing at random and imputed by multiple imputation techniques (Table S2).[30] The method of multiple imputation was done by fully conditional specification using Monte Carlo Markov Chain,[30] with 10 iterations for each of 30 imputations. The data set generated by the multiple imputation procedure was used for the logistic regression analyses. 95% confidence intervals (CI) were calculated and regarded significant when not crossing 1.0. In analyses of neonatal outcomes solely defined by ICD-10 codes, 297 infants completely lacking ICD-10 codes were excluded. In post hoc analyses, we explored potential mediating factors and investigated the robustness of results by subgroup analyses. SPSS, version 28 (IBM Corporation, Armonk, NY) was used for all statistical analyses.

3 | RESULTS

In comparison with women managed on nutrition therapy, most maternal characteristics were significantly different in women requiring pharmacological treatment ($p < 0.001$; Table 3). Macrosomia (>4.5 kg) was less common in infants exposed to metformin compared with nutrition therapy ($p < 0.001$; Table 4). Infants exposed to pharmacological treatment were more often delivered by planned cesarean section ($p < 0.001$) and prior to gestational week 41 + 0 days ($p < 0.001$), and they were more likely to receive supplemental feeding in addition to breastfeeding ($p < 0.001$) compared with infants exposed to nutrition therapy alone (Table 4).

Metformin as single adjunctive treatment was associated with a lower risk of neonatal hypoglycemia compared with nutrition therapy (aOR 0.85, 95% CI: 0.74–0.96; Table 5), combined metformin-insulin treatment (aOR 0.74, 95% CI: 0.64–0.87; Table 6), and insulin as single adjunctive treatment (aOR 0.47, 95% CI: 0.40–0.55; Table 6).

Single metformin treatment was associated with a similar risk of LGA as nutrition therapy alone (aOR 0.96, 95% CI: 0.84–1.10; Table 5), and with a lower risk of LGA compared with combined metformin-insulin treatment (aOR 0.69, 95% CI: 0.59–0.82; Table 6), and insulin alone (aOR 0.62, 95% CI: 0.52–0.74; Table 6). Exposure to any pharmacological treatment was associated with a lower risk of 5-min Apgar score < 4 compared with nutrition therapy alone (aOR 0.33, 95% CI: 0.11–0.96, aOR 0.23, 95% CI: 0.06–0.85, and aOR 0.23, 95% CI: 0.06–0.98 for single metformin treatment, combined metformin-insulin treatment, and insulin alone respectively; Table 5). All other secondary outcomes were comparable among treatment groups (Tables 5 and 6).

Among infants exclusively breastfed during hospital stay, the risk of neonatal hypoglycemia was similar following metformin as single treatment and nutrition therapy alone and increased following combined metformin-insulin treatment vs nutrition therapy alone, thus modified compared with the main analysis (Table S3). By contrast, the risk was consistently lower following metformin alone vs insulin exposure, alone or combined with metformin (Table S4). The risk of low Apgar score at 5 min was only marginally affected when the analysis was restricted to infants born prior to 41 + 0 gestational weeks, or infants not delivered by planned cesarean section (Table S3).

4 | DISCUSSION

In this Swedish population-based cohort study of 16 181 pregnancies complicated by GDM, the main finding was that offspring exposed to metformin as single adjunctive treatment had similar or more favorable neonatal outcome compared with offspring exposed to nutrition therapy alone, combined metformin-insulin treatment, and insulin treatment alone. As hypothesized, metformin as single treatment was associated with a lower risk of neonatal hypoglycemia compared with combined metformin-insulin treatment. In addition, metformin as single adjunctive treatment was associated with a lower risk of neonatal hypoglycemia compared with nutrition therapy alone, although the risk was similar among infants exclusively breastfed.

Neonatal outcome following metformin treatment has been thoroughly investigated relative to insulin treatment, and current evidence indicates a lower risk of neonatal hypoglycemia in favor of metformin.[10] Our study confirms these data and provides extended knowledge regarding the differential risk following single metformin treatment and combined metformin-insulin treatment. Far less attention has been paid to evaluating neonatal outcome following metformin treatment against nutrition therapy, and the few observational studies that have investigated neonatal hypoglycemia are inconclusive. While Balani et al.[14] and McGrath et al.[13] observed no difference between nutrition therapy and single metformin treatment, Simeonova-Krsterska et al.[12] reported a significantly higher incidence. By contrast, we found a significantly lower risk of neonatal hypoglycemia in offspring exposed to metformin as single adjunctive treatment compared with offspring exposed to nutrition therapy alone. We adjusted for several confounders whereas others have reported crude data only.[12–14] This complicates a direct comparison with our results and may contribute to our different conclusions. However, residual confounding cannot be ruled out as an explanation for our finding as we, in line with our hypothesis and with results reported by others,[13,14] found a similar risk of neonatal hypoglycemia among exclusively breastfed infants exposed to nutrition therapy alone or single adjunctive metformin treatment. The Swedish Neonatology Society advocates early supplemental feeding within the first hour when the mother was treated with metformin and/or insulin and suggests that supplemental feeding may be delayed in offspring exposed to nutrition therapy alone if sufficient breastfeeding is established early and the infant is appropriate for gestational age. A recent comprehensive overview of local guidelines on supplemental feeding at Swedish delivery units demonstrated that all guidelines identified GDM as a risk factor for neonatal hypoglycemia, but the recommended neonatal management showed heterogeneity among units.[31] Eighteen of 43 units referred to the

TABLE 3 Maternal characteristics of the women with singleton pregnancies with gestational diabetes that are included in the study population. Presented overall ($N = 16\,181$) and stratified by mode of treatment at the time of delivery.

		Mode of treatment at delivery				
	Overall	Nutrition therapy alone	Metformin as single adjunctive treatment	Metformin combined with insulin as adjunctive treatment	Insulin as single adjunctive treatment	
	$N = 16\,181$	$N = 9708$	$N = 2972$	$N = 1893$	$N = 1608$	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*p*-value
Age (years) at delivery	32.7 ± 5.2	32.3 ± 5.2[a,b,c]	33.1 ± 5.3[a,d]	33.7 ± 5.0[b,d,f]	33.2 ± 5.2[c,f]	<0.001
BMI (kg/m^2) at first antenatal visit	30.3 ± 6.5	29.6 ± 6.4[a,b,c]	31.5 ± 6.2[a,d,e]	32.9 ± 6.4[b,d,f]	30.0 ± 6.2[c,e,f]	<0.001
Missing	375 (2.3)	235 (2.4)	60 (2.0)	37 (2.0)	43 (2.7)	
Parity						
Nulliparous	5542 (34.3)	3633 (37.4)[a,b,c]	910 (30.6)[a,d]	475 (25.1)[b,d,f]	524 (32.6)[c,f]	<0.001
Missing	1 (0.0)	0 (0)	0 (0)	0 (0)	1 (0.0)	
Country of birth						
Sweden	8446 (52.2)	5495 (56.6)[a,b,c]	1311 (44.1)[a]	882 (46.6)[b]	758 (47.1)[c]	<0.001
European (other than Sweden)	1606 (9.9)	968 (10.0)	298 (10.0)	182 (9.6)	158 (9.8)	0.964
African	1792 (11.1)	974 (10.0)[a]	439 (14.8)[a,d,e]	225 (11.9)[d]	154 (9.6)[e]	<0.001
Asian	4071 (25.2)	2127 (21.9)[a,b,c]	859 (28.9)[a]	571 (30.2)[b]	514 (32.0)[c]	<0.001
Other country	266 (1.6)	144 (1.5)	65 (2.2)	33 (1.7)	24 (1.5)	0.063
Educational level						
Elementary (0–9 years)	2490 (15)	1327 (13.8)[a,b,c]	545 (18.6)[a]	338 (18.1)[b]	280 (17.7)[c]	<0.001
Upper secondary (10–12 years)	6220 (38)	3658 (38.1)	1161 (39.7)	769 (41.2)	632 (39.9)	0.046
University (≥13 years)	7267 (44.9)	4614 (48.1)[a,b,c]	1222 (41.7)[a]	760 (40.7)[b]	671 (42.4)[c]	<0.001
Missing	204 (1.3)	109 (1.1)	44 (1.5)	26 (1.4)	25 (1.6)	
Smoking at first antenatal visit	737 (4.6)	418 (4.5)	136 (4.8)	98 (5)	85 (5.6)	0.401
Missing	744 (4.6)	451 (4.6)	123 (4.1)	93 (4.9)	77 (4.8)	
In vitro fertilization	775 (4.8)	491 (5.1)[b]	141 (4.8)	67 (3.6)[b]	76 (4.8)	0.040
Missing	257 (1.6)	177 (1.8)	28 (0.9)	26 (1.3)	38 (2.3)	
Care due to IUGR	407 (2.5)	252 (2.6)	56 (1.9)	49 (2.6)	50 (3.1)	0.059
Gestational weeks at OGTT	26.9 ± 6.5	28.1 ± 6.1[a,b,c]	25.8 ± 6.2[a,d]	23.2 ± 6.9[b,d,f]	25.7 ± 6.9[c,f]	<0.001
Missing	4308 (26.6)	2479 (25.2)	717 (23.9)	587 (30.6)	600 (36.8)	
Fasting plasma glucose (mmol/L)	5.5 ± 0.8	5.3 ± 0.6[a,b,c]	5.6 ± 0.7[a,d,e]	6.1 ± 1.1[b,d,f]	5.9 ± 1.1[c,e,f]	<0.001
Missing	4505 (27.8)	2611 (26.5)	719 (23.9)	611 (31.8)	641 (39.3)	
2 h post load glucose (mmol/L)	8.8 ± 2.2	8.5 ± 2.0[a,b,c]	8.9 ± 2.3[a,d,e]	9.6 ± 2.6[b,d,f]	10.1 ± 2.5[c,e,f]	<0.001
Missing	5505 (34.0)	3278 (33.3)	913 (30.4)	733 (38.2)	676(1.5)	

Note: Continuous variables are displayed as mean ± one standard deviation, and categorical variables as numbers and percent of *N* for overall, and as numbers and percent of valid cases when stratified according to treatment. Missing are displayed as numbers (%). Analysis of overall between group difference was by Kruskal Wallis test or chi-square test as appropriate. Significance level was set at $p < 0.05$.

Abbreviations: BMI, body mass index; h, hour; IUGR, intrauterine growth restriction; OGTT, 75 g oral glucose tolerance test; SD, standard deviation.

[a]Nutrition therapy alone was significantly different vs metformin as single adjunctive treatment.

[b]Nutrition therapy alone was significantly different vs metformin combined with insulin as adjunctive treatment.

[c]Nutrition therapy alone was significantly different vs insulin as single adjunctive treatment.

[d]Metformin as single adjunctive treatment was significantly different vs metformin combined with insulin as adjunctive treatment.

[e]Metformin as single adjunctive treatment was significantly different vs insulin as single adjunctive treatment.

[f]Metformin combined with insulin as adjunctive treatment was significantly different vs insulin as single adjunctive treatment.

TABLE 4 Characteristics of offspring of mothers with gestational diabetes included in the study population. Presented overall ($N = 16\,181$) and stratified by maternal mode of treatment at the time of delivery.

		Mode of treatment at delivery				
	Overall	Nutrition therapy alone	Metformin as single adjunctive treatment	Metformin combined with insulin as adjunctive treatment	Insulin as single adjunctive treatment	
	$N = 16\,181$	$N = 9708$	$N = 2972$	$N = 1893$	$N = 1608$	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*p*-value
Mode of delivery						
Spontaneous vaginal delivery	11 308 (69.9)	6946 (71.5)[b,c]	2091 (70.4)[d,e]	1229 (64.9)[b,d]	1042 (64.8)[c,e]	<0.001
Operative vaginal delivery	696 (4.3)	447 (4.6)	107 (3.6)	64 (3.4)	78 (4.9)	0.013
Planned cesarean delivery	2010 (12.4)	1067 (11.0)[a,b,c]	394 (13.3)[a,d]	310 (16.4)[b,d]	239 (14.9)[c]	<0.001
Emergency cesarean delivery	2167 (13.4)	1248 (12.9)[b,c]	380 (12.8)	290 (15.3)[b]	249 (15.5)[c]	0.001
Gestational age						
In days	275 ± 11.5	276 ± 11.9[a,b,c]	274 ± 10.8[a,d,e]	273 ± 10.6[b,d]	273 ± 10.4[c,e]	<0.001
In completed gestational weeks						
<32	100 (0.6)	65 (0.7)	17 (0.6)	11 (0.6)	7 (0.4)	0.697
32–36	936 (5.8)	511 (5.3)[b,c]	177 (6.0)	135 (7.1)[b]	113 (7.0)[c]	0.001
37–40	13 385 (82.7)	7720 (79.5)[a,b,c]	2558 (86.1)[a,d]	1679 (88.7)[b,d]	1428 (88.8)[c]	<0.001
≥41	1760 (10.9)	1412 (14.5)[a,b,c]	220 (7.4)[a,d,e]	68 (3.6)[b,d]	60 (3.7)[c,e]	<0.001
Sex (*n*)						
Male	8384 (51.8)	5042 (51.9)	1538 (51.7)	970 (51.2)	834 (51.9)	0.957
Female	7797 (48.2)	4666 (48.1)	1434 (48.3)	923 (48.8)	774 (48.1)	0.957
Birthweight categorized						
<2500 (g)	510 (3.2)	323 (3.3)	85 (2.9)	57 (3.0)	45 (2.8)	0.466
2500–4500 (g)	15 011 (92.8)	8971 (92.7)[a]	2804 (94.5)[a,e]	1762 (93.6)	1474 (92.3)[e]	0.003
>4500 (g)	603 (3.7)	384 (4.0)[a]	77 (2.6)[a,e]	64 (3.4)	78 (4.9)[e]	<0.001
Missing	57 (0.4)	30 (0.3)	6 (0.2)	10 (0.5)	11 (0.7)	
Birthweight (g)	3580 ± 560	3580 ± 570[a]	3550 ± 530[a,d]	3600 ± 560[d]	3600 ± 550	0.001
Missing	57 (0.4)	30 (0.3)	6 (0.2)	10 (0.5)	11 (0.7)	
Birth length (cm)	50.2 ± 2.4	50.3 ± 2.4[a]	50.1 ± 2.3[a]	50.2 ± 2.4	50.2 ± 2.3	0.001
Missing	171 (1.1)	107 (1.1)	18 (0.6)	24 (1.2)	22 (1.4)	
Head circumference (cm)	35.2 ± 1.8	35.2 ± 1.8	35.1 ± 1.7	35.2 ± 1.8[f]	35.1 ± 1.8[f]	0.022
Missing	190 (1.2)	111 (1.1)	23 (0.8)	32 (1.7)	24 (1.5)	
Birthweight *z*-score	0.82 ± 1.1	0.78 ± 1.1[b,c]	0.79 ± 1.0[d,e]	0.96 ± 1.1[b,d]	0.96 ± 1.1[c,e]	<0.001
missing	61 (0.4)	34 (0.3)	7 (0.2)	10 (0.5)	11 (0.7)	
Birth length *z*-score	0.67 ± 1.1	0.64 ± 1.1[b,c]	0.64 ± 1.1[d,e]	0.77 ± 1.1[b,d]	0.79 ± 1.1[c,e]	<0.001
Missing	175 (1.1)	110 (1.1)	19 (0.6)	24 (1.3)	22 (1.4)	
Head circumference *z*-score	1.16 ± 1.2	1.12 ± 1.2[b]	1.17 ± 1.2[d]	1.31 ± 1.2[b,d]	1.21 ± 1.2	<0.001
Missing	194 (1.2)	114 (1.2)	24 (0.8)	32 (1.7)	24 (1.5)	
Apgar score						
At 1 min	8.7 ± 1.4	8.7 ± 1.4	8.7 ± 1.3	8.7 ± 1.4	8.7 ± 1.4	0.893
At 5 min	9.7 ± 0.9	9.7 ± 0.9	9.7 ± 0.9	9.7 ± 0.9	9.7 ± 0.9	0.962
At 10 min	9.9 ± 0.6	9.9 ± 0.6	9.9 ± 0.5	9.9 ± 0.5	9.9 ± 0.5	0.241
Missing	107 (0.7)	63 (0.6)	19 (0.6)	13 (0.7)	12 (0.8)	

TABLE 4 (Continued)

	Overall	Mode of treatment at delivery				
		Nutrition therapy alone	Metformin as single adjunctive treatment	Metformin combined with insulin as adjunctive treatment	Insulin as single adjunctive treatment	
	N = 16 181	*N* = 9708	*N* = 2972	*N* = 1893	*N* = 1608	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*p*-value
Supplemental feeding	9353 (57.8)	4583 (58.7)[a,b,c]	2146 (88.8)[a,d,e]	1416 (94.7)[b,d]	1208 (93.5)[c,e]	<0.001
Missing	3174 (19.6)	1906 (19.6)	554 (18.6)	398 (21.0)	316 (19.7)	

Note: Continuous variables are displayed as mean (SD) and categorical variables as number (% of total) for overall, and as numbers (% of valid cases) when stratified according to treatment. Analysis of overall between group difference was by Kruskal Wallis test or chi-square test as appropriate. Significance level was set at $p < 0.05$.

[a]Nutrition therapy alone was significantly different vs metformin as single adjunctive treatment.

[b]Nutrition therapy alone was significantly different vs metformin combined with insulin as adjunctive treatment.

[c]Nutrition therapy alone was significantly different vs insulin as single adjunctive treatment.

[d]Metformin as single adjunctive treatment was significantly different vs metformin combined with insulin as adjunctive treatment.

[e]Metformin as single adjunctive treatment was significantly different vs insulin as single adjunctive treatment.

[f]Metformin combined with insulin as adjunctive treatment was significantly different vs insulin as single adjunctive treatment.

Swedish Neonatology Society's care-program, and 50% advocated early breastfeeding within 1 h.[31] The lower rate of supplemental feeding in offspring exposed to nutrition therapy alone had impact on the risk of neonatal hypoglycemia associated with metformin treatment. However, our register data did not discriminate between supplemental feeding introduced within the first hour as a preventive measure and delayed introduction, and whether documentation of supplemental feeding includes expressed breast milk given following breastfeeding or is restricted to infant formula is further unclear to us. This is a potential weakness in our study. The impact of routine supplemental feeding on neonatal hypoglycemia has not been thoroughly investigated. Interestingly, Dalsgaard et al.[32] observed a significantly higher incidence of neonatal hypoglycemia, when supplemental feeding was routinely given within 1 h to offspring exposed to nutrition therapy alone, prior to the implementation of a routine advocating uninterrupted skin-to-skin contact, early frequent breastfeeding, and expectant management regarding supplemental feeding. We cannot determine if metformin per se reduces the risk of neonatal hypoglycemia with this observational study design, and for this reason our observations should be interpreted with caution.

As we expected, the requirement of supplemental insulin to achieve maternal normoglycemia was associated with a higher risk of neonatal hypoglycemia in the offspring. This was in contrast to Goh et al.[16] who found a similar risk of neonatal hypoglycemia regardless of concurrent insulin treatment. However, Goh et al.[16] applied a lower diagnostic threshold for neonatal hypoglycemia diagnosis, which makes a direct comparison with our results problematic. There is no clear cutoff glucose threshold defining neonatal hypoglycemia in the literature, and different thresholds used both clinically and among studies complicates comparison and interpretation of results. Even with identical diagnostic thresholds, the prevalence of neonatal hypoglycemia varies considerably among studies.[12–14,33] This suggests other dissimilarities, such as different routines for screening and prevention of hypoglycemia in the newborn, although this information is rarely provided. Our study demonstrates a consistent prevalence over time in Sweden. Our results were comparable to those reported by Valgeirsdottir et al. in another population-based register study covering the period 1998 to 2012, although they provided no information for metformin due to infrequent use at that time.[3]

Concern has been raised about metformin exposure and attenuated fetal growth. Indeed, mean birthweight was significantly lower, and macrosomia significantly less prevalent in infants exposed to metformin as single adjunctive treatment compared with nutrition therapy alone. However, the difference in mean birthweight disappeared when infant sex and gestational age at birth was taken into consideration, and in line with results reported by Brand et al.[2,11] we found no association between SGA and metformin treatment. Our results further support a similar risk of LGA as previously reported by some authors,[13,15] and contradicts results favoring metformin treatment over nutrition therapy.[11,12,14] Different definitions of SGA and LGA are used in the literature, and different reference populations yield different proportions of inappropriate growth when using a fixed definition on the same data.[34] This likely explains contradictory findings between studies. Offspring exposed to single metformin treatment had lower risk of LGA compared with offspring exposed to combined metformin-insulin treatment, and insulin alone which corroborates previous observations.[15]

An unexpected finding in our study was that pharmacological treatment in comparison with nutrition therapy was associated with significantly lower risk of Apgar score < 4 at 5 min. Planned cesarean delivery was more prevalent among those requiring pharmacological treatment, as was delivery prior to week 41 + 0 days. Planned

TABLE 5 Neonatal outcome in offspring of mothers with gestational diabetes treated with either nutrition therapy alone, or with adjunctive treatment with metformin alone, metformin combined with insulin, or insulin alone at the time of delivery. Nutrition therapy is the reference treatment category.

	Overall *N* = 16 181 % missing	Nutrition therapy alone *N* = 9708 % with the outcome	Metformin alone *N* = 2972 % with the outcome, and OR (95% CI)	Metformin combined with insulin *N* = 1893 % with the outcome, and OR (95% CI)	Insulin alone *N* = 1608 % with the outcome, and OR (95% CI)
Primary outcome					
Neonatal hypoglycemia[a]	1.8	19.5	18.8	24.4	32.2
Crude		Reference	0.96 (0.86–1.06)	1.33 (1.18–1.50)	1.96 (1.74–2.20)
Adjusted model[b]		Reference	0.85 (0.74–0.96)	1.14 (0.99–1.30)	1.81 (1.54–2.12)
Secondary outcomes					
LGA (+2 SD)	0.4	14.3	13.1	17.4	19.3
Crude		Reference	0.91 (0.80–1.02)	1.26 (1.11–1.44)	1.44 (1.25–1.65)
Adjusted model[b]		Reference	0.96 (0.84–1.10)	1.39 (1.19–1.63)	1.56 (1.34–1.82)
SGA (−2 SD)	0.4	0.7	0.4	0.5	0.4
Crude		Reference	0.61 (0.33–1.13)	0.72 (0.36–1.45)	0.66 (0.30–1.45)
Adjusted model[b]		Reference	0.67 (0.32–1.39)	0.57 (0.25–1.32)	0.57 (0.23–1.45)
Respiratory morbidity[c]	1.8	5.7	5.4	6.5	6.2
Crude		Reference	0.95 (0.79–1.14)	1.15 (0.93–1.41)	1.10 (0.88–1.37)
Adjusted model[b]		Reference	0.88 (0.72–1.09)	1.03 (0.81–1.30)	1.00 (0.78–1.29)
Hyperbilirubinemia[d]	1.8	6.6	7.3	8.0	8.5
Crude		Reference	1.10 (0.94–1.29)	1.22 (1.01–1.47)	1.31 (1.08–1.49)
Adjusted model[b]		Reference	0.92 (0.76–1.11)	1.01 (0.81–1.25)	1.18 (0.93–1.49)
Apgar score < 7 at 5 min	0.6	2.0	1.8	1.8	1.9
Crude		Reference	0.88 (0.65–1.19)	0.86 (0.59–1.24)	0.92 (0.62–1.35)
Adjusted model[b]		Reference	0.70 (0.49–1.01)	0.66 (0.43–1.01)	0.73 (0.46–1.15)
Apgar score < 4 at 5 min	0.6	0.4	0.3	0.2	0.2
Crude		Reference	0.69 (0.32–1.47)	0.54 (0.19–1.51)	0.48 (0.15–1.54)
Adjusted model[b]		Reference	0.33 (0.11–0.96)	0.23 (0.06–0.85)	0.23 (0.06–0.98)
Preterm birth[e]	0	5.9	6.5	7.7	7.5
Crude		Reference	1.11 (0.94–1.31)	1.33 (1.10–1.60)	1.28 (1.04–1.57)
Adjusted model[b]		Reference	0.90 (0.74–1.09)	0.97 (0.78–1.21)	0.96 (0.74–1.23)
NICU	0	11.4	11.8	13.5	14.3

TABLE 5 (Continued)

	Overall *N* = 16 181 % missing	Nutrition therapy alone *N* = 9708 % with the outcome	Metformin alone *N* = 2972 % with the outcome, and OR (95% CI)	Metformin combined with insulin *N* = 1893 % with the outcome, and OR (95% CI)	Insulin alone *N* = 1608 % with the outcome, and OR (95% CI)
Crude		Reference	1.05 (0.92–1.19)	1.22 (1.05–1.41)	1.30 (1.12–1.52)
Adjusted model[b]		Reference	0.88 (0.75–1.02)	0.96 (0.81–1.13)	1.06 (0.87–1.30)

Note: Risk was estimated as odds ratio with 95% confidence interval relative to nutrition therapy, which was the reference treatment, and displayed as crude and confounder adjusted odds ratio. Significant when the 95% confidence interval does not include 1.00.

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; ICD-10, International Classification of Disease, 10th revision; LGA, large for gestational age; NICU, neonatal intensive care unit; OR, odds ratio; SGA, small for gestational age; SNQ, Swedish Neonatal Quality Register.

[a]Identified by the ICD-10 codes P70.0/P70.1/P70.4, or ticked checkbox for hypoglycemia in SNQ, or plasma glucose <2.6 mmol/L recorded in SNQ.

[b]Covariates adjusted for in the model:

- Maternal age at delivery
- Maternal first trimester body mass index
- Parity
- Maternal country of birth (categorized as Sweden, other European country, African country, Asian country, and other country)
- Year of delivery (categorized as 2019, 2020, or 2021)
- Annual frequency of GDM in region of care (representing region of care, to account for the regional difference in factors determining diagnosis of GDM/selection for the study, such as the prevalence of risk factors in the pregnant population, screening frequency and screening policy, and diagnostic criteria for gestational diabetes)
- Gestational age at GDM diagnosis
- Initial mode of treatment at GDM diagnosis (categorized as nonpharmacological and pharmacological treatment, to account for difference in severeness of hyperglycemia at diagnosis)
- Maternal care due to suspected intrauterine growth restriction (identified by the ICD-10 code O36.5).

[c]Identified by the ICD-10 codes P22.0/P22.1/P22.8/P22.9.

[d]Identified by the ICD-10 codes P59.0-P59.9.

[e]Delivery prior to gestational week 37 + 0 days.

TABLE 6 Neonatal outcome in offspring of mothers with gestational diabetes treated with adjunctive treatment with either metformin alone, metformin combined with insulin, or insulin alone at the time of delivery. Metformin combined with insulin treatment or insulin as single treatment is the reference treatment category.

	Metformin alone vs metformin combined with insulin (reference) OR (95% CI)	Metformin alone vs insulin alone (reference) OR (95% CI)	Metformin combined with insulin vs insulin alone (reference) OR (95% CI)
Primary outcome			
Neonatal hypoglycemia[a]			
Crude	0.72 (0.63–0.83)	0.49 (0.43–0.56)	0.68 (0.59–0.79)
Adjusted model[b]	0.74 (0.64–0.87)	0.47 (0.40–0.55)	0.63 (0.53–0.75)
Secondary outcomes			
LGA (+2 SD)			
Crude	0.72 (0.61–0.84)	0.64 (0.54–0.75)	0.88 (0.74–1.04)
Adjusted model[b]	0.69 (0.59–0.82)	0.62 (0.52–0.74)	0.89 (0.75–1.07)
SGA (−2 SD)			
Crude	0.85 (0.36–2.01)	0.92 (0.36–2.35)	1.09 (0.41–2.94)
Adjusted model[b]	1.18 (0.46–3.03)	1.17 (0.42–3.28)	0.99 (0.34–2.96)
Respiratory morbidity[c]			
Crude	0.83 (0.65–1.06)	0.87 (0.67–1.12)	1.05 (0.79–1.38)
Adjusted model[b]	0.86 (0.67–1.10)	0.89 (0.67–1.16)	1.03 (0.77–1.37)
Hyperbilirubinemia[d]			
Crude	0.90 (0.72–1.12)	0.84 (0.67–1.05)	0.93 (0.73–1.19)
Adjusted model[b]	0.91 (0.72–1.15)	0.78 (0.61–1.01)	0.86 (0.66–1.11)
Apgar score < 7 at 5 min			
Crude	1.02 (0.66–1.59)	0.95 (0.61–1.50)	0.93 (0.57–1.54)
Adjusted model[b]	1.06 (0.68–1.67)	0.96 (0.59–1.54)	0.90 (0.54–1.51)
Apgar score < 4 at 5 min			
Crude	1.28 (0.38–4.24)	1.44 (0.38–5.45)	1.13 (0.25–5.06)
Adjusted model[b]	1.41 (0.41–4.85)	1.41 (0.35–5.80)	1.01 (0.21–4.84)
Preterm birth[e]			
Crude	0.84 (0.67–1.04)	0.87 (0.68–1.10)	1.04 (0.81–1.33)
Adjusted model[b]	0.93 (0.73–1.17)	0.94 (0.71–1.24)	1.02 (0.76–1.35)
NICU			
Crude	0.86 (0.72–1.02)	0.80 (0.67–0.96)	0.93 (0.77–1.13)
Adjusted model[b]	0.92 (0.77–1.10)	0.83 (0.68–1.01)	0.90 (0.73–1.11)

Note: Risk was estimated as odds ratio with 95% confidence intervals relative to the reference treatment (metformin combined with insulin or insulin as single treatment) and displayed as crude odds ratio and confounder adjusted odds ratio. Significant when the 95% confidence interval does not include 1.00.

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; ICD-10, International Classification of Disease, 10th revision; LGA, large for gestational age; NICU, neonatal intensive care unit, OR, odds ratio; SGA, small for gestational age; SNQ, Swedish Neonatal Quality Register.

[a]Identified by the ICD-10 codes P70.0/P70.1/P70.4, or ticked checkbox for hypoglycemia in SNQ, or plasma glucose <2.6 mmol/L recorded in SNQ.

[b]Covariates adjusted for in the model: maternal age at delivery, maternal first trimester body mass index, parity, maternal country of birth (categorized as Sweden, other European country, African country, Asian country, and other country), year of delivery, annual frequency of GDM in region of care, gestational age at GDM diagnosis, initial mode of treatment at GDM diagnosis (categorized as nonpharmacological and pharmacological treatment), maternal care due to suspected intrauterine growth restriction (identified by the ICD-10 code O36.5).

[c]Identified by the ICD-10 codes P22.0/P22.1/P22.8/P22.9.

[d]Identified by the ICD-10 code P59.0-P59.9.

[e]Delivery prior to gestational week 37 + 0.

cesarean delivery has previously been associated with lower risk of Apgar score < 7 at 5 min in diabetic pregnancies,[35] and prolonged pregnancy is associated with increased risk of low Apgar score at 5 min in general.[36] However, results from subgroup analyses excluding infants delivered by planned cesarean section, or born after week 40 + 6 days were consistent with the main analysis. This implies

that other explanations for this difference must be considered. GDM is generally assumed to be a milder condition when nutrition therapy sufficiently achieves normoglycemia, as opposed to when pharmacological treatment is required. Obstetrical management and intensity of fetal surveillance during pregnancy and labor could therefore differ between treatments, and if so, mediate and explain our finding.

In all, 4865 of the 16 181 infants in our cohort were exposed to metformin in utero, which makes this the largest observational study that has investigated neonatal outcome following metformin treatment against nutrition therapy. The large sample size, reliable data of metformin and insulin dispensation, and adjustment for a number of relevant confounders are major strengths of our study. The population-based design further minimizes the risk of selection bias, and the prospectively collected data reduces the risk of recall bias. Another strength is the inclusion of an ethnically diverse study population, which increases external validity. Evaluating metformin as single treatment separately from combined treatment with insulin further enables assessment of neonatal outcome according to actual treatment, which is more relevant in the clinical context. However, there are some limitations. Implementation of IADPSG/WHO 2013 thresholds increase GDM prevalence vs other criteria.[18] Diagnostic thresholds were not uniform among regions and were further changed within some regions during the study period. Alongside different screening protocols and different regional prevalence of risk factors for GDM, this affected regional contribution to inclusion in the study and may have impacted on maternal characteristic profiles. However, we controlled for inclusion bias by adjusting for the regional annual year-specific GDM prevalence which captures both known and unknown determinants of GDM diagnosis, and the large sample size can further be expected to sufficiently overcome issues with skewed predictor covariates in logistic regression analyses, thereby compensating for these limitations.[37] The evidence for an impact on clinical outcome by the implementation of lower diagnostic thresholds is further inconclusive.[38] Moreover, the exposure was not GDM diagnosis but the mode of treatment at the time of delivery, and the proportion managed on the reference treatment nutrition therapy in regions applying IADPSG/WHO 2013 criteria was not significantly different from regions applying higher diagnostic thresholds (data not shown). Relying on ICD-10 codes is another limitation. ICD-10 codes for neonatal hypoglycemia in SPR and SNQ have not been validated against glucose measurements documented in the medical records. We reviewed medical records in a subcohort to verify which ICD-10 codes that were used in cases of neonatal hypoglycemia, and further found that any discrepancies between register data and medical records were comparable among the subcohort treatment groups. We therefore find it unlikely that misclassification of the primary outcome would introduce significant bias in between treatment comparisons. We had reliable data on metformin and insulin dispensing but lacked information regarding clinician- and patient treatment preferences, adherence to medication, and glycemic control during treatment. Treatment preferences is an important issue when comparing metformin with insulin treatment in observational studies but is less likely to cause significant bias in comparisons with nutrition therapy. We refrained from including plasma glucose values obtained from OGTT as a covariate due to uncertainties regarding measurement levels derived from different sampling medium and assay methods but adjusted for the mode of treatment initiated at diagnosis. A recent study concluded that third trimester HbA1c and hyperglycemia during labor were not predictors of neonatal hypoglycemia in offspring of mothers with GDM treatment, which is further corroborated by findings reported by others,[39,40] and the HAPO-study showed no association between maternal glucose levels and neonatal hypoglycemia.[1] We lacked information regarding labor duration, intensity of fetal surveillance during labor, and the timing and duration of supplemental feeding which could provide insight into the mechanisms behind our results. This was an observational study and causality may therefore not be determined. There may still be unmeasured residual confounding not controlled for that could modify our results, and the results of this study should therefore be interpreted with caution.

5 | CONCLUSION

The risk of neonatal hypoglycemia appears to be similar among offspring exposed to metformin as single adjunctive treatment and nutrition therapy alone. The lower risk that we observed in favor of metformin is probably explained by a difference in supplemental feeding practices rather than by metformin per se, as offspring exposed to nutrition therapy only were less likely to receive supplemental feeding. By contrast, the lower risk of neonatal hypoglycemia that favored metformin exposure over insulin exposure was in spite of similar or lower supplemental feeding rates among offspring exposed to metformin. However, further investigations are required to determine if these observations are an effect of metformin per se or mediated by other external factors.

AUTHOR CONTRIBUTIONS

Johanna Molin, and Marie Bixo conceptualized and designed the study. Magnus Domellöf, Christel Häggström, and Eszter Vanky contributed to the study design. Marie Bixo acquired the permission to access the data and perform the study. Johanna Molin performed the statistical analysis. Magnus Domellöf, and Christel Häggström advised on, and Christel Häggström supervised the statistical analysis. All authors contributed to interpretation of the results. Johanna Molin drafted the initial manuscript, and all authors edited, reviewed, and approved of the final version of the manuscript. Johanna Molin is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

MB is a member of the advisory board for Asarina Pharma (this company has no commercial activity in relation to metformin). EV has been advisor for NovoNordisk and Merck. JM, MD, CH, IZ, and EÖ have no conflict of interest to declare.

ETHICS STATEMENT

Participants included in the Swedish Pregnancy Register, and legal guardians of infants included in the Swedish Neonatal Quality Register have given informed consent to participation in research projects approved by the Swedish Ethical Review Authority. The study was approved by the Swedish Ethical Review Authority (Dnr 2021-04410) on September 20, 2021, and individual participant informed consent was waived by the review authority.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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