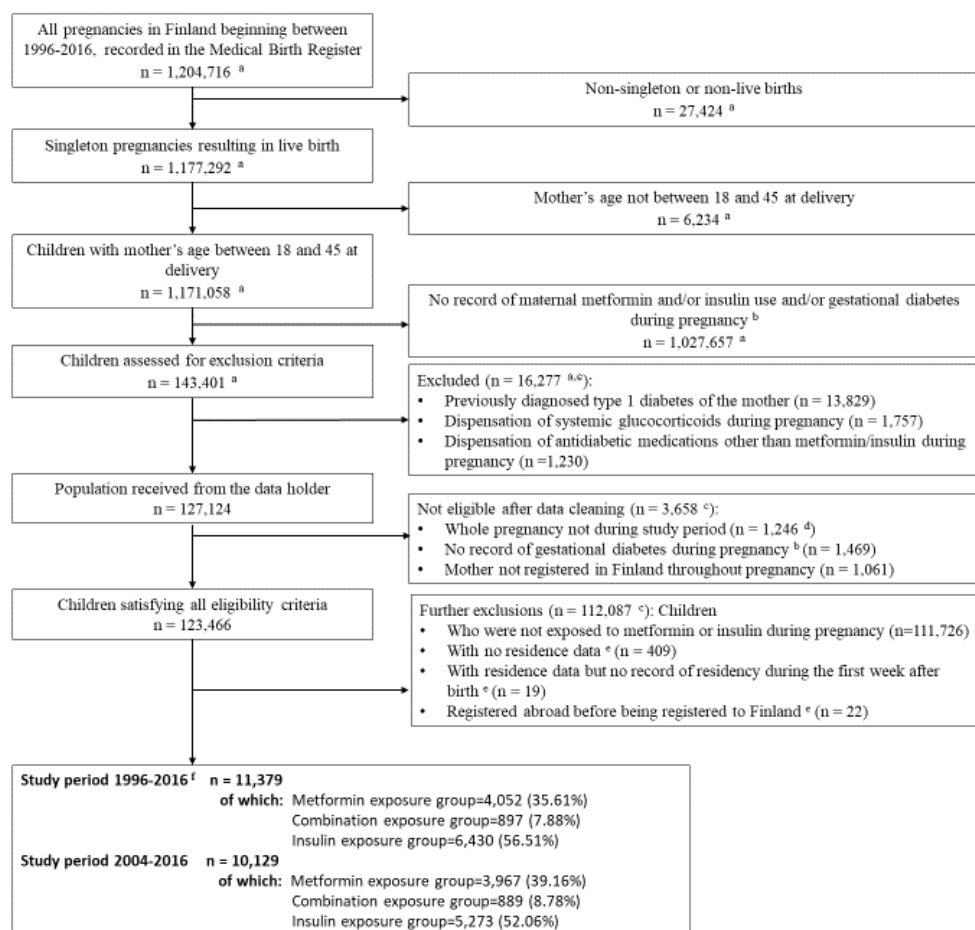


Supplementary files

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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.

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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) A10BB A10BC A10BD A10BF A10BG	Biguanides Sulfonylureas Sulfonamides (heterocyclic) Combinations of oral blood glucose lowering drugs Alpha glucosidase inhibitors 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

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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	-		

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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 \geq	R73	Elevated blood glucose level	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9 ^a	ICPC-2	ICPC-2 (description)
	11.1 mmol/l, or HbA1c \geq 48 mmol/mol (or \geq 6.5%), or plasma glucose \geq 11.1 mmol/l, as recorded in the regional laboratory databases					
Hypertension	At least one record of a diagnosis code for hypertension 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-	-	-	-

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Outcome	Outcome (definition)	ICD-10	ICD-10 (description)	ICD-9 ^a	ICPC-2	ICPC-2 (description)
anomalies -			deficiency syndrome			
Congenital		E00.1	Congenital iodine-	-	-	-
hypothyroidism			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 ^c	Birth weight (g) recorded in the Medical Birth Register two standard deviations above the gestational age and sex-specific reference mean in Finland	-	-	-	-	-
SGA ^c	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 E16.10 ^c E16.11 ^c E16.17 ^c E16.19 ^c E16.2 P70.0	Other hypoglycaemia Hyperinsulinism Hyperinsulinism NOS Functional non-hyperinsulinaemic hypoglycaemia Other specified hypoglycaemia Hypoglycaemia, unspecified Syndrome of infant of mother with gestational diabetes	- - - - - - -	T87 - - - - T87 - -	Hypoglycaemia - - - - Hypoglycaemia - -

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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 $\geq 6.5\%$), 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/m ²) 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;	W81	Toxaemia of pregnancy
		Mild preeclampsia		
Persistence of diabetes in the mother after birth	E10-E14	Diabetes mellitus, excluding type 1 diabetes	F83	Retinopathy
	excluding E11	mellitus	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.

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.

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)

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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/m²), 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 (%)^e			
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 (DDD)			
Dispensed cumulative dose of metformin during pregnancy (DDD), 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	Combination treatment	Insulin
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	(n=2361)	(n=577)	(n=4865)
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^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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Supplementary file

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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