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Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study

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ABSTRACT

Introduction This study aimed to investigate if maternal pregnancy exposure to metformin is associated with increased risk of long-term and short-term adverse outcomes in the child.

Research design and methods This register-based cohort study from Finland included singleton children born 2004–2016 with maternal pregnancy exposure to metformin or insulin (excluding maternal type 1 diabetes): metformin only (n=3967), insulin only (n=5273) and combination treatment (metformin and insulin; n=889). The primary outcomes were long-term offspring obesity, hypoglycemia, hyperglycemia, diabetes, hypertension, polycystic ovary syndrome, and challenges in motor–social development. In a sensitivity analysis, the primary outcomes were investigated only among children with maternal gestational diabetes. Secondary outcomes were adverse outcomes at birth. Analyses were conducted using inverse- probability of treatment weighting (IPTW), with insulin as reference.

Results Exposure to metformin or combination treatment versus insulin was not associated with increased risk of long-term outcomes in the main or sensitivity analyses. Among the secondary outcomes, increased risk of small for gestational age (SGA) was observed for metformin (IPTW-weighted OR 1.65, 95% CI 1.16 to 2.34); increased risk of large for gestational age, preterm birth and hypoglycemia was observed for combination treatment. No increased risk was observed for neonatal mortality, hyperglycemia, or major congenital anomalies.

Conclusions This study found no increased long-term risk associated with pregnancy exposure to metformin (alone or in combination with insulin), compared with insulin. The increased risk of SGA associated with metformin versus insulin suggests caution in pregnancies with at-risk fetal undernutrition. The increased risks of adverse outcomes at birth associated with combination treatment may reflect confounding by indication or severity.

Significance of this study

What is already known about this subject?

- The effects of pregnancy exposure to metformin on child outcomes are limited. The association between metformin exposure in pregnancy and adverse child outcomes, notably adverse weight outcomes at birth and long term is limited. The link of maternal drug exposure to the outcomes to mother and child at birth have been rarely assessed on a whole country level. Being a safety study, the risk for adverse outcomes with metformin was compared with the most commonly used medication for gestational hyperglycemia, insulin. Protective effects are therefore not highlighted.

What are the new findings?

- Maternal exposure to metformin and combination treatment of metformin and insulin was not associated with long-term increased risk of obesity, hypoglycemia, hyperglycemia, diabetes, or challenges in motor–social development, compared with insulin.
- The results were generally consistent in sensitivity analyses restricted to children with maternal gestational diabetes.
- The analyses of adverse outcomes at birth showed significantly increased risk of being small for gestational age associated with exposure to metformin, compared with insulin. It remains to be determined whether this is relative to an overall increase in body weight due to insulin.
- Combination treatment of metformin and insulin was associated with increased risk of being large for gestational age, preterm birth and hypoglycemia, although this association may be explained by confounding, namely more severe maternal hyperglycemia.

How might these results change the focus of research or clinical practice?

- This study represents the largest data set of pregnancies exposed with metformin to date, especially regarding long-term outcomes. It adds to the emerging positive benefit–risk balance of the use of metformin during pregnancy.

INTRODUCTION

Metformin is the first-line monotherapy for type 2 diabetes mellitus (T2DM) after failure of lifestyle modifications in all major guidelines and the most commonly prescribed drug for T2DM worldwide.[1 2] While no approved indication in

pregnant women exists, metformin is increasingly being used for the treatment of gestational diabetes (GDM).[3] In women with polycystic ovary syndrome (PCOS), metformin is commonly prescribed off-label to improve anovulation and conception, with some evidence also suggesting decreased risk of adverse pregnancy outcomes, if metformin is continued into pregnancy.[4]

Although generally considered safe in pregnancy, metformin, unlike insulin,[5–7] crosses the placenta and may have comparable plasma concentrations in the mother and child at birth.[8] Several studies have investigated the association between metformin and fetal outcomes at birth; while diverse in analytic approach and study population, results have indicated that metformin may be associated with lower risk of being large for gestational age (LGA) and neonatal hypoglycemia, compared with insulin.[9] Although increased risk of preterm birth was observed relative to insulin in one study,[10] the majority of previous data have suggested no association.[9] No association has been observed for the risk of major congenital anomalies (MCAs).[11–13]

Current evidence on long-term outcomes of maternal metformin in the child mainly consists of follow-up studies of randomized controlled trials (RCTs) in GDM,[10 14] which did not differentiate metformin use alone or in combination with insulin in comparison with insulin. In these, metformin use was sometimes associated with higher offspring weight or weight–height ratio between 1 and 9 years of age.[15–17] In a large observational study, no difference was observed at 4 years.[18] Pregnancy exposure with metformin versus placebo for PCOS from first trimester to delivery[19] was associated with higher child weight or body mass index (BMI) z-score at the age of 4–10 years,[20 21] whereas metformin versus placebo for pregnancy obesity did not lead to a difference in weight in 4-year-old children.[22] Evidence regarding long-term neurologic development has indicated no increased risk.[15 18 20 21 23]

There is an important need to further elucidate the long-term effects of in utero exposure to metformin. While the short-term safety of metformin during pregnancy has been investigated in several large studies,[10 19 24] the primary objective of this study was to investigate whether maternal pregnancy exposure to metformin is associated with long-term adverse outcomes in the child, including obesity, hypoglycemia, hyperglycemia, hypertension, diabetes, PCOS and challenges in motor–social development (MSD). The secondary objective was to investigate potential adverse fetal outcomes at birth, including LGA, small for gestational age (SGA), preterm birth, neonatal mortality, hypoglycemia, hyperglycemia, and MCAs.

METHODS

Cohort

This was a register-based cohort study in Finland, including children with maternal exposure to metformin or insulin regardless of the indication (GDM, pregestational T2DM or PCOS), born after a pregnancy starting in 2004–2016. The cohort of children was identified using the Finnish Medical Birth Register, which holds information on all births in Finland, including date of birth and gestational age (GA).[25] The date of start of pregnancy was calculated by subtracting GA (recorded in weeks and days) from the date of delivery to obtain the date of the last menstrual period (LMP). The cohort included singleton children born to women 18–45 years of age at the time of delivery. Exclusion criteria were maternal diagnosis of type 1 diabetes (T1DM), maternal dispensation of systemic glucocorticoids during pregnancy (agents in this drug class are known to interfere with metformin and insulin) and maternal dispensation of antidiabetic medications other than metformin or insulin during pregnancy. To ensure adequate capture of information on exposure and baseline characteristics, children born to women not registered in Finland throughout the entire duration of pregnancy were also excluded. Definitions of all exclusion criteria are provided in online supplemental table S1. Information on emigration and death for the children in the cohort was obtained from the Finnish Population Register Centre, which holds census information for all persons living in Finland.

Exposure

Information on maternal exposure to the study drugs was obtained from the Finnish Prescription Register,[26] which contains information on all reimbursed drugs dispensed at all community pharmacies in Finland, including date of dispensation and Anatomical Therapeutic Chemical code (codes for study drugs in online supplemental table S2). Maternal exposure to metformin or insulin was defined as a dispensed prescription in the time period from the LMP until the date of delivery. The children in the cohort were classified into three exposure groups, based on maternal exposure captured via dispensed prescriptions: metformin, insulin, and combination treatment (both metformin and insulin, sequentially or concomitant).

Outcomes

The primary long-term outcomes were childhood obesity, hypoglycemia, hyperglycemia, hypertension, diabetes (T1DM and T2DM), PCOS (analyzed among girls only), and challenges in MSD. Children were followed from the age of 1 week until the date of the first occurring event of death, emigration, or end of study period (31 December 2016). Cases of the primary outcomes during the follow-up period were ascertained based on diagnosis codes from the Care Register for Health Care (HILMO) and the Register of Primary Health Care Visits (AvoHILMO),[27 28] which hold information on contacts in secondary (hospitals) and primary (healthcare centers with general practitioners) healthcare services, respectively. Both registers include information on date of contact (visit or admission) and all diagnoses made (classified according to International Statistical Classification

of Diseases and Related Health Problems, Tenth Revision codes (ICD-10) in HILMO and ICD-10 and the International Classification of Primary Care, second revision in AvoHILMO).

The secondary outcomes were adverse fetal outcomes at birth: LGA, SGA, preterm birth, neonatal mortality, neonatal hypoglycemia and hyperglycemia and MCAs. Cases of LGA (birth weight two SD above the gestational age-specific and sex-specific reference mean in Finland), SGA (birth weight two SD below the gestational age-specific and sex-specific reference mean), preterm birth (delivery before 37 gestational weeks), and neonatal mortality (death during the first week of life) were identified from the Medical Birth Register. Cases of neonatal hypoglycemia and hyperglycemia were identified using diagnosis codes from HILMO and AvoHILMO and, additionally, plasma glucose values recorded in regional laboratory databases from primary and secondary care; the time point for assessment was up to 28 days after birth. Major congenital malformations were identified using diagnosis codes from the Register of Congenital Malformations and classified according to the EUROCAT classification;[29 30] the time for assessment was up to 1 year of age.

Full definitions of all primary and secondary outcomes are provided in online supplemental table S3.

Confounding control

Inverse probability of treatment weighting (IPTW) with stabilized weights was used to control for confounding.[31] The propensity score (PS) estimation (using logistic regression) and weighting was conducted separately for the pairwise comparisons of metformin versus insulin and combination treatment versus insulin. The predictors of the PS models were a broad range of covariates, including demographic factors, comorbidities before and during pregnancy, lifestyle factors and gestational week of GDM diagnosis. Other covariates included were region of residence for the child and calendar year of delivery. The covariates included in the PS estimation are listed in table 1 (covariate definitions in online supplemental table S4). To avoid violations of the positivity assumption, children with an estimated PS outside the overlapping area of the PS distribution in the respective two exposure groups (ie, PS higher than the highest and lower than lowest in the other exposure group) were excluded.[31] The distributions of the stabilized weights were investigated to identify influential observations; large weights were truncated to a maximum of 10. Covariate balance after weighting was assessed using the standardized mean difference. A standardized mean difference less than 0.10 was assumed to indicate that the covariate was well balanced. Covariates that were not balanced after weighting were included as separate independent variables in the outcome models.

Statistical analysis

Incidence rates (IRs) with 95% CIs were estimated according to age period (description in online supplemental methods 1). Different analytic setups were used to calculate IRs for outcomes considered permanent (diabetes, PCOS, and challenges in MSD) and temporary (obesity, hypoglycemia, hyperglycemia, and hypertension).

The primary outcomes were analyzed using proportional hazards regression to estimate HRs with 95% CIs. For the analyses of the permanent outcomes, the children in the cohort were followed to the date of the first occurrence of an outcome event. For the temporary outcomes, multiple events per child were allowed. Temporal clustering of events in the same child was taken into account using a time-dependent covariate, indicating whether an event had occurred in the previous 365 days. Additionally, the variance of the outcome models was estimated using a robust estimator. The timescale for all analyses was days since birth. The analyses of the secondary outcomes were conducted using logistic regression to estimate ORs with 95% CIs. In addition, the mean difference in birth weight associated with maternal exposure to metformin and combination treatment, compared with insulin, was estimated using linear regression. Both unadjusted and IPTW-weighted analyses were conducted.

Two sensitivity analyses for the primary outcomes were conducted. First, the study cohort was restricted to children with maternal GDM. While indications for maternal exposure (ie, GDM, pregestational T2DM, and PCOS) were accounted for in the IPTW weighting, this sensitivity analysis was designed to assess the consistency of results across different indications (description of the subcohort for maternal GDM is provided online supplemental methods 2). Second, the analyses of the primary outcomes were repeated among those with at least two dispensed maternal prescriptions for metformin or insulin at different dates from LMP to birth (as women who refilled prescriptions might be more likely to have used the dispensed medications).

All analyses were conducted using R V.3.5.0.

The study methods were planned prior to conduct and are described in full in the study protocol registered in the European Union PAS Register (EUPAS number 19686).[32] Of note, the protocol describes two study periods, 1996–2016 and 2004–2016, which was originally intended. However, given the observation of very limited maternal pregnancy exposure to metformin in Finland before 2004, results are presented only for 2004–2016. A description of the numbers exposed in each study period is provided in online supplemental figure S1.

RESULTS

A total of 10 129 children with maternal exposure to metformin, insulin or both fulfilled the criteria for inclusion. Among these, 3967 were exposed to metformin, 889 were exposed to combination treatment and 5273 were exposed to insulin. For the IPTW-weighted analyses, 296 and 55 exposed to metformin and insulin, respectively, were excluded from the analyses of metformin versus insulin due to non-overlapping PSs; 7 and 21 exposed

Table 1 Baseline characteristics of children with maternal exposure to metformin, combination treatment, or insulin

Characteristics	Metformin (n=3967)	Combination treatment (n=889)	Insulin (n=5273)	Standardized difference*			
				Metformin versus insulin		Combination treatment versus insulin	
				Before IPTW weighting	After IPTW weighting†	Before IPTW weighting	After IPTW weighting†
Gestational age at birth (weeks), median (IQR)‡	39.4 (38.6–40.3)	38.9 (38.0–39.6)	39.1 (38.4–40.0)	Not included in propensity score			
Sex, n (%)				Not included in propensity score			
Female	1884 (47.5)	431 (48.5)	2487 (47.2)				
Male	2083 (52.5)	458 (51.5)	2786 (52.8)				
Year of birth, n (%)				0.536	0.067	1.060	**0.117**
2004–2008	608 (15.3)	47 (5.3)	1479 (28.1)	0.288	0.010	0.634	0.013
2009–2013	1632 (41.1)	337 (37.9)	2359 (44.7)	0.091	0.024	0.136	0.057
2014–2016	1727 (43.5)	505 (56.8)	1435 (27.2)	0.344	0.033	0.619	0.048
Child's region of residency at birth, n (%)§				0.451	0.027	0.378	**0.114**
Helsinki	1071 (27.0)	272 (30.6)	914 (17.4)				
Pirkanmaa	399 (10.1)	167 (18.8)	1029 (19.5)				
Varsinais-Suomi	1068 (26.9)	86 (9.7)	167 (3.2)				
Other (18 regions)	1429 (36.0)	364 (40.9)	3163 (60.0)				
Type of delivery, n (%)				Not included in propensity score			
Vaginal birth	3000 (75.6)	597 (67.2)	3914 (74.2)				
Caesarean section	966 (24.4)	292 (32.8)	1358 (25.8)				
Missing	1 (0.0)	0 (0.0)	1 (0.0)				
Maternal age at delivery, median (IQR)	32.0 (28.0–35.0)	34.0 (30.0–37.0)	33.0 (29.0–37.0)	−0.111	−0.040	0.181	0.051
Maternal pre-pregnancy BMI, median (IQR)¶**	29.7 (25.0–34.7)	34.0 (29.4–38.7)	30.1 (26.1–34.9)	0.130	0.046	0.985	**0.135**
Maternal parity, n (%)				0.187	0.036	0.035	0.024
Nulliparous	1711 (43.1)	239 (26.9)	1482 (28.1)	0.264	0.048	0.031	0.030
Parity 1–2	1849 (46.6)	487 (54.8)	2879 (54.6)	0.127	0.019	0.003	0.009
Parity ≥3	406 (10.2)	163 (18.3)	910 (17.3)	0.177	0.036	0.032	0.024
Missing	1 (0.0)	0 (0.0)	2 (0.0)	NA	NA	NA	NA
Maternal educational level during pregnancy, n (%)				0.130	0.039	0.030	0.062

Continued

Table 1 Continued

Characteristics	Metformin (n=3967)	Combination treatment (n=889)	Insulin (n=5273)	Standardized difference*			
				Metformin versus insulin		Combination treatment versus insulin	
				Before IPTW weighting	After IPTW weighting†	Before IPTW weighting	After IPTW weighting†
Higher education	1802 (45.4)	319 (35.9)	1995 (37.8)	0.115	0.051	0.038	0.084
High school	1562 (39.4)	425 (47.8)	2450 (46.5)	0.118	0.022	0.030	0.041
Missing	603 (15.2)	145 (16.3)	828 (15.7)	0.006	0.038	0.010	0.059
Maternal smoking during pregnancy, n (%)				0.123	0.043	0.063	**0.132**
Yes	570 (14.4)	146 (16.4)	948 (18.0)	0.078	0.037	0.061	**0.128**
No	3338 (84.1)	721 (81.1)	4147 (78.6)	0.113	0.044	0.042	**0.132**
Missing	59 (1.5)	22 (2.5)	178 (3.4)	0.100	0.025	0.051	0.012
Maternal comorbidities before pregnancy							
Pregestational T2DM, n (%)	154 (3.9)	168 (18.9)	130 (2.5)	0.095	0.003	0.536	0.017
PCOS, n (%)	464 (11.7)	42 (4.7)	124 (2.4)	0.279	0.011	0.119	0.006
Obesity at the beginning of pregnancy, n (%)				Not included in propensity score			
Yes	1897 (47.8)	641 (72.1)	2614 (49.6)				
No	2019 (50.9)	240 (27.0)	2549 (48.3)				
Missing	51 (1.3)	8 (0.9)	110 (2.1)				
Toxemia in pregnancy, n (%)	557 (14.0)	204 (22.9)	834 (15.8)	0.045	0.005	0.173	**0.106**
GDM, n (%)	2897 (73.0)	719 (80.9)	5134 (97.4)	Not included in propensity score			
Gestational week of maternal gestational diabetes diagnosis, median (IQR)†††‡	24.4 (15.0–27.7)	16.6 (13.6–23.1)	25.4 (16.7–29.3)	0.713	**0.221**	0.915	0.081
Essential hypertension in pregnancy, n (%)	58 (1.5)	39 (4.4)	71 (1.3)	0.012	0.012	0.179	0.045
Gestational hypertension in pregnancy, n (%)	293 (7.4)	104 (11.7)	449 (8.5)	0.040	0.011	0.093	0.083
Pre-eclampsia in pregnancy, n (%)	155 (3.9)	55 (6.2)	198 (3.8)	0.007	0.028	0.104	0.031
Other characteristics							
Dispensation of antidiabetic medications within 3 months before the beginning of pregnancy, n (%)§§				Not included in propensity score			

Continued

Table 1 Continued

Characteristics	Metformin (n=3967)	Combination treatment (n=889)	Insulin (n=5273)	Standardized difference*			
				Metformin versus insulin		Combination treatment versus insulin	
				Before IPTW weighting	After IPTW weighting†	Before IPTW weighting	After IPTW weighting†
No pre-pregnancy pharmacological antidiabetic treatment	2892 (72.9)	745 (83.8)	5220 (99.0)				
Prepregnancy metformin only	1074 (27.1)	130 (14.6)	47 (0.9)				
Other	1 (0.0)	14 (1.6)	6 (0.1)				
Gestational week of initiating the pharmacological antidiabetic treatment, median (IQR)	24.3 (4.1–31.6)	20.1 (14.0–26.1)	31.3 (26.4–34.0)	Not included in propensity score			
Persistence of diabetes in the mother after birth	60 (1.5)	109 (12.3)	72 (1.4)	Not included in propensity score			
Dispensed cumulative dose of metformin during pregnancy (DDDs), median (IQR)	50.0 (25.0–75.0)	100.0 (50.0–150.0)	0.0 (0.0–0.0)	Not included in propensity score			

*The distributions of the variables used in propensity score weighting were compared between exposure groups (metformin only exposure: yes/no), by means of standardized difference of prevalence (binary variable), standardized difference of mean (continuous variable), or Mahalanobis distance (categorical variables with more than two levels).
†Numbers >0.1 are in bold, meaning the variable was not balanced after IPTW weighting.
‡Information missing for two children in the metformin group (<0.1%) and three in the insulin group (<0.1%).
§The three hospital regions with the largest total number of study subjects are presented; counts from the other 18 regions are pooled.
¶Information missing for 51 children in the metformin group (1.3%), 8 in the combination treatment group (0.9%), and 110 in the insulin group (2.1%).
**BMI was categorized as ≤18.5, 18.6–25.0, 25.1–30.0, and >30.0.
††Gestational week of gestational diabetes diagnosis was categorized as: <12; 12–19; 20–23; 24–26; 27–30; >30; GDM detected, time unknown; and no diagnosis of gestational diabetes diagnosis.
‡‡Information missing for 1135 children in the metformin group (28.6%), 172 in the combination treatment group (19.4%), and 177 in the insulin group (3.4%).
§§Subject counts for two most frequent categories are presented. Counts for other six combinations of prepregnancy use of metformin, insulin, and other antidiabetic medications than metformin and insulin are pooled.
BMI, body mass index; GDM, gestational diabetes mellitus; IPTW, inverse probability of treatment weighting; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

to combination treatment and insulin, respectively, were excluded from the analyses of combination treatment versus insulin.

Baseline characteristics for the children included are shown in table 1. After weighting, children exposed to metformin and insulin were balanced on all measured characteristics, except week of diagnosis for maternal GDM. Comparing children exposed to combination treatment with those exposed to insulin, after weighting, the exposure groups were balanced on all characteristics, except child's year of birth and region of residence and the maternal characteristics toxemia in pregnancy, smoking, and body mass index.

Primary outcomes

The median time of follow-up among the children in the cohort was 3.5 years (IQR 1.6–6.4) for those exposed to metformin, 2.4 years (IQR 1.1–4.4) for those exposed to combination treatment, and 5.5 years (IQR 2.8–8.4) for those exposed to insulin.

IRs (per 1000 person-years) for the primary outcomes are presented in table 2. For obesity, the incidence appeared to increase with age; the highest IRs were observed for combination treatment (IR 40.34; 95% CI 19.23 to 84.61 in the age group 6–8 years). The large majority of hypoglycemia events were observed in the age group 1 week–2 years; the highest IR was observed in the combination cohort (IR 20.71; 95% CI 14.94 to 28.72), whereas the IRs in the metformin and in the insulin cohorts were 6.44 (95% CI 4.98 to 8.33) and 4.49 (95% CI 3.49 to 5.77), respectively. For hyperglycemia, IRs appeared to increase with age, with no marked differences between the exposure groups, however. There were few events of diabetes with no distinct pattern, neither by age nor exposure group. Regarding challenges in MSD, the IR appeared highest in the age periods from 3 to 11 years of age. No distinct pattern according to exposure group could be seen, although, in the youngest age periods (1 week–2 years and 3–5 years), the highest IRs were observed for combination treatment (IR 19.99; 95% CI 14.35 to 27.84 in age group 1 week–2 years and IR 75.42; 95% CI 56.31 to 101.01 in age group 3–5 years). No events of hypertension or PCOS were observed in the metformin or combination treatment groups.

The results for the primary long-term outcomes are shown in table 3. In weighted analyses, exposure to metformin was not associated with increased risk of obesity (IPTW-weighted HR (wHR) 1.14; 95% CI 0.83 to 1.55), hypoglycemia (wHR 1.00; 95% CI 0.61 to 1.64), hyperglycemia (wHR 1.23; 95% CI 0.63 to 2.42), diabetes (wHR 1.19; 95% CI 0.51 to 2.82), or challenges in MSD (wHR 1.09; 95% CI 0.93 to 1.27). Combination treatment was not associated with increased risk of obesity (wHR 1.09; 95% CI 0.76 to 1.58), hypoglycemia (wHR 1.14; 95% CI 0.71 to 1.83), hyperglycemia (wHR 0.22; 95% CI 0.05 to 1.01), diabetes (wHR 0.14; 95% CI 0.02 to 1.15), or challenges in MSD (wHR 1.11; 95% CI 0.77 to 1.59). Given the absence of events, the risk of hypertension and PCOS could not be estimated.

Sensitivity analyses of the primary outcomes

The analyses of children with maternal GDM included 2361 children exposed to metformin, 577 exposed to combination treatment, and 4865 exposed to insulin (baseline characteristics in online supplemental table S5). For children exposed to metformin, the results were similar to the main analysis; no significant increased risk of any of the primary outcomes was observed. Exposure to combination treatment was associated with a significantly increased risk of neonatal hypoglycemia (wHR 4.98; 95% CI 1.28 to 19.35) but not with any other outcome (online supplemental table S6).

In the sensitivity analysis requiring at least two dispensed prescriptions of metformin or insulin for inclusion, results were similar to the main analyses for all primary outcomes, except for a significantly increased risk of challenges in MSD associated with combination treatment (wHR 2.09; 95% CI 1.21 to 3.61; online supplemental table S7).

Secondary outcomes

The results of the analyses of the secondary outcomes are shown in table 4. After IPTW weighting, exposure to metformin was associated with significantly lower mean birth weight, compared with insulin (weighted mean difference (wMD) −38.5 g; 95% CI −60.8 to −16.1), in line with a significantly increased risk of SGA (IPTW-weighted OR (wOR) 1.65; 95% CI 1.16 to 2.34). No significantly increased risk associated with metformin for any other secondary outcome was observed in IPTW-weighted analyses. In the analyses of combination treatment, a significantly increased risk was observed for LGA (wOR 1.58; 95% CI 1.22 to 2.05), preterm birth (wOR 1.46; 95% CI 1.10 to 1.95), and neonatal hypoglycemia (wOR 1.29; 95% CI 1.09 to 1.53), but not for any other secondary outcome. No significant difference in mean birth weight for combination treatment, compared with insulin, was observed (wMD −9.7 g; 95% CI −47.6 to 28.2).

DISCUSSION

This large register-based cohort study found that maternal exposure to metformin and combination treatment of metformin and insulin was not associated with long-term increased risk of obesity, hypoglycemia, hyperglycemia, diabetes, or challenges in MSD, compared with insulin. The results were generally consistent in sensitivity analyses restricted to children with maternal GDM. The analyses of adverse outcomes at birth showed significantly lower birth weight and significantly increased risk of SGA associated with exposure to metformin, compared with insulin; combination treatment was associated with increased risk of LGA, preterm birth, and hypoglycemia.

In general, results from this study follow the trend seen in other studies, namely that the obesity risk increases with age of the children. At the age of 3–5 years, the incidence

Table 2 Incidence rates per 1000 person-years (95% CI) for the long-term primary outcomes by exposure and age group

		Metformin		Combination treatment		Insulin	
Outcome*	**Age group**	**No. of events/ no. at risk**	**IR/1000 p-y (95% CI)**	**No. of events/ no. at risk**	**IR/1000 p-y (95% CI)**	**No. of events/ no. at risk**	**IR/1000 p-y (95% CI)**
Obesity	1 week–2 years	11/3950	1.21 (0.67 to 2.19)	0/884	NA	10/5264	0.73 (0.39 to 1.36)
	3–5 years	19/2224	3.96 (2.52 to 6.20)	10/382	15.04 (8.09 to 27.96)	40/3817	4.34 (3.18 to 5.91)
	6–8 years	24/1088	11.26 (7.55 to 16.80)	7/112	40.34 (19.23 to 84.61)	83/2448	16.34 (13.18 to 20.27)
	9–11 years	8/373	18.69 (9.35 to 37.38)	0/24	NA	32/1070	20.93 (14.80 to 29.60)
Hypoglycemia	1 week–2 years	58/3950	6.44 (4.98 to 8.33)	36/884	20.71 (14.94 to 28.72)	61/5264	4.49 (3.49 to 5.77)
	3–5 years	5/2224	1.04 (0.43 to 2.49)	2/382	2.99 (0.75 to 11.94)	0/3817	NA
	6–8 years	2/1088	0.93 (0.23 to 3.71)	0/112	NA	1/2448	0.19 (0.03 to 1.37)
	9–11 years	0/373	NA	0/24	NA	0/1070	NA
Hyperglycemia	1 week–2 years	11/3950	1.21 (0.67 to 2.19)	1/884	0.56 (0.08 to 3.96)	15/5264	1.10 (0.66 to 1.82)
	3–5 years	8/2224	1.66 (0.83 to 3.32)	1/382	1.49 (0.21 to 10.59)	14/3817	1.51 (0.90 to 2.56)
	6–8 years	4/1088	1.86 (0.70 to 4.95)	0/112	N/A	11/2448	2.13 (1.18 to 3.85)
	9–11 years	2/373	4.60 (1.51 to 18.39)	0/24	NA	9/1070	5.79 (3.01 to 11.12)
Diabetes†	1 week–2 years	5/3950	0.55 (0.23 to 1.32)	1/884	0.56 (0.08 to 3.96)	6/5264	0.44 (0.20 to 0.97)
	3–5 years	7/2220	1.46 (0.69 to 3.05)	0/382	NA	9/3811	0.97 (0.51 to 1.87)
	6–8 years	1/1080	0.47 (0.07 to 3.30)	0/112	NA	3/2437	0.58 (0.19 to 1.81)
	9–11 years	0/370	NA	0/24	NA	1/1063	0.64 (0.09 to 4.57)

Continued

Table 2 Continued

Outcome*	Age group	Metformin		Combination treatment		Insulin	
		No. of events/ no. at risk	IR/1000 p-y (95% CI)	No. of events/ no. at risk	IR/1000 p-y (95% CI)	No. of events/ no. at risk	IR/1000 p-y (95% CI)
Hypertension	1 week–2 years	0/3950	NA	0/884	NA	5/5264	0.36 (0.15 to 0.88)
	3–5 years	0/2224	NA	0/382	NA	1/3817	0.11 (0.02 to 0.77)
	6–8 years	0/1088	NA	0/112	NA	1/2448	0.19 (0.03 to 1.37)
	9–11 years	0/373	NA	0/24	NA	0/1070	NA
Challenges in motor–social development†	1 week–2 years	155/3950	17.41 (14.87 to 20.38)	35/884	19.99 (14.35 to 27.84)	133/5264	9.82 (8.29 to 11.64)
	3–5 years	264/2114	60.71 (53.81 to 68.49)	45/361	75.42 (56.31 to 101.01)	439/3716	51.56 (41.91 to 55.38)
	6–8 years	80/899	46.67 (37.49 to 58.10)	5/81	36.75 (15.30 to 88.29)	198/2057	48.18 (41.91 to 55.38)
	9–11 years	6/290	17.13 (7.69 to 38.12)	1/20	50.48 (7.11 to 358.33)	38/815	31.62 (23.00 to 43.45)

*No events of PCOS were observed in any of the exposure groups; no events were observed for any outcome and exposure group in the age group ≥12 years.
†Children with the diagnosis were removed from population at risk in the following age groups after the first diagnosis. Therefore, the number at risk were different for the outcomes after the youngest age group.
IR, incidence rate; NA, not applicable; PCOS, polycystic ovary syndrome; p-y, person-years.

Table 3 Risk of the primary long-term outcomes by exposure group

Outcome*	Unadjusted HR (95% CI)†		IPTW-weighted HR (95% CI)‡	
	Metformin versus insulin	Combination treatment versus insulin	Metformin versus insulin	Combination treatment versus insulin
Obesity	1.15 (0.82 to 1.60)	1.35 (1.02 to 1.78)	1.14 (0.83 to 1.55)	1.09 (0.76 to 1.58)
Hypoglycemia	0.80 (0.49 to 1.30)	1.11 (0.65 to 1.89)	1.00 (0.61 to 1.64)	1.14 (0.71 to 1.83)
Hyperglycemia	1.00 (0.61 to 1.64)	0.42 (0.14 to 1.25)	1.23 (0.63 to 2.42)	0.22 (0.05 to 1.01)
Diabetes mellitus	1.32 (0.65 to 2.67)	0.70 (0.09 to 5.21)	1.19 (0.51 to 2.82)	0.14 (0.02 to 1.15)
Challenges in motor–social development	1.25 (1.11 to 1.40)	1.58 (1.26 to 1.98)	1.09 (0.93 to 1.27)	1.11 (0.77 to 1.59)

*No events of the long-term primary outcomes hypertension and PCOS were observed in the metformin or combination treatment groups.
†Metformin and combination treatment were compared with insulin. In the unadjusted comparison, 3967 children were exposed to metformin; 889 children were exposed to combination treatment; and 5273 were exposed to insulin.
‡Metformin and combination treatment were analyzed separately, in pairwise comparisons with insulin (reference in all analyses). Analyses were conducted in the main cohort after trimming of children outside the overlapping range of the propensity score. In the IPTW analyses of metformin versus insulin, 3671 children exposed to metformin and 5218 exposed to insulin included; in the analyses of combination treatment versus insulin, 882 children exposed to combination treatment and 5252 exposed to insulin included.
IPTW, inverse probability of treatment weighting; PCOS, polycystic ovary syndrome.

of obesity after metformin was comparable with that of insulin, in line with two GDM follow-ups from Finland and New Zealand, which found no increased risk of obesity associated with maternal exposure to metformin at 18 months and 4 years of age, respectively.[15 18] In the age group 6–8 years, the obesity incidence was still more than twice as high in the combination treatment group compared with the metformin and insulin groups, but the IPTW-related HR was not significantly increased, suggesting a strong influence by confounders. In the long-term outcomes of the Australian GDM study,[16] no stratification by the use of metformin alone or in combination with insulin was made, but still the results differ. Two Norwegian RCT follow-up studies in children with maternal PCOS also found increased risk of obesity at a follow-up of 4 and up to 10 years of age, compared with placebo.[20 21] The key differences in study population, that is, metformin used for GDM or T2DM or PCOS in this study versus single indications in the prospective studies and treatment comparator, that is, metformin with/without supportive insulin versus insulin and placebo, respectively, make this comparison difficult. Nevertheless, this study represents the largest investigation of the long-term association between obesity and maternal exposure to metformin at the age of 9–12 years to date, and in this age group, exposure to metformin and insulin had comparable obesity IRs.

To our knowledge, this is the first study to investigate the association between exposure to metformin and risk of hypoglycemia or hyperglycemia beyond the age of 1 week, aiming to capture incidents of prolonged neonatal hyperinsulinemia or permanent alterations to metabolism. A small number of previous studies have investigated glucose levels among children with maternal exposure to metformin, observing no significant increase compared with insulin or placebo.[16 21 33] In this study, neither metformin nor combination treatment was associated with increased risk of hypoglycemia or hyperglycemia. Notably, combination treatment was associated with lower risk of hyperglycemia, although not significantly and based on few events. In the analyses among children with maternal GDM, combination treatment was associated with increased risk of hypoglycemia within the first 2 years, probably due to the prolonged postnatal hyperinsulinism, as mothers prescribed both insulin and metformin likely represent those with the most severe gestational diabetes.[34 35]

The previous evidence regarding long-term risk of hypertension, diabetes, and PCOS associated with maternal exposure to metformin is scarce; to our knowledge, no previous investigations have been published. In this study, no cases of hypertension or PCOS were identified, which prevents conclusions regarding these outcomes being drawn. Indeed, PCOS is generally not diagnosed before late adolescence, which may explain the absence of events for this outcome.[36] For diabetes, exposure to metformin was not associated with increased risk; combination treatment was associated with non-significantly lower risk, although based on few events.

The finding of no increased risk in the main analyses of long-term challenges in MSD aligns with previous reports assessing developmental outcomes with maternal exposure to metformin.[15 18 23] However, increased risk associated with combination treatment was observed in the sensitivity analysis requiring two prescriptions. Notably, the incidence of challenges in MSD showed a clear

Table 4 Risk of adverse outcomes at birth by exposure group

	Metformin (n=3967)				Combination treatment (n=889)				Insulin (reference) (n=5273)	
	Events*		OR (95% CI)		Events*		OR (95% CI)†		Events*	
Outcome	No.	%	Unadjusted	IPTW weighted‡	No.	%	Unadjusted	IPTW weighted‡	No.	%
LGA	159	4.0	0.63 (0.52 to 0.76)	0.82 (0.67 to 0.99)	104	11.7	2.00 (1.58 to 2.52)	1.58 (1.22 to 2.05)	328	6.2
SGA	92	2.3	1.93 (1.40 to 2.67)	1.65 (1.16 to 2.34)	15	1.7	1.40 (0.79 to 2.46)	1.21 (0.65 to 2.28)	64	1.2
Preterm birth	265	6.7	1.28 (1.07 to 1.52)	1.10 (0.91 to 1.31)	80	9.0	1.76 (1.36 to 2.28)	1.46 (1.10 to 1.95)	280	5.3
Neonatal mortality	5	0.1	2.22 (0.53 to 9.28)	1.30 (0.25 to 6.70)	3	0.3	5.95 (1.20 to 29.52)	1.31 (0.09 to 19.91)	3	0.1
Neonatal hypoglycemia	694	17.5	0.74 (0.67 to 0.82)	0.80 (0.72 to 0.89)	272	30.6	1.54 (1.32 to 1.80)	1.29 (1.09 to 1.53)	1173	22.3
Neonatal hyperglycemia	5	0.1	6.65 (0.78 to 56.97)	9.66 (0.72 to 130.37)	0	0.0	NA	NA	1	<0.1
Any major congenital anomaly	151	4.5	0.90 (0.73 to 1.11)	0.79 (0.63 to 0.99)	35	5.1	1.03 (0.71 to 1.48)	0.75 (0.50 to 1.14)	242	4.9

*The event numbers represent counts in the main cohort before trimming of children outside the overlapping range.
†Metformin and combination treatment were analyzed separately, in pairwise comparisons with insulin (reference in all analyses).
‡Analyses were conducted in the main cohort after trimming of children outside the overlapping range of the propensity score. In the IPTW analyses of metformin versus insulin, 3671 children exposed to metformin and 5218 exposed to insulin included; in the analyses of combination treatment versus insulin, 882 children exposed to combination treatment and 5252 exposed to insulin included.
IPTW, inverse probability of treatment weighting; LGA, large for gestational age; NA, not applicable; SGA, small for gestational age.

increase over calendar time (data not shown), which may be explained by the availability of data from primary care only from 2011. Coupled with imbalances in year of birth between the combination treatment and insulin groups (standardized difference after weighting=0.117), this could potentially explain the observed risk increase. The current study expands on the available evidence by providing analyses at a follow-up of up to 12 years, compared with a maximum 4-year follow-up in previous data.[18]

In the analyses of SGA, maternal exposure to metformin was associated with increased risk versus insulin. While a significant association between metformin alone and SGA has not been previously reported, a meta-analysis of RCTs found a non-significant tendency toward increased risk, compared with insulin.[9] Several potential pathways through which metformin may influence risk of SGA have been suggested, including reduced maternal food intake, inhibition of the mammalian target of rapamycin (mTOR), and inhibition of folate-related pathways.[24] As metformin crosses the placenta,[5–7] direct fetal effects, for example, affecting the fetal metabolic milieu and cell metabolism, are also plausible.[1 24] Notably, a recent RCT found an almost twofold significantly increased risk of SGA associated with combination treatment (metformin and insulin), compared with insulin alone.[24] Possible correlations between SGA birth and maternal variables after exposure to metformin may be subject to a follow-up analysis.

Previous evidence regarding metformin and LGA and macrosomia is conflicting; while most reports have not found an association,[37–39] some studies and meta-analyses have reported lower risk compared with insulin.[9 40–42] Furthermore, a recent RCT found that maternal combination treatment (metformin and insulin) was associated with lower risk of being extremely LGA, compared with insulin alone.[24] Given that increased risk of LGA was only observed for combination treatment (ie, the exposure group including those with the likely most severe types of diabetes and the highest maternal BMI) in this study and, also, given the known association between glucose control and birth weight, confounding by disease severity appears a probable explanation.

In the analyses of preterm birth and neonatal hypoglycemia, an increased risk was observed only for combination treatment. Although previous data on preterm birth is conflicting,[9 10 37 38 43] residual or unmeasured confounding appears as a possible explanation. Specifically, several risk factors for preterm birth (including maternal BMI, toxemia, and smoking) remained unbalanced between the combination treatment and insulin groups after weighting and may not have been fully accounted for.

With regard to MCAs, no increased risk was observed, neither for metformin alone nor combination treatment. This is consistent with previous reports that found no increased risk of major congenital malformations associated with metformin, compared with, respectively, insulin, non-exposure to metformin, and non-exposure to any diabetic medication.[11–13 44–46]

This study had several strengths. First, the use of the comprehensive national Finnish health registers allowed for long-term follow-up, extending up to 12 years of age. Second, the nationwide coverage of data likely provided high representativeness and generalizability. Third, information on drug exposure was ascertained from a national prescription register, likely providing high completeness and precision regarding timing of use. Fourth, the use of IPTW methods based on PSs including a broad range of maternal characteristics reduced the potential for confounding by baseline characteristics.

There were also limitations. First, non-use of dispensed drugs would lead to exposure misclassification; given that metformin is known to more commonly be discontinued than insulin (eg, due to gastrointestinal side effects), this could potentially obscure a true association. However, in sensitivity analyses requiring at least two dispensed prescriptions for inclusion, the results were similar to those in the main analysis. For the combination treatment group, it was not possible to determine if metformin and insulin were used sequentially or concomitantly. Although the content of the Finnish national health registers is known to be of satisfactory to very good quality,[47] outcome misclassification remains possible. In particular, the ascertainment of the long-term outcomes relied on diagnoses that have not been formally validated for sensitivity or specificity. It is possible that sensitivity may have been limited for some outcomes, including obesity and less severe events of hypoglycemia. If sensitivity and misclassification was non-differential between exposure groups, this would likely bias results toward no effect. Also, the study population consisted of live births; thus, MCAs that led to elective termination of pregnancy were not included. In addition, the metformin group included children with maternal GDM, T2DM, and PCOS, whereas maternal indications for insulin include GDM and T2DM alone. While indications for treatment were accounted for in the IPTW, any remaining unmeasured differences in baseline risk between the groups would lead to confounding. However, in sensitivity analysis restricted to children with maternal GDM, the results were similar to the main analysis. While the study allowed for 12-year follow-up, the median follow-up time (3.5 years) was relatively short, thus limiting the sample size and precision at the older age periods. Still the number of children in the 9–11 year period is larger than in any other report we are aware of. Furthermore, although it has an influence on long-term outcomes, notably childhood obesity, breast feeding was not accounted for in the study as information on breast feeding is not available in Finnish data sources. However, it is unlikely that breast feeding would vary differentially across exposure groups.[48] Also, metformin passes into the maternal milk with very low to neglectable concentrations and breastfed versus formula-fed infants did not show a difference after 6 months.[49] Therefore, it is unlikely that adjustment for breast feeding would

considerably change the findings. Finally, maternal disease severity (eg, level of glucose control) and individual risk factors (eg, gestational weight gain) could not be accounted for in the analysis, although being known potential confounders.

Although a longer median follow-up time could bring better confidence to its findings, this study found no increased long-term risk of obesity, hypoglycemia, hyperglycemia, diabetes, or challenges in MSD associated with in utero exposure to metformin (alone or in combination with insulin), compared with insulin alone. The observed increased risk of SGA associated with metformin alone versus insulin may warrant caution for use in pregnancies with risk of foetal undernutrition. The associations between combination treatment and increased risk of LGA, preterm birth, and hypoglycemia may be explained by confounding.

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Collaborators Members of the CLUE Study Group are Minna Vehkala (Global Database Studies, IQVIA), Robyn Thorén (Global Database Studies, IQVIA), Henrik Svanström (Global Database Studies, IQVIA).

Contributors KMGB developed the study idea, backbone and synopsis as the outcome of a cumulative assessment on the benefit/risk profile of metformin during pregnancy in 2016, in her role as Global Medical representative of the metformin originator Merck KGaA, Darmstadt, Germany . KMGB represented the company, which was the study sponsor, acts as guarantor and significantly contributed to the manuscript. JuS, CF and EB (all Merck KGaA, Darmstadt, Germany) contributed to finetuning the study concept, protocol development, data analysis and manuscript. The study was conducted by IQVIA, contracted by Merck KGaA, Darmstadt, Germany. LM-P and MV provided independent medical expertise to the study and manuscript.

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Competing interests KMGB, CF, EB, and JuS are employees of Merck Healthcare KGaA, Darmstadt, Germany, the metformin originator and sponsor of this study, and participated in the authoring/revision of the manuscript. IQVIA performs commissioned pharmacoepidemiological studies, including this one, for several pharmaceutical companies. LS, JaS, MV, RT and KMH are employees of IQVIA, which performs commissioned pharmacoepidemiological studies for several pharmaceutical companies. HS is an employee of IQVIA and has received consulting fees from Celgene, outside the submitted work. PK was at the time of conducting the study an employee of IQVIA.

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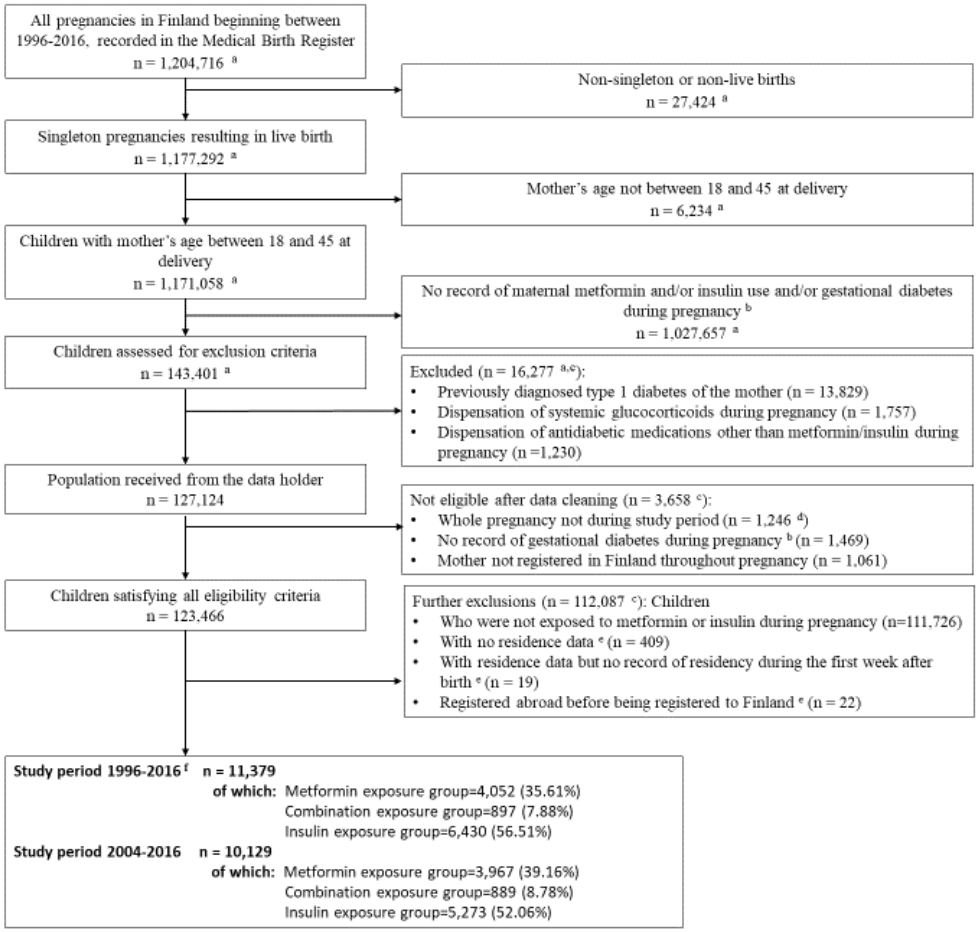
Supplementary files

Contents

Metformin in pregnancy and risk of adverse long-term outcomes: register-based cohort study
Supplementary file

Supplemental Figure S1. Selection of study population and the number of children in each exposure group during the study periods 1996-2016 and 2004-2016. Only the 2004-2016 study period is reported in this paper.



[a] Number reported by the data holder.

[b] Defined as one of the following: dispensation of metformin/insulin during pregnancy, or a diagnosis of gestational diabetes, or a pathological oral glucose tolerance test.

[c] The sub-categories overlap, thus this number is not the sum of numbers in sub-categories.

[d] The first day of last menstrual period had to be recorded during the study inclusion period.

[e] Migration abroad triggered end of follow-up. Children not registered as residing in Finland were thus excluded.

[f] The protocol describes two study periods, 1996-2016 and 2004-2016, which was originally intended. However, given the observation of very limited maternal pregnancy exposure to metformin in Finland before 2004, results are presented only for 2004-2016.

Supplemental Table S1. Definitions of exclusion criteria

Exclusion criteria			**Definition**	
	Time frame for the criteria	**Data source**	**Code**	**Description of the code**
Previously diagnosed or post-partum Type 1 diabetes	After delivery	HILMO and AvoHILMO (ICD-10 code, ICPC-2 code)	ICD-10: E10, O24.0 ICPC-2: T89	Type 1 diabetes mellitus
Dispensation of systemic glucocorticoids during pregnancy	During pregnancy, i.e. on the first day of the last menstrual period or any time after it until the date of delivery	The Prescription Register (ATC code)	H02AB	Glucocorticoids
Dispensation of antidiabetic medications other than metformin or insulin during pregnancy	During pregnancy, i.e. on the first day of the LMP or any time after it until the date of delivery	The Prescription Register (ATC code)	A10BA (Except for A10BA02)	Biguanides
			A10BB	Sulfonylureas
			A10BC	Sulfonamides (heterocyclic)
			A10BD	Combinations of oral blood glucose lowering drugs
			A10BF	Alpha glucosidase inhibitors
			A10BG	Thiazolidinediones

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	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
	A10BJ	Glucagon-like peptide-1 (GLP-1) analogues
	A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors
	A10BX	Other blood glucose lowering drugs, excl. insulins
	A10XA	Aldose reductase inhibitors

Abbreviations: ATC, Anatomical Therapeutic Chemical; AvoHILMO, the Register of Primary Health Care Visits; HILMO, the Care Register for Health Care; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ICPC-2, International Classification of Primary Care, 2nd revision.

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Supplemental Table S2. ATC codes for the study drugs

Medication	ATC (code)	ATC (text)
Metformin	A10BA02	Metformin
Insulins	A10A	Insulins and analogues

Abbreviations: ATC, Anatomical Therapeutic Chemical

Brand KMG, *et al. BMJ Open Diab Res Care* 2022; 10:e002363. doi: 10.1136/bmjdrc-2021-002363

Supplemental Table S3. Definitions of primary and secondary outcomes

Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
Primary (binary) outcomes - Long-term diagnoses:						
Data collection from age one week until the date of the first occurring event of death, emigration, or end of study period (December 31, 2016)						
Obesity	At least one record of a diagnosis code for obesity in HILMO or AvoHILMO, or BMI (kg/m^2) recorded in AvoHILMO above the threshold for obesity according to the Finnish growth references considering the sex and age of the child[b] (BMI available only from 2011 onwards)	E66	Obesity	-	T82	Obesity
					T83	Overweight
Hypoglycaemia	At least one record of a diagnosis code for hypoglycaemia in HILMO or AvoHILMO, or plasma glucose < 2.9 mmol/l as recorded in the regional laboratory databases	E16.1	Other hypoglycaemia	-	T87	Hypoglycaemia
		E16.10[c]	Hyperinsulinism	-		
		E16.11[c]	Hyperinsulinism NOS	-		
		E16.17[c]	Functional non-hyperinsulinaemic hypoglycaemia	-		

Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
		E16.19[c]	Other specified hypoglycaemia	-		
		E16.2	Hypoglycaemia, unspecified	-	T87	Hypoglycaemia
		P70.0	Syndrome of infant of mother with gestational diabetes	-	-	-
		P70.1	Syndrome of infant of a diabetic mother	-	-	-
		P70.3	Iatrogenic neonatal hypoglycaemia	-	-	-
		P70.4	Other neonatal hypoglycaemia	-	-	-
Hyperglycaemia	At least one record of a diagnosis code for hyperglycaemia in HILMO or AvoHILMO, or fasting plasma glucose ≥ 7.0 mmol/l, or 2h plasma glucose during OGTT ≥	R73	Elevated blood glucose level	-	-	-

Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
	11.1 mmol/l, or HbA1c ≥ 48 mmol/mol (or ≥ 6.5%), or plasma glucose ≥11.1 mmol/l, as recorded in the regional laboratory databases					
Hypertension	At least one record of a diagnosis code for hyper tension in HILMO or AvoHILMO	I10-I15	Hypertensive diseases		K86	Hypertension uncomplicated
				-	K87	Hypertension complicated
		P29.2	Neonatal hypertension	-	-	-
Diabetes mellitus	At least one record of a diagnosis code for any diabetes, including type 1 diabetes mellitus or type 2 diabetes mellitus, in HILMO or AvoHILMO	E10-E14	Diabetes Mellitus		F83	Retinopathy
				-	T89	Diabetes insulin dependent
				-	T90	Diabetes non-insulin dependent
		P70.2	Neonatal diabetes mellitus	-	-	-
Subcategories of diabetes mellitus		E10, O24.0	Type 1 diabetes mellitus	-	T89	Diabetes insulin dependent
		E11, O24.1	Type 2 diabetes mellitus	-	T90	Diabetes non-insulin dependent
		E12-E14, P70.2	Other diabetes	-	F83	Retinopathy

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
PCOS	At least one record of a diagnosis code for PCOS in HILMO or AvoHILMO	E28.2	Polycystic ovarian syndrome	-	T99	Endocrine/metabolic/nutritional disease other
Diagnoses related to challenges in motor-social development	At least one record of a diagnosis code for challenges in motor-social development in HILMO or AvoHILMO	F80	Specific developmental disorders of speech and language	-	P24	Specific learning problem
		-	-	-	P99	Psychological disorders, other
		F81	Specific developmental disorders of scholastic skills	-	P24	Specific learning problem
		F82	Specific developmental disorder of motor function	-	P24	Specific learning problem
		F83	Mixed specific developmental disorders - meeting the criteria for two or more of F80-F82	-	P24	Specific learning problem
		F84	Pervasive developmental disorders (includes Autism)	-	P99	Psychological disorders, other
		F88	Other disorders of	-	P99	Psychological disorders, other

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
			psychological development			
		F89	Unspecified disorder of psychological development	-	P99	Psychological disorders, other
		F90	Hyperkinetic disorders	-	P81	Hyperkinetic disorder
		F91	Conduct disorders	-	P22	Child behaviour symptom/complaint
		F92	Mixed disorders of conduct and emotions	-	P22	Child behaviour symptom/complaint
		F93	Emotional disorders with onset specific to childhood	-	P22	Child behaviour symptom/complaint
		F94	Disorders of social functioning with onset specific to childhood and adolescence	-	P22	Child behaviour symptom/complaint
		F95	Tic disorders	-	P10	Stammering/stuttering/tic
		F98	Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	-	P10	Stammering/stuttering/tic
				-	P11	Eating problem in child
				-	P12	Bedwetting/enuresis
				-	P13	Encopresis/bowel training problem
				-	P29	Psychological symptom/complaint other

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
				-	P28	Limited function/disability
				-	P85	Mental retardation
Sub-categories of diagnoses related to challenges in motor-social development		F80-F89	Disorders of psychological development	-	-	-
		F80-F83	Learning disabilities and abnormalities in motor development	-	P24	Specific learning problem
		F84	Autism spectrum disorders	-	-	-
		F90-F98	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	-	P10	Stammering/stuttering/tic
				-	P11	Eating problem in child
				-	P12	Bedwetting/enuresis
				-	P13	Encopresis/bowel training problem
				-	P22	Child behaviour symptom/complaint
				-	P29	Psychological symptom/complaint other
				-	P81	Hyperkinetic disorder
		F90	Hyperkinetic disorders	-	P81	Hyperkinetic disorder
		F91-F94	Conductive disorders	-	P22	Child behaviour symptom/complaint

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
Secondary (binary and continuous) outcomes A - Immediate effects: Data collection at birth up to 1 year (maximum follow-up one year)						
Major congenital anomalies[d]	Major congenital anomalies recorded in the Register of Congenital Malformations by the age of one year	See below	Major congenital anomalies - structural anomalies	See below	-	-
		See below	Major congenital anomalies - Chromosomal defect	See below	-	-
		See below	Congenital anomalies - Congenital hypothyroidism	See below	-	-
Major congenital anomalies - structural anomalies[d]		Q00-Q89	Congenital malformations and deformations	74, 75, 27910, 76076, 76280	-	-
Major congenital anomalies - Chromosomal defect[d]		Q90-Q99	Chromosomal abnormalities, not elsewhere classified (including trisomies)	7580-7583, 7585-7589	-	-
Congenital		E00	Congenital iodine-	-	-	-

Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
anomalies - Congenital hypothyroidism			deficiency syndrome			
		E00.1	Congenital iodine-deficiency syndrome, myxoedematous type - Hypothyroid	-	-	-
		E00.2	Congenital iodine-deficiency syndrome, mixed type	-	-	-
		E00.9	Congenital iodine-deficiency hypothyroidism NOS, within Congenital iodine-deficiency syndrome, unspecified	-	-	-
		E02	Subclinical iodine-deficiency hypothyroidism	-	-	-
		E03	Other hypothyroidism	-	-	-
		E03.0	Congenital hypothyroidism with diffuse goitre	-	-	-
		E03.1	Congenital hypothyroidism	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
			without goitre			
		E03.2	Hypothyroidism due to medicaments and other exogenous substances	-	-	-
		E03.8	Other specified hypothyroidism	-	-	-
		E03.80[c]	Hypothyroidism caused by autoimmune thyroiditis	-		
		E03.82[c]	Hypothyroidism caused by autoimmune thyroiditis	-		
		E03.89[c]	Other specified hypothyroidism	-		
		E03.9	Hypothyroidism, unspecified	-	-	-
Weight	Birth weight (g) recorded in the Medical Birth Register	-	-	-	-	-
Length	Length (cm) at birth recorded in the Medical Birth Register	-	-	-	-	-
Ponderal index	Ponderal index (kg/m^3) at birth	-	-	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
	recorded in the Medical Birth Register					
Head circumference	Head circumference (cm) at birth recorded in the Medical Birth Register	-	-	-	-	-
LGA[e]	Birth weight (g) recorded in the Medical Birth Register two standard deviations above the gestational age and sex-specific reference mean in Finland	-	-	-	-	-
SGA[e]	Birth weight (g) recorded in the Medical Birth Register two standard deviations below the gestational age and sex-specific reference mean in Finland	-	-	-	-	-
Preterm birth	Length of gestation (gestational age) less than 37 completed weeks, as recorded in the Medical Birth Register	-	-	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
Perinatal mortality	Death during the first week of life, recorded in the Medical Birth Register. Stillbirth is excluded from the definition, as exclusively live births are included in the study population	-	-	-	-	-
Neonatal hypoglycaemia	At least one record of a diagnosis code for hypoglycaemia in HILMO or AvoHILMO, or plasma glucose < 2.9 mmol/l as recorded in the regional laboratory databases, up to 28 days from birth. The definition also includes neonatal hypoglycaemia, defined as plasma glucose < 1.7 mmol/l at the date of birth or plasma glucose < 2.5 mmol/l between 2-28 days from birth	E16.1	Other hypoglycaemia	-	T87	Hypoglycaemia
		E16.10[c]	Hyperinsulinism	-		
		E16.11[c]	Hyperinsulinism NOS	-		
		E16.17[c]	Functional non-hyperinsulinaemic hypoglycaemia	-		
		E16.19[c]	Other specified hypoglycaemia	-		
		E16.2	Hypoglycaemia, unspecified	-	T87	Hypoglycaemia
		P70.0	Syndrome of infant of mother with gestational diabetes	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
		P70.1	Syndrome of infant of a diabetic mother	-	-	-
		P70.3	Iatrogenic neonatal hypoglycaemia	-	-	-
		P70.4	Other neonatal hypoglycaemia	-	-	-
Neonatal hyperglycaemia	At least one record of a diagnosis code for hyperglycaemia in HILMO or AvoHILMO, or fasting plasma glucose ≥ 7.0 mmol/l, or 2h plasma during OGTT ≥ 11.1 mmol/l, or HbA1c ≥ 48 mmol/mol (or ≥ 6.5%), or plasma glucose ≥11.1 mmol/l, as recorded in the regional laboratory databases, up to 28 days from birth	R73	Elevated blood glucose level	-	-	-
Secondary (binary and continuous) outcomes B - Long-term growth-related effects:						

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9[a]	ICPC-2	ICPC-2 (description)
Data collection from age one week until the date of the first occurring event of death, emigration, or end of study period (December 31, 2016)						
Overweight	BMI (kg/m^2) recorded in AvoHILMO above the threshold for overweight according to the Finnish growth references considering the sex and age of the child	-	-	-	-	-
Ponderal index	Ponderal index (kg/m^3) recorded in AvoHILMO	-	-	-	-	-
High Ponderal index	Ponderal index (kg/m^3) recorded in AvoHILMO > 10th percentile considering the age and sex of the child	-	-	-	-	-
BMI	BMI (kg/m2) recorded in AvoHILMO	-	-	-	-	-

Abbreviations: ICD-9, International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision; ICPC-2, International Classification of Primary Care, 2nd revision; HILMO, Care Register for Health Care Visits; AvoHILMO, Register of Primary Health Care Visits; BMI, body mass index; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; LGA, large for gestational age; SGA, small for gestational age

[a] ICD-9 was used only for anomalies in the Register of Congenital Malformations

[b] Saari A, Sankilampi U, Hannila M-L, et al. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. Ann Med 2011;43:235–48. doi:10.3109/07853890.2010.515603

[c] Finnish adaptation of the ICD-10 code

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[d] Major congenital anomalies were based on ICD-9 and ICD-10 diagnoses from the Register of Congenital Malformations. The site-specific sub-categories were further categorised in accordance with EUROCAT guide v1.4. Minor congenital anomalies were excluded in accordance with EUROCAT guide v1.4

[e] Sankilampi U, Hannila M-L, Saari A, et al. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med 2013;45:446–54. doi:10.3109/07853890.2013.803739

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Supplemental Table S4. Definitions of covariates (maternal diagnoses)

Covariates	**ICD-10**	**ICD-10 (description)**	**ICPC-2**	**ICPC-2 (description)**
Gestational diabetes mellitus	O24.4	Diabetes mellitus arising in pregnancy	W85	Gestational diabetes
	O24.9	Diabetes mellitus in pregnancy, unspecified	-	-
PCOS	E28.2	Polycystic ovarian syndrome	T99	Endocrine/metabolic/nutritional disease other
Type 1 diabetes mellitus	E10	Type 1 diabetes mellitus	T89	Diabetes insulin dependent
	O24.0	Pre-existing type 1 diabetes mellitus	-	-
Preeclampsia	O14	Pre-eclampsia	W81	Toxaemia of pregnancy
Type 2 diabetes mellitus	E11	Type 2 diabetes mellitus	T90	Diabetes non-insulin dependent
	O24.1	Pre-existing type 2 diabetes mellitus	-	-
Essential hypertension	I10	Essential (primary) hypertension	K86	Hypertension uncomplicated
Gestational hypertension	O13	Gestational [pregnancy-induced] hypertension; Mild preeclampsia	W81	Toxaemia of pregnancy
Persistence of diabetes in the mother after birth	E10-E14 excluding E11	Diabetes mellitus, excluding type 1 diabetes mellitus	F83	Retinopathy
			T90	Diabetes non-insulin dependent

Abbreviations: ICD-10, International Classification of Diseases, 10th revision; ICPC-2, International Classification of Primary Care, 2nd revision; PCOS, polycystic ovary syndrome

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Supplemental Methods 1. Calculation of incidence rates

Incidence rates (IRs) with 95% confidence intervals (CIs) were estimated according to age period, using categories 1 week-2 years, 3-5 years, 6-8 years, 9-11 years, and age 12 years or older. Different analytic setups were used to calculate IRs for outcomes considered permanent (diabetes, PCOS, and challenges in motor-social development) and temporary (obesity, hypoglycaemia, hyperglycaemia, and hypertension). For permanent outcomes, children were censored at the date of the first event during follow-up period (and contributed person-time and events only to age periods up to that point). For temporary outcomes, children contributed to all age periods for the entire duration of follow-up; the first occurrence of an outcome event within each age period was counted, regardless of previous events in earlier age periods. At the date of an event, follow-up was censored for the remaining duration within the specific age period.
A small proportion of children had missing information on the estimated last menstrual period (LMP) and gestational age in the Medical Birth Registry; in this case, the date of LMP was imputed based on date of birth and the average gestational age observed in the data. For covariates with missing information, a separate missing category was added and used in the analysis.

Brand KMG, *et al. BMJ Open Diab Res Care* 2022; 10:e002363. doi: 10.1136/bmjdrc-2021-002363

Supplemental Methods 2. Description of the subcohort for maternal gestational diabetes

In additional analysis, a subcohort including children to mothers with gestational diabetes was created. Children born to mothers who were dispensed metformin or insulin after the gestational week 11 were included. All children born to mothers with dispensations of metformin or insulin before gestational week 12 were excluded, as it was thought likely that the drug was used for some other indication, such as PCOS or type 2 diabetes. Additionally, children of mothers who had a diagnosis of type 2 diabetes or PCOS recorded by the end of pregnancy were excluded, if they did not have a diagnosis of gestational diabetes.

Children in this subcohort were classified into three exposure groups (i.e., metformin, insulin, and combination treatment), consistent with the main analyses.

The PS-weighted model was re-fitted for all primary outcomes with the additional covariate of the categorical version of the variable gestational week of initiating pharmacological antidiabetic treatment and its interaction terms with cohort indicator. The following categories were used for gestational week of initiating the pharmacological antidiabetic treatment: 12–19, 20–23, 24–26, 27–30, and >30 weeks. The results of the sensitivity analyses are presented in the results section.

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Supplemental Table S5. Baseline characteristics of children exposed to metformin, combination treatment, and insulin in the subcohort for maternal gestational diabetes.

Characteristic	Metformin (n=2361)	Combination treatment (n=577)	Insulin (n=4865)
Gestational age at birth (weeks), median (IQR)[a]	39.3 (38.4-40.0)	38.9 (38.1-39.7)	39.1 (38.4-40.0)
Sex, n (%)			
Female	1133 (48.0)	274 (47.5)	2297 (47.2)
Male	1228 (52.0)	303 (52.5)	2568 (52.8)
Year of birth, n (%)			
2004-2008	152 (6.4)	14 (2.4)	1380 (28.4)
2009-2013	939 (39.8)	205 (35.5)	2154 (44.3)
2014-2016	1270 (53.8)	358 (62.1)	1331 (27.4)
Child's region of residency at birth, n (%)[b]			
Helsinki	634 (26.9)	176 (30.5)	822 (16.9)
Pirkanmaa	274 (11.6)	125 (21.7)	992 (20.4)
Varsinais-Soumi	814 (34.5)	57 (9.9)	126 (2.6)
Other (18 regions)	639 (27.1)	219 (38.0)	2925 (60.1)
Type of delivery, n (%)			
Vaginal birth	1787 (75.7)	399 (69.2)	3627 (74.6)

Characteristic	**Metformin (n=2361)**	**Combination treatment (n=577)**	**Insulin (n=4865)**
Caesarean section	574 (24.3)	178 (30.9)	1237 (25.4)
Missing	0 (0.0)	0 (0.0)	1 (0.0)
Maternal age at delivery, median (IQR)	32.0 (29.0, 36.0)	34.0 (30.0, 37.0)	33.0 (29.0, 36.0)
Maternal pre-pregnancy BMI (kg/m^2), median (IQR)[c]	30.5 (26.0-35.4)	33.8 (28.8-38.3)	30.0 (26.1-34.7)
Maternal parity, n (%)			
Nulliparous	762 (32.3)	136 (23.6)	1390 (28.6)
Parity 1-2	1262 (53.5)	332 (57.5)	2658 (54.6)
Parity ≥3	337 (14.3)	109 (18.9)	815 (16.8)
Missing	0 (0.0)	0 (0.0)	2 (0.0)
Maternal educational level during pregnancy, n (%)			
Higher education	865 (36.6)	204 (35.4)	1866 (38.4)
High school	1010 (42.8)	281 (48.7)	2247 (46.2)
Missing	486 (20.6)	92 (15.9)	752 (15.5)
Maternal smoking during pregnancy, n (%)			
Yes	450 (19.1)	99 (17.2)	880 (18.1)

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Characteristic	Metformin (n=2361)	Combination treatment (n=577)	Insulin (n=4865)
No	1880 (79.6)	463 (80.2)	3819 (78.5)
Missing	31 (1.3)	15 (2.6)	166 (3.4)
Maternal comorbidities before pregnancy			
Pre-gestational type 2 diabetes, n (%)	0	0	0
PCOS, n (%)	71 (3.0)	14 (2.4)	108 (2.2)
Obesity at the beginning of pregnancy, n (%)			
Yes	1242 (52.6)	399 (69.2)	2376 (48.8)
No	1092 (46.3)	172 (29.8)	2392 (49.2)
Missing	27 (1.1)	6 (1.0)	97 (2.0)
Toxemia in pregnancy, n (%)	313 (13.3)	116 (20.1)	759 (15.6)
Gestational diabetes in pregnancy, n (%)	2350 (99.5)	577 (100.0)	4860 (99.9)
Gestational week of maternal gestational diabetes, median (IQR)[d]	24.3 (15.1-27.4)	16.3 (13.7-21.3)	25.7 (17.0-29.3)
Essential hypertension in pregnancy, n (%)	33 (1.4)	19 (3.3)	64 (1.3)
Gestational hypertension in pregnancy, n (%)	152 (6.4)	66 (11.4)	408 (8.4)
Preeclampsia in pregnancy, n (%)	91 (3.9)	29 (5.0)	187 (3.8)
Other characteristics			

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Characteristic	Metformin (n=2361)	Combination treatment (n=577)	Insulin (n=4865)
Dispensation of antidiabetic medications within 3 months before the beginning of pregnancy, n (%)[c]			
No pre-pregnancy pharmacological antidiabetic treatment	2312 (97.9)	571 (99.0)	4828 (99.2)
Pre-pregnancy metformin only	49 (2.1)	6 (1.0)	34 (0.7)
Other	3 (0.0)	0 (0.0)	3 (0.1)
Gestational week of initiating the pharmacological antidiabetic treatment			
Gestational week of initiating the pharmacological antidiabetic treatment, median (IQR)	30.7 (26.4-33.3)	22.9 (19.0-28.1)	31.4 (27.1-34.0)
Persistence of diabetes in the mother after birth, n (%)			
Yes	14 (0.6)	18 (3.1)	43 (0.9)
No	2347 (99.4)	559 (96.9)	4822 (99.1)
Dispensed cumulative dose of metformin during pregnancy (DDDs)			
Dispensed cumulative dose of metformin during pregnancy (DDDs), median (IQR)	50.0 (25.0-75.0)	75.0 (50.0-120.0)	0.0 (0.0-0.0)

Abbreviations: BMI, body mass index; IQR, interquartile range; PCOS, polycystic ovary syndrome

[a] Information missing for 3 children in the insulin group (0.06%).

[b] The three hospital regions with the largest total number of study subjects are presented; counts from the other 18 regions are pooled

[c] Information missing for 27 children in the metformin group (1.14%), 6 children in the combination group (1.04%), and 97 children in the insulin group (1.99%).

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Characteristic	Metformin (n=2361)	Combination treatment (n=577)	Insulin (n=4865)

[d] Information missing for 16 children in the metformin group (0.68%), 1 child in the combination group (0.17%), and 39 children in the insulin group (0.80%).

[e] Subject counts for two most frequent categories are presented. Counts for other six combinations of pre-pregnancy use of metformin, insulin, and other antidiabetic medications than metformin and insulin, are pooled

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Supplemental Table S6. Association between exposure to metformin in pregnancy (compared to exposure to only insulin) and risk of obesity, hypoglycaemia, hyperglycaemia, diabetes, hypertension, PCOS, and challenges in motor-social development in the subcohort for maternal gestational diabetes

Outcome[a]	IPTW-weighted HR (95% CI)[b,c]	
	Metformin vs. Insulin	Combination treatment vs. Insulin
Obesity	1.52 (0.93-2.48)	1.78 (0.53-5.94)
Hypoglycaemia	0.76 (0.37-1.57)	4.98 (1.28-19.35)
Hyperglycaemia	1.66 (0.63-4.40)	Not estimable[d]
Diabetes mellitus	1.19 (0.30-4.79)	Not estimable[d]
Challenges in motor-social development	1.07 (0.81-1.42)	1.79 (0.55-5.87)

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PCOS, polycystic ovary syndrome

[a] No events of the primary long-term outcomes hypertension and PCOS were observed in the metformin or combination treatment groups

[b] Metformin and combination treatment were analysed separately, in pairwise comparisons with insulin (reference in all analyses)

[c] The subcohort for maternal gestational diabetes consisted of children of mothers with gestational diabetes who were analysed to study the effect of the timing of metformin/insulin initiation during pregnancy

[d] The effect of exposure could not be estimated (model could not be fitted, or the estimate did not converge)

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Supplemental Table S7. Association between exposure to metformin in pregnancy and risk of obesity, hypoglycaemia, hyperglycaemia, diabetes, hypertension, PCOS, and challenges in motor-social development, requiring a least two prescriptions of the study drugs

Outcome[a]	**IPTW-weighted HR (95% CI)**[b]	
	Metformin vs. Insulin	**Combination treatment vs. Insulin**
Obesity	0.77 (0.52-1.16)	0.89 (0.38-2.10)
Hypoglycaemia	1.34 (0.56-3.24)	1.62 (0.66-3.99)
Hyperglycaemia	1.54 (0.71-3.33)	1.97 (0.36-10.87)
Diabetes mellitus	3.15 (0.75-13.27)	Not estimable[c]
Challenges in motor-social development	1.22 (0.94-1.58)	2.09 (1.21-3.61)

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PCOS, polycystic ovary syndrome

[a] No events of the primary long-term outcomes hypertension and PCOS were observed in the metformin or combination treatment groups

[b] Metformin and combination treatment were analysed separately, in pairwise comparisons with insulin (reference in all analyses)

[c] The effect of exposure could not be estimated (model could not be fitted, or the estimate did not converge).

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