Non-Interventional Study Protocol

Study Protocol Number	Merck study number: MS200084_0011 EPID Research: ER-9550
Title	Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study
Protocol Date/Version	15 May 2017/ Version 1.0
Replaces Version	*Not applicable*
EU PAS register number	Study not yet registered, to be registered with EU PAS
Active substance	Metformin (A10BA02), as part of Blood Glucose lowering drugs, excl. insulins (A10B)
Medicinal product	Metformin, all single substance products with ATC code A10BA02
Product reference as per MAH	EMR200084
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
MAH contact persons	Dr. Kerstin Brand, GMA, Merck KGaA, Darmstadt, Germany (Medical)
Joint PASS	No

Research question and objectives

The aim of this study is to investigate the long-term and immediate effects of exposure to metformin in utero among the children of all pregnant women treated with metformin, regardless of the purpose of the use. The long-term effects include diagnoses of obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, and polycystic ovary syndrome (PCOS) (girls only), diagnoses related to challenges in motor-social development, and growth outcomes, all from the age of one week and for as long as data are available. In addition, immediate effects of exposure to metformin in utero will be investigated, including growth outcomes at birth, preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia at birth, and major congenital anomalies.

The long-term effects described above in the children of women pregnant from 1996 onwards and treated during their pregnancy with metformin only, or with a combination of insulin and metformin (subsequently or in parallel), will be compared to the children of women treated during their pregnancy with insulin only. Additionally, and making use of the availability of gestational diabetes mellitus (GDM) diagnosis data from 2004 onwards, a cohort of children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment (thus presumably hyperglycaemic, but treated with dietary recommendations only) will be added for comparison.

Primary objective:

- To estimate longitudinally the prevalence, incidence and risk of diagnoses (obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development) from the age of one week for as long as data are available in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

Secondary objectives:

- A) To estimate immediate effects at birth in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only, relating to:
  1 Prevalence and risk of abnormal growth outcomes (large for gestational age, small for gestational age).
  2 Differences in continuous growth outcomes (weight, length, ponderal index, head circumference).
  3 Prevalence and risk of preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia.
  4 Prevalence and risk of major congenital anomalies recorded by the age of one year.
- B) To estimate long-term growth-related effects longitudinally in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only, relating to:
  1 The frequency and risk of abnormal growth outcomes (overweight, high ponderal index)
  2 Longitudinal estimation of the differences in continuous growth outcomes (body mass index, ponderal index)

Country of study

Finland

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Confidential
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2 List of abbreviations

ATC	Anatomical Therapeutic Chemical
AvoHILMO	Register of Primary Health Care Visits (Finland)
BMI	Body mass index
CI	Confidence interval
DDD	Defined Daily Dose
DPP	Drugs and Pregnancy Project
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS register	European Union electronic Register of Post-Authorisation Studies.
FIN	Finland
GDM	Gestational diabetes mellitus
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HbA1c	Glycohaemoglobin
HILMO	Care Register for Health Care (secondary care, Finland)
HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th revision
ICPC-2	International Classification of Primary Care, 2nd revision
LGA	Large for gestational age
LMP	Last menstrual period
MAH	Marketing Authorisation Holder
OGTT	Oral glucose tolerance test
OR	Odds ratio
PCOS	Polycystic ovary syndrome
PGDM	Pre-gestational diabetes mellitus
PIN	Personal identification number
SAP	Statistical analysis plan
SD	Standard deviation
SGA	Small for gestational age
SID	Study identification number
SII	Social Insurance Institute (Finland)
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
THL	National Institute for Health and Welfare (Finland)

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4 Abstract

Title	Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study Protocol date: 15 May 2017/ Version 1.0 Protocol authors: Katja Hakkarainen, Rosa Juuti, Anna Lundin, Juha Mehtälä, and Pasi Korhonen; EPID Research
Rationale and background	Metformin is used during pregnancy outside of the approved metformin indications to treat hyperglycaemia in gestational diabetes mellitus (GDM) and pre-gestational diabetes (PGDM), and to treat the polycystic ovary syndrome (PCOS). GDM is defined as impaired glucose tolerance resulting in hyperglycaemia, present for the first time during pregnancy. PGDM refers to type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) existing prior to conception. PCOS is a disease characterised by morphologically polycystic ovaries shown in ultrasound, causing oligomenorrhea, anovulation and hyperandrogenism. Despite the use of metformin during pregnancy in these three conditions, the long-term effects of metformin exposure in utero have not been widely studied in the children beyond two years of age. Evidence on the effects of in utero metformin exposure beyond the age of two years is of major interest, as metformin crosses the placenta and might therefore have long-term effect on the children. Using population-level data from Finland, this study will provide information on these long-term effects among children of women who used metformin during pregnancy.
Research question and objectives	The aim of this study is to investigate the long-term and immediate effects of exposure to metformin in utero among the children of all pregnant women treated with metformin, regardless of the purpose of the use. The long-term effects include diagnoses of obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, and PCOS (girls only), diagnoses related to challenges in motor-social development, and growth-related outcomes, all from the age of one week for as long as data are available. In addition, immediate effects of exposure to metformin in utero will be investigated, including growth outcomes at birth, preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia at birth, and major congenital anomalies. The long-term effects described above in the children of women pregnant from 1996 onwards and treated during their pregnancy with metformin only, or with a combination of insulin and metformin, will be compared to the children of pregnant women treated during their pregnancy with insulin only. Additionally, and making use of the

	availability of GDM diagnosis data from 2004 onwards, a cohort of children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment (thus presumably hyperglycaemic, but treated with dietary recommendations only) will be added for comparison. Primary objective: ● To estimate longitudinally the prevalence, incidence and risk of diagnoses (obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development) from the age of one week for as long as data are available in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only. Secondary objectives: ● A) To estimate immediate effects at birth in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only, relating to: 1 Prevalence and risk of abnormal growth outcomes (large for gestational age, small for gestational age). 2 Differences in continuous growth outcomes (weight, length, ponderal index, head circumference). 3 Prevalence and risk of preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia. 4 Prevalence and risk of major congenital anomalies recorded by the age of one year. ● B) To estimate long-term growth-related effects longitudinally in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only, relating to: 1 The prevalence, incidence and risk of abnormal growth outcomes (overweight, high ponderal index). 2 Longitudinal estimation of the differences in continuous growth outcomes (body mass index (BMI), ponderal index).
Study Design	This is a retrospective cohort study based on population-based register data from Finland. The children born to women with the most common

	antihyperglycemic treatments (insulin and metformin) will be compared based on in utero drug exposures. Children with in utero exposure to metformin only, children with in utero exposure to both metformin and insulin (subsequently or in combination), and children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment will be compared to children with in utero exposure to insulin only. The children born to the included women in 1996-2016 will be followed, starting from date of birth of the children. The children will be followed until the end of the study period (2016), death, or migration abroad, whichever occurs first. The maximum follow-up period for the primary outcomes (long-term diagnoses) is up to the age of 20 years, and for secondary outcomes (long-term growth-related effects) up to the age of 16 years. The maximum follow-up periods originate from the availability of data in the data sources.
Population	The study population of the children will be assembled using the following criteria relative to the mothers. Inclusion criteria: 1 Singleton pregnancy resulting in live birth. 2 Record of GDM during the pregnancy and / or dispensation of metformin and/or insulin during the pregnancy. 3 Age between 18 and 45 years at delivery. 4 Registered in Finland throughout the pregnancy. Exclusion criteria: 1 Previously diagnosed or post-partum T1DM. 2 Dispensation of systemic glucocorticoids known to interfere with metformin or insulin during pregnancy. 3 Dispensation of antidiabetic medications other than metformin or insulin during pregnancy. The study population will consist of the children of women fulfilling all of the inclusion criteria and none of the exclusion criteria.
Variables	***Outcomes*** The primary outcomes (long-term diagnoses) in the children will be collected from the age of one week until the end of follow-up (data available up to the age of 20 years), including the following diagnoses: obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development. Of these binary long-term effects, diabetes mellitus, PCOS, and diagnoses related to challenges in motor-social development are considered permanent, while obesity, hypoglycaemia, hyperglycaemia, and hypertension are considered temporary. As part of the secondary outcomes, immediate effects in the children

	will be collected and analysed at birth: growth outcomes (weight, length, ponderal index, head circumference, large for gestational age, small for gestational age), preterm birth, perinatal mortality, hypoglycaemia, and hyperglycaemia. Moreover, major congenital anomalies recorded by the age of one year will be included as part of the immediate effects. Long-term growth-related outcomes in the children (overweight, high ponderal index, BMI, ponderal index) will also be observed as part of secondary outcomes, from the age of one week until the end of follow-up (data available up to 16 years). Of the long-term growth-related outcomes, overweight, high ponderal index are binary and they are considered temporary. ***Covariates*** The following covariates will be considered in the analyses: pregnancy-related variables (age at conception, parity, type of delivery), maternal comorbidities during pregnancy (previously diagnosed T2DM, essential hypertension, PCOS, obesity, gestational hypertension, preeclampsia, GDM), mother's demographic factors (civil status, educational level), characteristics of the children at birth (sex, gestational age at birth, Apgar score, umbilical artery pH), and other variables of interest (maternal smoking, dispensation of antidiabetic medications within three months before the pregnancy, calendar year of child birth). In addition, the potential association between the following covariates and the outcomes will be assessed: gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative defined daily doses of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant).
Data Sources	The study database will be constructed from the following Finnish registers: Prescription register, Medical Birth Register, Register of Congenital Malformations, Care Register for Health Care (HILMO; secondary care), Register of Primary Health Care Visits (AvoHILMO), Population Register Centre, Statistics Finland, and regional laboratory databases.
Study Size	The study size was evaluated based on a prior feasibility assessment. During the study period (1996-2016), the estimated number of children in each study cohort was ● 4,301 children with in utero exposure to metformin only ● 1,416 children with in utero exposure to a combination of metformin and insulin (subsequently or in combination) ● 15,754 children with in utero exposure to insulin only (reference group)

	● In total 21,471 children. Power calculations were performed for primary outcomes (diagnoses), with a two-sided type 1 error probability of 5%. Based on power calculations for logistic regression analyses, comparing metformin exposed children to insulin exposed children, an odds ratio (OR) of 1.5 can be detected with approximately 100% power, if 3% of the population has an outcome at any time during the follow-up, considering the entire population in the analyses. When analyses are conducted at specific ages, the power decreases with an increasing age of the children, because the total number of the children as well as the proportion of the children with in utero metformin exposure are lower for older individuals (children born earlier). At the follow-up age of seven years, an OR of 1.5 can be detected with 89% power if 5% of the population has an outcome. At the follow-up age of 10 years, an OR of 1.7 can be detected with 83% power only if a larger proportion of the population, 7%, has an outcome. At later ages, the power is inadequate (<80%) for detecting an OR of 1.5 or 1.7, with the estimated population sizes and population proportions with an outcome. Based on power calculations for Cox regression analyses, with average follow-up time estimated to five years, a hazard ratio (HR) of 1.5 can be detected with adequate power (≥80%) if 5% of the population has an outcome by the end of follow-up. If a smaller proportion, 3%, of the population has an outcome, an HR of 1.7 can be detected with adequate power.
Data Analysis	In the analyses of children born from 1996 onwards, the analysis population will consist of three cohorts: children with in utero exposure to metformin only, children with in utero exposure to a combination of metformin and insulin (subsequently or in combination), and children with in utero exposure to insulin only. In analyses of children born from 2004 onwards, the analysis population will have an additional fourth cohort: children of women with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment. In all regression analyses, the children with in utero exposure to insulin only will be considered as the reference group. The population baseline characteristics will be reported descriptively. For the primary objectives, the prevalence and incidence of children having a long-term diagnosis listed as an outcome will be estimated with 95% confidence interval (CI) separately within each study cohort by exposure status and in the total population. For outcomes considered permanent, the prevalence will be counted among children who are still followed-up when reaching a given age (separately for 0, 1, 2, …, 20 years) and the prevalent cases are those who have ever been diagnosed between birth and the given age. The

<table>
<tr><td></td><td>number of new cases between each yearly age period (yearly incidence) will also be reported together with the proportion counted among those who were at risk (in follow-up without the diagnosis) at the beginning of each specific age period. The cumulative risk of permanent outcomes will also be characterised using the Kaplan-Meier estimator.

For primary outcomes considered temporary, the cases between each yearly age period (yearly incidence) will be reported as the number and proportion among those who were at risk (followed-up) at the beginning of each age period. For temporary outcomes, cases will be counted if a child had a recorded diagnosis within the yearly age period regardless of diagnoses recorded prior to that age period.

As formal main analyses, the risk of each permanent and temporary long-term effect will be investigated as a time-to-event variable where the start time is at birth. For permanent outcomes the event time will be the first indication of the given long-term diagnosis. For temporary outcomes, multiple event times will be allowed per child and in the analyses temporal and within subject correlations will be considered. In the analyses, three different Cox proportional hazards models will be used: unadjusted, adjusted, and adjusted using also propensity scores.

As formal subsidiary analyses, the yearly prevalence of each permanent long-term effect will be compared as a binary outcome (each year separately) using three different logistic regression models: unadjusted, adjusted, and adjusted using also propensity scores. Furthermore, the yearly incidences of each permanent and temporary outcome will be compared as a binary outcome i) using all years together as a repeated binary outcome and ii) using each yearly variable as a separate outcome. Three different logistic regression models will be considered (unadjusted, adjusted, and adjusted using also propensity scores) and in case i) temporal and within subject correlations will be considered.

For the secondary objectives, similar analyses will be conducted as for the primary objectives, considering the nature of the outcome (binary, continuous) and whether the outcomes are immediate at birth (secondary objectives A) or long-term (secondary objectives B). For continuous outcomes, linear regression analyses will be conducted.

In all regression analyses, the children with in utero exposure to insulin only will be considered as the reference group.

For all objectives, also subgroup and sensitivity analyses will be performed.</td></tr>
<tr><td>Milestones</td><td>
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<tr><th>Milestone</th><th>Planned date</th></tr>
<tr><td>Registration of the study in the EU PAS register</td><td>Q2 2017</td></tr>
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	Start of data permit process	Q2 2017
	End of data permit process	Q2 2018
	Start of data collection[a]	Q2 2018
	End of data collection[b]	Q4 2018
	Start of study reporting process	Q4 2018
	Final report of study results	Q4 2018
	Registration of the study results in the EU PAS register	Q4 2018
	Start of scientific reporting process[c]	Q1 2019

EU PAS register = European Union electronic Register of Post-Authorisation Studies; GVP = good pharmacovigilance practice; MAH = marketing authorisation holder.
[a] In the case of secondary use of data, the date from which data extraction starts (GVP Module VIII).
[b] The date from which the analytical dataset is completely available (GVP Module VIII).
[c] Publication process being the responsibility of the MAH.

5 Amendments and updates

None

6 Milestones

Milestone	Planned date
Registration of the study in the EU PAS register	Q2 2017
Start of data permit process	Q2 2017
End of data permit process	Q2 2018
Start of data collection[a]	Q2 2018
End of data collection[b]	Q4 2018
Start of study reporting process	Q4 2018
Final report of study results	Q4 2018
Registration of the study results in the EU PAS register	Q4 2018
Start of scientific reporting process[c]	Q1 2019

EU PAS register = European Union electronic Register of Post-Authorisation Studies; GVP = good pharmacovigilance practice.
[a] In the case of secondary use of data, the date from which data extraction starts (GVP Module VIII); MAH = marketing authorisation holder.
[b] The date from which the analytical dataset is completely available (GVP Module VIII).
[c] Publication process being the responsibility of the MAH.

7 Rationale and background

7.1 Metformin

Metformin is a biguanide used as a first-line oral therapy for the treatment of type 2 diabetes mellitus (T2DM) [1,2]. The widespread use of metformin in diabetes regimens is partly due to the vast experience of metformin use in this group of patients but also because metformin is generally well-tolerated [3]. Metformin promotes reduced glucose production by the liver through mitochondrial inhibition [4,5]. In addition, metformin has also been implicated in inhibition of glucose production by hepatocytes, by acting through other factors involving the cellular energy homeostasis [4,6].

7.2 Use of metformin during pregnancy

During pregnancy, metformin is used outside of the approved metformin indications to treat hyperglycaemia in gestational diabetes mellitus (GDM) and pre-gestational diabetes (PGDM), and to treat the polycystic ovary syndrome (PCOS). PGDM refers to type 1 diabetes mellitus (T1DM) or T2DM existing prior to conception [7].

7.2.1 Gestational diabetes mellitus

GDM is defined as impaired glucose tolerance resulting in hyperglycaemia, present for the first time during pregnancy [8]. Of all types of diabetes, GDM accounts for approximately 90–95% of all cases of hyperglycaemia in pregnancy [9]. The first-line approach to managing GDM is diet and exercise counselling. Life-style counselling is normally a sufficient treatment in women with milder forms of gestational hyperglycaemia [10]. If normoglycaemia is not attained solely with this approach, medication will be started.

Until recently, insulin has been the only approved and recommended treatment for managing GDM [10]. Firstly, insulin is unlikely to cross the placenta, thus minimising potential impact on the foetus [11–13]. Secondly, during pregnancy, natural metabolic changes in the mother occur leading to a decreased insulin sensitivity, especially in the later stages of pregnancy [14], as well as an increased glomerular filtration in the kidneys [15]. Due to this metabolic adaptation, individual insulin dosing could more easily sustain appropriate blood glucose levels, when compared to oral antidiabetics. This is mainly due to the varying levels of insulin resistance in the mothers and the requirement of individual dose adjustments for oral antidiabetics mainly eliminated through the kidneys, such as metformin [16].

Metformin has been used on single case basis since the 1970s, but has increasingly been studied in recent years as a treatment option for GDM, as it has some advantages over insulin: not inducing hypoglycaemia, causing less weight gain than insulin (in both mother and child) and being simpler to use (insulin injections vs. oral metformin). However, in contrast to insulin, metformin crosses the placenta and may thus have immediate and long-term effects on the child [17]. Metformin has been observed to be effective in achieving normoglycaemia, especially in women with no or little overweight and who develop GDM late in gestation. Women with considerable overweight, high fasting blood glucose levels and in early need for medication

might nevertheless not reach and hold normoglycemia during pregnancy with metformin alone, thus leading to the need to add or replace with insulin [10].

7.2.2 Pre-gestational diabetes mellitus

PGDM is a chronic disease and therefore requires continuous treatment throughout life, also during pregnancy [7]. For treating PGDM, both insulin and metformin have been options of standard care [7] as per clinical guidelines.

7.2.3 Polycystic ovary syndrome

In addition to PGDM and GDM, PCOS can cause metabolic syndrome-like symptoms during pregnancy [18]. PCOS is a disease characterised by morphologically polycystic ovaries shown in ultrasound, causing oligomenorrhea, anovulation and hyperandrogenism [19]. PCOS is also increasingly treated with metformin, to improve conception and continued in the first trimester or even throughout pregnancy to prevent early miscarriages and the development of GDM [19–21].

7.3 Effects of the conditions, and their treatment, on the child

GDM, PGDM and PCOS have various effects on the child, both immediately and long-term [22–25]. The most important immediate effects include e.g. foetal macrosomia that results from the foetus reacting to the high maternal blood glucose levels. The adverse pregnancy outcomes are mostly related to the newborn being large for gestational age (LGA) or presenting an excess of adiposity, and the antidiabetic treatment is mainly targeted to prevent these [8,10,26]. However, the extent to which these effects are the result of the particular conditions or other concomitant factors and disorders, e.g. maternal obesity, is still unclear [22].

When studying the effects of antidiabetic medication on the child, perinatal complications, growth, body composition and neurodevelopmental findings have been of particular interest. Metformin, alone or with supplemental insulin, has not been associated with higher risk of a composite of perinatal complications [17,27,28]. Quite in contrast, metformin is considered more beneficial than insulin with regard to macrosomia and LGA birth, neonatal hypoglycemia and NICO admission risk [29]. However, Rowan et al. (2008) reported preterm birth to be more frequent in the metformin group, compared to mothers using insulin [17]. Tertti et al. (2008) reported similar findings with higher rates of less severe hypoglycaemia in the insulin group compared to the metformin group [30].

When following the development of children after birth, Glueck et al. (2004) reported that metformin exposure in utero did not affect weight, height, growth or motor-social development in the first 18 months of life in children of PCOS patients [31]. In contrast, studies by two independent research groups reported that exposure to metformin in utero increases the child's weight significantly, compared to exposure to insulin [32,33]. In one of the two studies, children in the metformin group were heavier at the age of one year, while height was not measured [33]. In the other study, children in the metformin group were heavier at 12 months as well as both taller and heavier at the age of 18 months compared to the insulin group [32]. In two separate studies investigating the possible effect on children's neurodevelopmental at the age of 18

months and two years, respectively, no differences were detected between those whose mothers were treated with metformin or insulin during pregnancy [32,34].

Studies on the effects of GDM on the child have mainly been investigating the different treatment alternatives, namely, diet only, metformin, insulin or a combination of these [10,17,23,32,35–37]. Thus, this information can be deemed to apply somewhat also to PGDM and PCOS patients. The studies have focused on the effects during the pregnancy and at birth [10,17], as well as on mid-term effects on the child, mostly up to two years of age [23,32,35–37]. Evidence on the effects of in utero metformin exposure beyond the age of two years is of major interest, as metformin crosses the placenta and might therefore have long-term effect on the children. Hence, this is an area that requires further investigation, which is the goal of this observational study.

8 Research question and objectives

The aim of this study is to investigate the long-term and immediate effects of exposure to metformin in utero among the children of all pregnant women treated with metformin, regardless of the purpose of the use. The long-term effects include diagnoses of obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, and PCOS (girls only), diagnoses related to challenges in motor-social development, and growth outcomes, all from the age of one week for as long as data are available. In addition, immediate effects of exposure to metformin in utero will be investigated, including growth outcomes at birth, preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia at birth, and major congenital anomalies.

To address this research question, incidence and prevalence of the above described potential effects in the children of women pregnant from 1996 onwards and treated during their pregnancy with metformin only, or with a combination of insulin and metformin, will be compared to the children of pregnant women treated during their pregnancy with insulin only. Additionally, and making use of the availability of GDM diagnosis data from 2004 onwards, a cohort of children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment (thus presumably hyperglycaemic, but treated with dietary recommendations only) will be added for comparison.

8.1 Primary objective: Long term diagnoses

To estimate longitudinally the prevalence, incidence and risk of diagnoses (obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development) from the age of one week and for as long as the data are available in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

8.2 Secondary objectives

8.2.1 Secondary objectives A: Immediate effects

1. To estimate the prevalence and risk of abnormal growth outcomes (LGA, small for gestational age (SGA)) at birth in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

2. To estimate differences in continuous growth outcomes (weight, length, ponderal index, head circumference) at birth in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

3. To estimate the prevalence and risk of preterm birth, perinatal mortality, hypoglycaemia and hyperglycaemia at birth in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

4. To estimate the prevalence and risk of major congenital anomalies recorded by the age of one year in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

8.2.2 Secondary objectives B: Long-term growth-related effects

1. To estimate longitudinally the prevalence, incidence and risk of abnormal growth outcomes (overweight, high ponderal index) from the age of one week and for as long as the data are available in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

2. To estimate longitudinally the difference in continuous growth outcomes (body mass index (BMI), ponderal index) from the age of one week and for as long as the data are available in children with in utero exposure to metformin only, in children with in utero exposure to a combination of metformin and insulin, and in children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, as compared to children exposed in utero to insulin only.

8.3 Exploratory objectives

1. To characterise the relationship of drug treatment, in terms of gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative defined daily dose (DDD) of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant), with long-term diagnoses in the children (as set in the primary objective).

2. To characterise the relationship of drug treatment, in terms of gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative DDD of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant), with immediate effects at birth (as set in secondary objectives A).

3. To characterise the relationship of drug treatment, in terms of gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative DDD of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant), with long-term growth-related effects (as set in secondary objectives B).

9 Research methods

9.1 Study design

9.1.1 Design overview

This is a retrospective cohort study based on population-based register data from Finland. The children born to women with the most common antihyperglycaemic treatments (insulin and metformin) will be compared based on in utero drug exposures. Children with in utero exposure to metformin only, children with in utero exposure to both metformin and insulin (subsequently or in combination), and children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment will be compared to children with in utero exposure to insulin only. The availability of a unique personal identification number (PIN) in Finland enables linking data from different registers and obtaining data on all pregnant women, all medications dispensed during pregnancy, and data on the children they gave birth to.

Data from the children born to the included women in 1996-2016 will be collected, starting from date of birth of the child (Figure 1). The children will be followed until the end of the study period (2016), death, or migration abroad, whichever occurs first. The maximum follow-up period for the primary outcomes (long-term diagnoses) is up to the age of 20 years, and for secondary outcomes (long-term growth-related effects) up to the age of 16 years. The maximum follow-up periods originate from the availability of data in the data sources (see 9.2.3 Study period and 9.4 Data source).

The primary outcomes (long-term diagnoses) in the children will be collected from the age of one week until the end of follow-up (data available up to the age of 20 years), including the following diagnoses: obesity, hypoglycaemia, hyperglycaemia, hypertension, diabetes mellitus, PCOS (girls only), and diagnoses related to challenges in motor-social development.

As part of the secondary outcomes, immediate effects in the children will be collected and analysed at birth: growth outcomes (weight, length, ponderal index, head circumference, large for gestational age, small for gestational age), preterm birth (delivery before 37 gestational weeks), perinatal mortality, hypoglycaemia, and hyperglycaemia. Moreover, major congenital anomalies recorded by the age of one year will be included as part of the immediate effects.

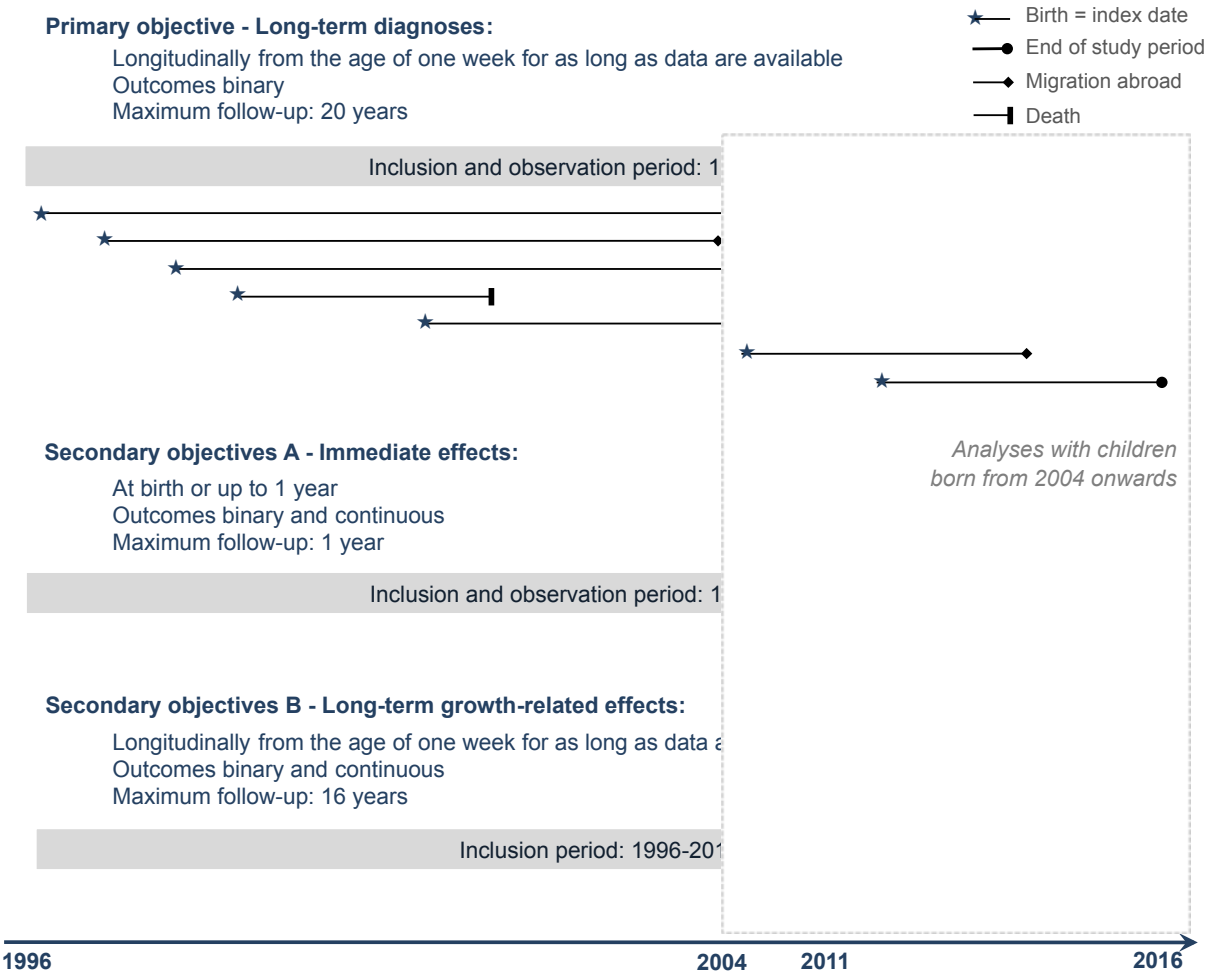


Figure 1. Study design and periods, with examples for the primary objective.

Long-term growth-related effects in the children (overweight, high ponderal index, BMI, ponderal index) will also be observed as part of secondary outcomes, from the age of one week until the end of follow-up (data available up to 16 years). However, as observation data on

growth are available from 2011 onwards (see 9.4), the maximum follow-up from the age of one week onwards is six years (from 2011-2016).

In analyses with children born from 1996 onwards with in utero exposure to metformin only, or to both metformin and insulin (subsequently or in combination) will be compared to children with in utero exposure to insulin only (see 9.2.2 Definition of study cohorts and description of treatments). In analyses including exclusively children born from 2004 onwards (Figure 1), a fourth cohort is added: children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment (due to the availability of GDM diagnosis from 2004 onwards, see 9.4). In these analyses, children with in utero exposure to metformin only, or children with in utero exposure to a combination of metformin and insulin or children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment will be compared to children exposed in utero to insulin only.

9.1.2 Outcomes

The study outcomes corresponding to the study objectives are summarised in Table 1. The primary outcomes are the long-term diagnoses collected from the age of one week for as long as data are available (maximum follow-up period 20 years). The secondary outcomes include the immediate effects at birth and up to one year of age. The secondary outcomes also include long-term growth-related effects (maximum follow-up period 16 years).

In the outcome definitions, diagnoses (Appendix 1) will be defined using the Finnish adaptation of the International Classification of Diseases, 10th revision (ICD-10), codes recorded in the Care Register for Health Care Visits (HILMO), the Register of Primary Health Care Visits (AvoHILMO), the Medical Birth Register, and the Register of Congenital Malformations. In AvoHILMO, additionally the Finnish adaptation of the International Classification of Primary Care, 2nd revision (ICPC-2) will be used for diagnoses.

9.1.2.1 Primary outcomes: Long-term diagnoses

The primary outcomes will be collected from the age of one week for as long as data are available:

- Obesity: at least one record of a diagnosis code for obesity (Appendix 1) in the Care Register for Health Care Visits (HILMO) or the Register of Primary Health Care Visits (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 [38] (BMI available only from 2011 onwards).

- Hypoglycaemia: at least one record of a diagnosis code for hypoglycaemia (Appendix 1) in HILMO or AvoHILMO, or plasma glucose < 2.9 mmol/l as recorded in the regional laboratory databases.

Table 1. Outcomes per each objective.

Objectives	**Outcomes**
Primary (long-term diagnoses)	
Longitudinally the prevalence, incidence and risk of diagnoses from the age of one week for as long as data are available	Binary long-term effects (yes/no): obesity[a], hypoglycaemia[a], hyperglycaemia[a], hypertension[a], diabetes mellitus[b], PCOS[b] (girls only), diagnoses related to challenges in motor-social development[b]
Secondary	
A) Immediate effects	
1) Prevalence and risk of abnormal growth outcomes at birth	Binary immediate outcomes (yes/no[c]): large for gestational age, small for gestational age
2) Differences in continuous growth outcomes at birth	Continuous: weight, length, ponderal index, head circumference
3) Prevalence and risk of preterm birth, perinatal mortality, hypoglycaemia, and hyperglycaemia at birth	Binary immediate outcomes (yes/no): preterm birth, perinatal mortality, hypoglycaemia, hyperglycaemia
4) Prevalence and risk of major congenital anomalies recorded by the age of one year	Binary immediate outcomes (yes/no): major congenital anomalies, any and by type (major structural anomaly, chromosomal defect or congenital hypothyroidism)
B) Long-term growth-related effects	
1) Longitudinally the frequency and risk of abnormal growth outcomes from the age of one week for as long as data are available	Binary long-term outcomes (yes/no[c]): overweight[a], high ponderal index[a]
2) Longitudinally the differences in continuous growth outcomes from the age of one week for as long as data are available	Continuous: BMI, ponderal index
Exploratory	
1) Characteristics associated with long-term diagnoses, as set in the primary objective	As for primary objective
2) Characteristics associated with immediate effects, as set in secondary objectives A	As for secondary objectives A
3) Characteristics associated with long-term growth-related effects, as set in secondary objectives B	As for secondary objectives B

BMI = body mass index; PCOS = polycystic ovary syndrome.
[a] In the statistical analyses (see 9.7), considered as a temporary binary long-term effect.
[b] In the statistical analyses (see 9.7), considered as a permanent binary long-term effect.
[c] Dichotomised from available continuous outcomes.

- Hyperglycaemia: at least one record of a diagnosis code for hyperglycaemia (Appendix 1) in HILMO or AvoHILMO, or fasting plasma glucose ≥ 7.0 mmol/l, or 2h plasma glucose oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l, or HbA1c ≥ 48 mmol/mol (or ≥ 6.5%), or plasma glucose ≥11.1 mmol/l [39], as recorded in the regional laboratory databases.

- Hypertension: at least one record of a diagnosis code for hypertension (Appendix 1) in HILMO or AvoHILMO.

- Diabetes mellitus: at least one record of a diagnosis code for any diabetes, including T1DM or T2DM (Appendix 1), in HILMO or AvoHILMO.

- PCOS (girls only): at least one record of a diagnosis code for PCOS (Appendix 1) in HILMO or AvoHILMO.

- Diagnoses related to challenges in motor-social development: at least one record of a diagnosis code for challenges in motor-social development (Appendix 1) in HILMO or AvoHILMO.

9.1.2.2 Secondary outcomes A: Immediate effects

Among secondary outcomes, abnormal growth outcomes will be collected at birth:

- Large for gestational age: birth weight (g) recorded in the Medical Birth Register 2 standard deviations above the gestational age and sex-specific reference mean in Finland [40].

- Small for gestational age: birth weight (g) recorded in the Medical Birth Register 2 standard deviations below the gestational age and sex-specific reference mean in Finland [40].

Among secondary outcomes, continuous growth outcomes will be collected at birth:

- 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 recorded in the Medical Birth Register.

- Head circumference: head circumference (cm) at birth recorded in the Medical Birth Register.

Among secondary outcomes, preterm birth, perinatal mortality, hypoglycaemia, and hyperglycaemia will be collected at birth:

- Preterm birth: length of gestation (gestational age) less than 37 completed weeks, as recorded in the Medical Birth Register.

- 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.

- Hypoglycaemia: at least one record of a diagnosis code for hypoglycaemia (Appendix 1) 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.

- Hyperglycaemia: at least one record of a diagnosis code for hyperglycaemia (Appendix 1) in HILMO or AvoHILMO, or fasting plasma glucose ≥ 7.0 mmol/l, or 2h plasma glucose oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l, or HbA1c ≥ 48 mmol/mol (or ≥ 6.5%), or plasma glucose ≥11.1 mmol/l [39], as recorded in the regional laboratory databases, up to 28 days from birth.

Among secondary outcomes, major congenital anomalies recorded by the age of one year will be collected:

- Any major congenital anomalies (major structural anomaly, chromosomal defect or congenital hypothyroidism): at least one record of a diagnosis code for major congenital anomalies (Appendix 1) in the Register of Congenital Malformations.

- Major congenital anomalies by type:

    - Major structural anomaly: at least one record of a diagnosis code for major structural anomaly (Appendix 1) in the Register of Congenital Malformations.

    - Chromosomal defect: at least one record of a diagnosis code for chromosomal defects (Appendix 1) in the Register of Congenital Malformations.

    - Congenital hypothyroidism: at least one record of a diagnosis code for congenital hypothyroidism (Appendix 1) in the Register of Congenital Malformations.

9.1.2.3 Secondary outcomes B: Long-term growth-related effects

Among secondary outcomes, abnormal growth outcomes will be collected from the age of one week, or as early as growth data are available, for as long as data are available:

- 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 [38].

- High Ponderal index: Ponderal index (kg/m^3) recorded in AvoHILMO >10^{th} percentile considering the age and sex of the child.

Among secondary outcomes, continuous growth outcomes will be collected from the age of one week for as long as data are available:

- BMI: BMI (kg/m^2) recorded in AvoHILMO.
- Ponderal index: Ponderal index (kg/m^3) recorded in AvoHILMO.

9.1.2.4 Outcomes for exploratory objectives

For exploratory objectives, the outcomes are the same as for the primary and secondary outcomes.

9.2 Setting

The study population consists of children born to women during the study period from 1996 to 2016 in Finland. A description of the data sources, the national registers and regional databases, within Finland is provided in Section 9.4. The use of the national register data and the availability of the unique PIN in Finland enable the linkage of the databases from different registers and obtaining data on all pregnant women, all medications dispensed during pregnancy, and data on the children they gave birth to. The coverage of the national registers is full and thereby the study results will represent the general population of children exposed in utero to metformin and/or insulin or born from mothers diagnosed with GDM.

9.2.1 Study population

The study population of the children will be assembled using the following criteria relative to the mothers.

Inclusion criteria:

1. Singleton pregnancy resulting in live birth, recorded in the Medical Birth Register during the study inclusion period (1996-2016).
2. Record of GDM during the pregnancy, defined as a diagnosis of GDM (Appendix 1) recorded in the Medical Birth Register, HILMO or AvoHILMO, or a pathological OGTT in the Medical Birth Register, or dispensation of metformin and/or insulin (Appendix 2) recorded in the Prescription register during the pregnancy, i.e. on the first day of the last menstrual period (LMP) or any time after it until the date of delivery.
3. Age between 18 and 45 years at delivery, recorded in the Medical Birth Register.
4. Registered in Finland throughout the pregnancy, based on the region of residency recorded in the Population Register Centre.

Exclusion criteria:

1. Previously diagnosed T1DM recorded in the Medical Birth Register, or post-partum T1DM defined as at least one record of a diagnosis code for T1DM (Appendix 1) in HILMO or AvoHILMO registers after delivery.

2. Dispensation of systemic glucocorticoids (Appendix 2) known to interfere with metformin or insulin recorded in the Prescription register during pregnancy, i.e. on the first day of the LMP or any time after it until the date of delivery.

3. Dispensation of antidiabetic medications other than metformin or insulin (e.g. acarbose, thiazolidinediones, sulphonylureas, glinides, or glucagon-like peptide 1 (GLP-1) agonists, Appendix 2) recorded in the Prescription register during pregnancy, i.e. on the first day of the LMP or any time after it until the date of delivery.

The study population will consist of the children of women fulfilling all of the inclusion criteria and none of the exclusion criteria.

9.2.2 Definition of study cohorts and description of treatments

Children born from 1996 onwards will be divided into the following cohorts based on their in utero exposure to pharmacological antidiabetic treatment (Figure 2), as defined in 9.3.1:

1. Children with in utero exposure to metformin only

2. Children with in utero exposure to a combination of metformin and insulin (subsequently or in combination)

3. Children with in utero exposure to insulin only.

In addition, a fourth cohort is added for children born from 2004 onwards (Figure 2), as defined in 9.3.1:

4. Children of women with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment.

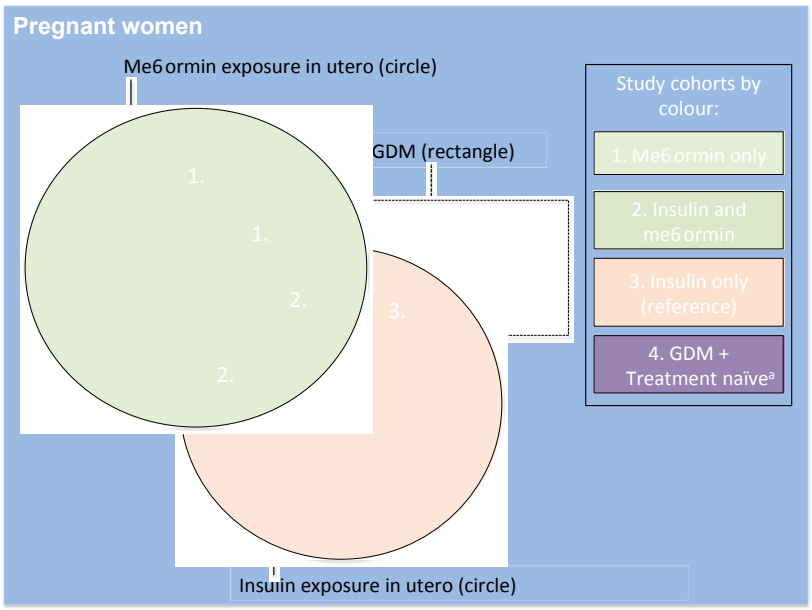


Figure 2. Study cohorts.
[a] Applied exclusively from 2004 onwards.
GDM = gestational diabetes mellitus

Table 2. Study periods per each objective.

Objective	Study periods	
	Analyses from 1996 onwards	**Analyses from 2004 onwards with the treatment naïve GDM cohort[a]**
Primary (long-term diagnoses)		
Prevalence, incidence and risk of diagnoses longitudinally from the age of one week for as long as data are available	Inclusion and observation 1996[b]-2016 Follow-up: maximum 20 years[d]	Inclusion and observation 2004[c]-2016 Follow-up: maximum 12 years[e]
Secondary		
A) Immediate effects		
1) Prevalence and risk of abnormal growth outcomes at birth	Inclusion and observation 1996[b]-2016 Follow-up: 1 year	Inclusion and observation 2004[c]-2016 Follow-up: 1 year
2) Differences in continuous growth outcomes by in utero exposure status at birth		
3) Prevalence and risk of preterm birth, perinatal mortality, hypoglycaemia, and hyperglycaemia at birth		
4) Prevalence and risk of major congenital anomalies recorded by the age of one year		
B) Long-term growth-related effects		
1) Longitudinally the frequency and risk of abnormal growth outcomes from the age of one week for as long as data are available	Inclusion 1996[b]-2016 and observation 2011[f]-2016 Follow-up: maximum 16 years[g]	Inclusion 2004[c]-2016 and observation 2011[f]-2016 Follow-up: maximum 12 years[g]
2) Longitudinally the differences in continuous growth outcomes from the age of one week for as long as data are available		
Exploratory		
1) Characteristics associated with long-term diagnoses, as set in the primary objective	As for primary objective	As for primary objective
2) Characteristics associated with immediate effects, as set in the secondary objectives A	As for secondary objectives A	As for secondary objectives A
3) Characteristics associated with long-term growth-related effects, as set in the secondary objectives B	As for secondary objectives B	As for secondary objectives B

GDM = gestational diabetes mellitus; ICD-10 = International Classification of Diseases, 10th revision.
[a] The treatment naïve GDM cohort: children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment.
[b] Since the availability of ICD-10 diagnosis codes in the Care Register for Health Care (HILMO).
[c] Since the availability GDM diagnosis in ICD-10 codes in the Medical Birth Register.
[d] The inclusion criteria are applied to women pregnant in 1996 onwards. Thus, the first children included are born in the second half of 1996 and their maximum follow-up is approximately 20.5 years.
[e] Children of women pregnant in 2004 onwards are included in these analyses. Thus, the first children included are born in the second half of 2004 and their maximum follow-up is approximately 12.5 years.
[f] Since the establishment the Register of Primary Health Care Visits (AvoHILMO), including growth data.
[g] Maximum follow-up from the age of one week onwards six years (from 2011 to 2016).

9.2.3 Study period

The children born to the included women in 1996-2016 will be followed, starting from date of birth of the children (Figure 1). The children's cohort entry date is their date of birth. Different study periods are applied for each of the objectives due to varying availability of the different data (see 9.4). The study periods are presented in Table 2 for each of the objectives. During each study period, the children will be followed until the end of the study period, death, or migration abroad, whichever occurs first. Different follow-up periods are available for each child. The maximum follow-up periods based on the availability of data in the data sources.

In the analyses with the fourth child cohort, children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment, the study period will start from 2004 due to the availability of GDM diagnosis from 2004 onwards (see Section 9.4).

9.3 Variables

In the variable definitions, diagnoses (Appendix 1) will be defined using the Finnish adaptation of the ICD-10 codes recorded in HILMO and the Medical Birth Register, and the Finnish adaptations of both ICD-10 and ICPC-2 codes in AvoHILMO.

Medications (Appendix 2) will be defined using the Anatomic Therapeutic Chemical (ATC) [41] codes recorded in the Prescription registers.

9.3.1 Exposure

The exposure statuses are defined as follows:

1. **Children with in utero exposure to metformin only**: children born to pregnant women with at least one prescription of metformin (ATC code A10BA02, Appendix 2) only dispensed on the first day of the LMP or at any point after it during the pregnancy, until the date of delivery. The children will be classified as in utero exposed to metformin only regardless of treatment duration. No addition or switch to insulin (ATC code A10A, Appendix 2) is allowed in this group during pregnancy.

2. **Children with in utero exposure to a combination of metformin and insulin**: children born to pregnant women with at least one prescription of metformin (ATC code A10BA02, Appendix 2) and at least one prescription of insulin (ATC code A10A, Appendix 2), subsequently or in combination, dispensed on the date of the first day of the LMP or at any point after it during the pregnancy, until the date of delivery. The children will be classified as in utero exposed to a combination of metformin and insulin regardless of treatment duration.

3. **Children with in utero exposure to insulin only**: children born to pregnant women with at least one prescription of insulin (ATC code A10A, Appendix 2) only dispensed on the first day of the LMP or any time after it during the pregnancy, until the date of delivery.

The children will be classified as in utero exposed to insulin only regardless of treatment duration. No addition or switch to metformin (ATC code A10BA02, Appendix 2) is allowed in this group during pregnancy.

In addition, the following exposure definition will be used in the analyses from 2004 onwards:

4. **Children of women with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment:** children born to pregnant women with GDM and no prescription of metformin, combination of metformin and insulin or insulin (Appendix 2) dispensed on the date of the first day of the LMP or at any point after it during the pregnancy, until the date of delivery. No addition or switch to metformin or insulin is allowed in this group during the time of the pregnancy. GDM is defined as, during the pregnancy in question, a record of a diagnosis code for GDM (Appendix 1) in the Medical Birth Register, HILMO or AvoHILMO, or a pathological OGTT in the Medical Birth Register, or fasting plasma glucose ≥ 5.3 mmol/l, or 1h OGTT ≥ 10.0 mmol/l, or 2h OGTT ≥ 8.6 mmol/l [42,43] in the regional laboratory databases (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

9.3.2 Covariates

The covariates included in the study are listed in Table 3.

Pregnancy-related covariates are defined as follows:

- Age at conception: age at conception (continuous in years) for the pregnancy in question in the Medical Birth Register.

- Parity: parity (continuous: 0, 1, 2, …) for the pregnancy in question in the Medical Birth Register.

- Type of delivery: type of delivery (categorical: vaginal birth/caesarean section) for the pregnancy in question in the Medical Birth Register.

Maternal co-morbidities during pregnancy are defined as follows:

- Previously diagnosed T2DM: a record (categorical: yes/no) of a diagnosis code for T2DM (Appendix 1) for the pregnancy in question in the Medical Birth Register.

- Essential hypertension: a record (categorical: yes/no) of a diagnosis code for essential hypertension (Appendix 1) for the pregnancy in question in the Medical Birth Register.

- PCOS: a record (categorical: yes/no) of a diagnosis code for PCOS (Appendix 1) for the pregnancy in question in the Medical Birth Register, or in HILMO or AvoHILMO during the pregnancy in question (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

Table 3. List of covariates and their use in the study.

Covariate (categorical or continuous)	Use in the study				
	Baseline characte-ristics	**Model adjustment for potential confounders (model 2)[a]**	**Propensity scores (model 3)[a]**	**Covariates in explorative objectives 1-3**	**Sensiti-vity analyses**
Pregnancy-related variables					
Age at conception	x	x	x	-	-
Parity	x	x	x	-	-
Type of delivery	x	x	-	-	-
Maternal comorbidities during pregnancy					
Previously diagnosed T2DM	x	x	x	-	-
Essential hypertension	x	x	x	-	-
PCOS	x	x	x	-	-
Obesity in the beginning of pregnancy	x	x	x	-	-
Gestational hypertension	x	x	x	-	-
Preeclampsia	x	x	x	-	-
GDM[b]	x	x	x	-	-
Mothers' demographic factors					
Civil status during pregnancy	x	x	x	-	-
Educational level during pregnancy	x	x	x	-	-
Characteristics of the children at birth					
Sex	x	x	-	-	-
Gestational age at birth	x	x	-	-	-
Apgar score in 5min	x	x	-	-	-
Umbilical artery pH	x	x	-	-	-
Other variables of interest					
Maternal smoking before pregnancy	x	x	x	-	-
Dispensation of antidiabetic medications within three months before the beginning of pregnancy	x	x	x	-	-
Calendar year of the child birth	x	x	x	-	-
Covariates potentially associated with outcomes					
Gestational week of initiating the pharmacological antidiabetic treatment[c]	-	x	x	x	-
Dispensed cumulative DDDs of metformin during pregnancy[d]	-	x	-	x	-
Maternal pre-pregnancy BMI	-	x	x	x	-
Persistence of diabetes in the mother after birth	-	x	-	x	-
Gestational week of GDM diagnosis[b]	-	x	x	x	-
Variables for sensitivity analyses					
≥2 dispensations of metformin/insulin during pregnancy	-	-	-	-	x
Child's region of residency during follow-up	-	-	x	-	x

BMI = body mass index; DDD = defined daily dose; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test; PCOS = polycystic ovary syndrome; SAP = statistical analysis plan; T2DM = type 2 diabetes mellitus.

[a] The covariates indicated the table are candidate variables. The final covariates to be used will be defined in the SAP.
[b] Used exclusively in analyses from 2004 with the fourth cohort: children born to mothers with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment.
[c] Available exclusively for pregnant women initiating pharmacological antidiabetic treatment during pregnancy, i.e. not for women with GDM naïve to pharmacological antidiabetic treatment or for women with pre-pregnancy metformin or insulin treatment.
[d] The cumulative DDD of metformin will be set to zero for the cohorts without metformin in utero exposure.

- Obesity in the beginning of pregnancy: BMI>30kg/m^2 (categorical: yes/no) for the first BMI measurement for the pregnancy in question in the Medical Birth Register.

- Gestational hypertension: a record (categorical: yes/no) of a diagnosis code for hypertension (Appendix 1) for the pregnancy in question in the Medical Birth Register.

- Preeclampsia: a record (categorical: yes/no) of a diagnosis code for preeclampsia (Appendix 1) for the pregnancy in question in the Medical Birth Register.

- GDM: during the pregnancy in question, a record (categorical: yes/no) of a diagnosis code for GDM (Appendix 1) in the Medical Birth Register, HILMO or AvoHILMO, or a pathological OGTT in the Medical Birth Register, or fasting plasma glucose ≥ 5.3 mmol/l, or 1h OGTT ≥ 10.0 mmol/l, or 2h OGTT ≥ 8.6 mmol/l [42,43] in the regional laboratory databases (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

Mothers' demographic factors are defined as follows:

- Civil status during pregnancy: civil status (categorical: single/married or register partnership/divorced/widowed) recorded in Statistics Finland, for the year of delivery for the pregnancy in question in the Medical Birth Register.

- Educational level during pregnancy: educational level (categorical: compulsory/high school/higher education) recorded in Statistics Finland, for the year of delivery for the pregnancy in question in the Medical Birth Register.

Characteristics of the children at birth are defined as follows:

- Sex: child's sex (categorical: female/male) in the Medical Birth Register.

- Gestational age at birth: gestational age at birth (continuous in weeks and days) in the Medical Birth Register.

- Apgar score in 5min: Apgar scores in 5min (categorical: severely depressed/depressed/normal) as recorded in the Medical Birth Register, with scores 0-4 defined as severely depressed, scores 5-6 as depressed, and scores 7-10 as normal [44].

- Umbilical artery pH: umbilical artery pH (categorical: normal/ low / very low) as recorded in the Medical Birth Register, pH<7.0 defined as very low, pH 7.0-7.20 as low, and pH>7.20 as normal [45].

Other variables of interest are defined as follows:

- Maternal smoking before pregnancy: smoking (categorical: yes/no) before the pregnancy question in the Medical Birth Register.

- Dispensation of antidiabetic medications within three months before the beginning of pregnancy: at least one dispensed prescription of antidiabetic medications (Appendix 2) in the Prescription register three months before the beginning of the pregnancy in question (i.e. exposure between three months and one day before the first day of the LMP, as recorded in the Medical Birth Register). The variable is categorised as following: pre-pregnancy metformin only, pre-pregnancy insulin only, both pre-pregnancy metformin and insulin but no other antidiabetic medications, exclusively other antidiabetic medications than metformin and insulin, and no pre-pregnancy pharmacological antidiabetic treatment.

- Calendar year of the child birth: calendar year of the child birth (categorical: 1996/1997/…/2016) as recorded in the Medical Birth Register.

Covariates potentially associated with outcomes are defined as follows:

- Gestational week of initiating the pharmacological antidiabetic treatment: continuous in weeks, derived from the date of birth and gestational week of birth in the Medical Birth Register and the date of the first record of a dispensed metformin or insulin prescription (Appendix 2) during the pregnancy in question in the Prescription register (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

- Dispensed cumulative DDDs of metformin during pregnancy: cumulative DDDs (continuous in grams) of metformin (Appendix 2) in the Prescription register during the pregnancy in question (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

- Maternal pre-pregnancy BMI: pre-pregnancy BMI (continuous in kg/m^2) for the pregnancy in question in the Medical Birth Register.

- Persistence of diabetes in the mother after birth: at least one record (categorical: yes/no) of a diagnosis code for diabetes (Appendix 1) 1 year after the pregnancy in question in HILMO or AvoHILMO (i.e. after the date of delivery, as recorded in the Medical Birth Register, until 1 year post-partum).

- Gestational week of GDM diagnosis: continuous in weeks, derived from the date of birth and gestational week of birth in the Medical Birth Register and the date of the first record of GDM (see the definition of GDM) during the pregnancy in question (i.e. from the first day of the LMP until the date of delivery, as recorded in the Medical Birth Register).

Variables used in sensitivity analyses, not defined elsewhere, are defined as follows:

- ≥2 dispensations of metformin/insulin during pregnancy: the exposure statuses are defined as in 9.3.1, but requiring at least two prescriptions of metformin and/or insulin (Appendix 2) dispensed at different time points between the first day of the LMP and the date of delivery.

- Child's region of residency during follow-up: child's region of residency recorded in the Population Register Centre, during follow-up.

9.3.3 Variables to collect outcomes

In addition to the variables listed in 9.1.2, dates for the outcomes will be retrieved from each data source.

9.4 Data source

The study database will be constructed from the registers described in Table 4.

Table 4. Utilised registers.

Registers	Register holder	Years of data extraction
Prescription register	Social Insurance Institute (SII)	1994[a]-2016
Medical Birth Register	National Institute for Health and Welfare (THL)	1996[b,c]-2016
Register of Congenital Malformations	National Institute for Health and Welfare (THL)	1996[b,c]-2016
Care Register for Health Care (HILMO; secondary care)	National Institute for Health and Welfare (THL)	1996[d]-2016
Register of Primary Health Care Visits (AvoHILMO)	National Institute for Health and Welfare (THL)	2011[a]-2016
Population Register Centre	Population Register Centre	1996[b]-2016
Statistics Finland	Statistics Finland	1996[b]-2016
Regional laboratory databases	Regional authorities	1996[e]-2016

GDM = gestational diabetes mellitus; ICD-10 = International Classification of Diseases, 10th revision.
[a] Since the establishment of the register.
[b] Start of data extraction based on the availability of other register data, although further historical data would be available for this register.
[c] Diagnosis of GDM in ICD-10 codes available from 2004 onwards.
[d] Since the availability of ICD-10 diagnosis codes.
[e] Start of data extraction based on the availability of other register data. The year of establishment of the laboratory databases varies between regions, from 1993 to 2007.

All the registers are national, with full (100%) population coverage. Additional regional laboratory databases will also be used to strengthen the data.

In Finland every permanent resident (at least for 1 year) has a PIN. All the registers listed in Table 4 include the PIN, enabling linkage of the data across all registers and thus the formation of the study dataset. The data linkage is described in further detail in Section 0.

The Prescription register is managed by the Social Insurance Institute (SII) and has data since 1994. Prescription register covers only reimbursed purchased medication. The register contains information on e.g. date of purchase and trade name, ATC code, strength and package size of the drug product. The data for previous year is available in March.

The purpose of the Drugs and Pregnancy Project database (DPP), initiated in 2003, is to evaluate the pattern of medication use during pregnancy and estimate the effect of medication use on pregnancy outcomes. The research data includes information from the Medical Birth Register and the Register of Congenital Malformations, both maintained by the National Institute for Health and Welfare (THL). Information on maternal medication use is obtained from the Prescription Register, maintained by the SII. The research database enables the evaluation of the frequency and type of maternal medication use during pregnancy retrospectively from the year 1996 onwards. At the time of the planned data extraction, the DPP is expected to cover data until the end of 2016. Medication purchases are recorded covering a time period from three months prior to pregnancy to the end of pregnancy in the DPP.

The HILMO register is managed by the THL and has data since 1994. This national register covers virtually 100% of the Finnish population (5.5 million in 2017). It contains information on secondary care (in- and out-patient care) details, e.g. duration of hospitalisation, diagnoses (ICD-10 codes) and procedures. Medical treatment is only recorded at procedure level. There is also more detailed information of the in-patient care of the specialty of psychiatry and of patients with an advanced cardiac condition. Quality of the data is considered mainly very high, but there is variation e.g. in the reporting rate and accuracy of secondary diagnoses. The data for previous year are available in September.

The AvoHILMO register is managed by the THL and this national register covers virtually 100% of the Finnish population since 2011. In this register, e.g. time and place of treatment as well as diagnoses (ICD-10 and ICPC-2 codes) and procedures are recorded. The validity of the data depends on the reliability and accuracy of the data reported to the register. The lag time is similar to the HILMO register. The child welfare check-ups are also included in this register, along with measurements of weight and height until 16 years of age. The growth data are recorded for 65% of the children, and are thus missing for 35% of the children.

The Population Register Centre collects demographic data on the population, including information on migration and date of death. The register is updated monthly, and data are normally available in one month.

Statistic Finland also collects demographic data on the population, including information on civil status and educational level. Data on civil status and education are updated continuously.

Regional laboratory databases contain data on the laboratory measurements taken in all domains of the public healthcare in Finland. Guidelines for accessing the data and the data contents of these numerous regional databases vary between the databases. In the current study, databases of

seven regions in Finland, representing 68% of the Finnish population, will be contacted separately to obtain access to their data. Thus, regional laboratory data will be unavailable for part of study population.

9.5 Study size

Statistical power was estimated for performing logistic regression or Cox regression analyses on the primary outcome variables (primary objective: long-term diagnoses) according to estimated population sizes, population proportions with in utero exposure to metformin, and population proportions with the primary outcomes.

9.5.1 Estimated population

The population size and the proportion of the children with in utero exposure to metformin for the primary objective (long-term diagnoses) are presented in Table 5. The children born in 1996-2016 will be included, and the children will be followed longitudinally from the age of one week for as long as data are available (up to the age of 20 years). The estimated population size and the proportion of children with in utero exposure to metformin are based on a prior feasibility assessment, in which data were available for children born in Finland in 2004-2014. The population size of the children born in 2015-2016 was extrapolated from the children born in 2014. The population size of the children born in 1996-2003 was extrapolated from those born in 2004-2005 for the exposure to metformin only group and from those born in 2004-2011 for the exposure to insulin only group, based on linearity of the curves. The number of the children in the combination exposure group was estimated 0 for the children born before 2004. Based on these estimations, the population sizes available for follow-up at the ages of 1, 3, 5, 7, 10 and 14 are presented in Table 5. The population sizes are not presented after the follow-up age of 14, because based on the extrapolation no individuals aged over 14 years were exposed to metformin in utero. However, the children will be followed for as long as data are available, up to the age of 20 years of age, because the extrapolation may not reflect the reality, and children aged over 14 years with in utero exposure to metformin might still be observed.

In the power calculations, the size of the groups “Exposure to metformin only” and “Exposure to insulin only (reference group)” are used, because metformin only exposure is of main interest and the children with in utero exposure to insulin will be used as a reference group in the analyses for the primary objective. In addition, the estimated population size and population proportion with in utero exposure to combination of metformin and insulin are presented in Table 5, because children with in utero exposure to the combination will also be compared to the reference group (exposure to insulin only) in the analyses.

Table 5. Estimated population size for the primary objective, by exposure status and age of follow-up.

Age of follow-up	Number (n) and percentage (%) of the children with follow-up data, by in utero exposure status				Used in power analyses[a]: M: Metformin only n (%) I: Insulin only n (%) T: Total n (%)
	Exposure to metformin only[a]	Exposure to combination of metformin and insulin[b]	Exposure to insulin only (reference group)[a]	Total	
Any age (all the children)	4,301 (20.0%)	1,416 (6.6%)	15,754 (73.4%)	21,471 (100%)	M: 4,301 (21.4%) I: 15,754 (78.6%) T: 20,055 (100%)
1 years	3,746 (19.0%)	1,213 (6.2%)	14,726 (74.8%)	19,685 (100%)	M: 3,746 (20.3%) I: 14,726 (79.7%) T: 18,472 (100%)
3 years	2,636 (16.4%)	807 (5.0%)	12,670 (78.6%)	16,113 (100%)	M: 2,636 (17.2%) I: 12,670 (82.8%) T: 15,306 (100%)
5 years	1,712 (13.1%)	445 (3.4%)	10,865 (83.4%)	13,022 (100%)	M: 1,712 (13.6%) I: 10,865 (86.4%) T: 12,577 (100%)
7 years	1,031 (10.0%)	214 (2.1%)	9,069 (87.9%)	10,314 (100%)	M: 1,031 (10.2%) I: 9,069 (89.8%) T: 10,100 (100%)
10 years	299 (4.5%)	54 (0.8%)	6,306 (94.7%)	6,659 (100%)	M: 299 (4.5%) I: 6,306 (95.5%) T: 6,605 (100%)
14 years	12 (0.3%)	0 (0.0%)	3,514 (99.7%)	3,526 (100%)	M: 12 (0.3%) I: 3,514 (99.7%) T: 3,526 (100%)

[a] In the power calculations, the size of the groups "Exposure to metformin only" and "Exposure to insulin only (reference group)" are used, because metformin exposure is of main interest and the children with in utero exposure to insulin will be used as a reference group in the analyses.
[b] The estimated population size and population proportion with in utero exposure to a combination of metformin and insulin are presented, because children with in utero exposure to the combination will be compared to the reference group (exposure to insulin only) in the analyses.

9.5.2 Estimated population proportions with primary outcomes

Of the primary outcomes, the proportion of the children with "diagnoses related to challenges in motor-social development" was conservatively estimated at 5%, based on a reported 5.5% cumulative incidence of specialised service use for learning and coordination disorders (ICD-10 codes F80-83) in children aged 0-14 years in Finland [46]. Based on this estimation, the population proportion with primary outcomes was varied in the power calculations, setting the proportion to 3%, 5% and 7%. Among the seven primary outcomes, the outcome "diagnoses related to challenges in motor-social development" was considered appropriate for estimating the population proportions with the outcome, because this outcome is anticipated not to be the most or the least common of the outcomes.

9.5.3 Power calculations for logistic regression analyses (for primary objective)

Power calculations for logistic regression analyses on the relationship between the exposure status and the primary outcomes are presented in Table 6. Power (1-β) was calculated using the estimated population sizes at the follow-up ages (Table 5), and by varying the detectable effect size (odds ratio, OR: 1.5, 1.7), varying the population proportions with an outcome (3%, 5%, 7%), and with a two-sided type 1 error (α) probability set to 5%. A power of ≥80% was considered adequate.

As presented in Table 6, an OR of 1.5 can be detected with approximately 100% power (adequate), if 3% of the population has an outcome any time during the follow-up, considering the entire population in the analyses. When analyses are conducted at specific ages, the power decreases with an increasing age of the children, because the total number of the children, and also the proportion of the children with in utero metformin exposure, are lower for older individuals (children born earlier). At the follow-up age of 7 years, an OR of 1.5 can be detected with 89% power (adequate) if 5% of the population has an outcome. At the follow-up age of 10 years, an OR of 1.7 can be detected with 83% power (adequate) only if a larger proportion of the population, 7%, has an outcome. At later ages, the power is inadequate (<80%) for detecting an OR of 1.5 or 1.7, with the estimated population sizes and population proportions with an outcome (data not shown).

Table 6. Calculated power (1-β) for logistic regression for the primary objective, using the estimated population sizes (Table 5), varying detectable effect size (odds ratio, OR), varying population proportion with outcome, and type 1 error probability (α) of 5%.

Estimated population size M: Metformin only n (%) I: Insulin only n (%) T: Total of them n (%)[a]	**Varying detectable effect size (odds ratio, OR**	**Varying population proportion with outcome**	**Power (1-β)**	**Comment**
Any time during follow-up (any age)				
M: 4,301 (21.4%) I: 15,754 (78.6%) T: 20,055 (100%)	1.5	3%	**100%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
	1.7	3%	**100%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
Age of follow-up: 1 year				
M: 3,746 (20.3%) I: 14,726 (79.7%) T: 18,472 (100%)	1.5	3%	**99%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
	1.7	3%	**100%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
Age of follow-up: 3 years				
M: 2,636 (17.2%) I: 12,670 (82.8%) T: 15,306 (100%)	1.5	3%	**96%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
	1.7	3%	**100%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
Age of follow-up: 5 years				
M: 1,712 (13.6%) I: 10,865 (86.4%) T: 12,577 (100%)	1.5	3%	**87%**	Power adequate[b]
		5%	**98%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
	1.7	3%	**98%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
Age of follow-up: 7 years				
M: 1,031 (10.2%) I: 9,069 (89.8%) T: 10,100 (100%)	1.5	3%	**71%**	Power inadequate[b]
		5%	**89%**	Power adequate[b]
		7%	**97%**	Power adequate[b]
	1.7	3%	**91%**	Power adequate[b]
		5%	**99%**	Power adequate[b]
		7%	**100%**	Power adequate[b]
Age of follow-up: 10 years				
M: 299 (4.5%) I: 6,306 (95.5%) T: 6,605 (100%)	1.5	3%	**34%**	Power inadequate[b]
		5%	**48%**	Power inadequate[b]
		7%	**61%**	Power inadequate[b]
	1.7	3%	**53%**	Power inadequate[b]
		5%	**71%**	Power inadequate[b]
		7%	**83%**	Power adequate[b]

OR = odds ratio.
[a] Denominator being the children with metformin only exposure + the children with insulin only exposure.
[b] Power ≥80% considered adequate.

9.5.4 Power calculations for Cox regression analyses (for primary objective)

Power calculations were also performed for Cox regression analyses on the relationship between the exposure status and time-to-event outcomes (Table 7). Power (1-β) was calculated using the estimated population size of all of the children (Table 5), and by varying the detectable effect size (hazard ratio, HR: 1.5, 1.7), varying the population proportions with an outcome (3%, 5%, 7%), and with type 1 error (α) probability set to 5%. The average follow-up time was estimated to five years, during the maximum of 20-year observation period. A power of ≥80% was considered adequate.

As presented in Table 7, an HR of 1.5 can be detected with adequate power (≥80%) if 5% of the population has an outcome by the end of follow-up. If a smaller proportion, 3%, of the population has an outcome, an HR of 1.7 can be detected with adequate power (≥80%).

Table 7. Calculated power (1-β) for Cox regression for the primary objective, using the estimated population size of all of the children (Table 5), varying detectable effect size (hazard ratio, HR), varying population proportion with outcome, and type 1 error probability (α) of 5%. The average follow-up time was estimated to five years, during the maximum of 20-year observation period.

Estimated population size M: Metformin only n (%) I: Insulin only n (%) T: Total of them n (%)[a]	**Varying detectable effect size (hazard ratio, HR**	**Varying population proportion with outcome**	**Power (1-β)**	**Comment**
M: 4,301 (21.4%) I: 15,754 (78.6%) T: 20,055 (100%)	1.5	3%	**68%**	Power inadequate[b]
		5%	**89%**	Power adequate[b]
		7%	**97%**	Power adequate[b]
	1.7	3%	**92%**	Power adequate[b]
		5%	**99%**	Power adequate[b]
		7%	**100%**	Power adequate[b]

HR = hazard ratio.
[a] Denominator being the children with metformin only exposure + the children with insulin only exposure.
[b] Power ≥80% considered adequate.

9.5.5 Power in the analyses of children born from 2004 onwards

Statistical power was also estimated for performing Cox regression analyses on the primary outcome variables (primary objective: long-term diagnoses), including exclusively children born from 2004 onwards and including the fourth cohort of children of treatment naïve women with GDM. In the power calculations for Cox regression analyses, power (1-β) was calculated using the estimated population size of the children born from 2004 onwards (Table 8), and by varying the detectable effect size (HR: 1.5, 1.7), varying the population proportions with an outcome (3%, 5%, 7%), and with type 1 error (α) probability set to 5%. The average follow-up time was estimated to four years, during the maximum of 12-year observation period. A power of ≥80% was considered adequate.

Table 8. Estimated population size for children born from 2004 onwards, by exposure status, including the additional cohort of children of treatment naïve women with GDM.

	Number (n) and percentage (%) of children, by in utero exposure status					Used in power analyses[a]: M: Metformin only n (%) I: Insulin only n (%) T: Total n (%)
	Exposure to metformin only	Exposure to combination of metformin and insulin	Exposure to insulin only (reference group)	Born to treatment-naïve women with GDM	Total	
Any age (all the children)	4,256 (7.1%)	1416 (2.4%)	11,581 (19.3%)	42,794 (71.3%)	60,047 (100.0%)	M: 4,256 (26.9%) I: 11,581 (73.1%) T: 15,837 (100%)

GDM = gestational diabetes mellitus.
[a] In the power calculations, the size of the groups "Exposure to metformin only" and "Exposure to insulin only (reference group)" are used, because metformin exposure is of main interest and the children with in utero exposure to insulin will be used as a reference group in the analyses.
[b] The estimated population size and population proportion with in utero exposure to a combination of metformin and insulin and those treatment naïve are presented, because these two populations will be compared to the reference group (exposure to insulin only) in the analyses.

As presented in Table 9, an HR of 1.5 can be detected with adequate power (≥80%) if 5% or 7% of the population has an outcome by the end of follow-up. An HR of 1.7 can be detected with adequate power (≥80%), if 3%, 5% or 7% of the population has an outcome.

Table 9. Calculated power (1-β) for Cox regression for the primary objective, using the estimated population size of the children born from 2004 onwards (Table 8), varying detectable effect size (hazard ratio, HR), varying population proportion with outcome, and type 1 error probability (α) of 5%. The average follow-up time was estimated to four years, during the maximum of 12-year observation period.

Estimated population size M: Metformin only n (%) I: Insulin only n (%) T: Total of them n (%)[a]	Varying detectable effect size (hazard ratio, HR	Varying population proportion with outcome	Power (1-β)	Comment
M: 4,256 (26.9%) I: 11,581 (73.1%) T: 15,837 (100%)	1.5	3%	**76%**	Power inadequate[b]
		5%	**94%**	Power adequate[b]
		7%	**99%**	Power adequate[b]
	1.7	3%	**95%**	Power adequate[b]
		5%	**100%**	Power adequate[b]
		7%	**100%**	Power adequate[b]

HR = hazard ratio.
[a] Denominator being the children with metformin only exposure + the children with insulin only exposure.
[b] Power ≥80% considered adequate.

9.6 Data management

Study permit approvals and access to the study data will be applied for by EPID Research. After the identification of the study population from the DPP, data from each relevant register will be extracted according to the PIN. This will be performed by the register holders. As the used data from the national registers and regional laboratory databases consist of automatically registered data, registered independent of the current study, the data collection process cannot affect the research question.

Once all relevant data have been extracted by the register holders, a unique dummy study identification number (SID) will be created for each PIN, prior to data delivery to EPID Research. EPID Research will then receive all raw data without PINs. At EPID Research, the SIDs will be used for data linkage on individual level. Therefore, the researchers at EPID have access to data where individuals cannot be directly identified.

Before the data delivery to EPID Research, the data holders have collected and managed data according to their own standards. After the data are delivered to EPID Research by the data holders, EPID Research will process data.

R language will be used in data management for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modelling. R language is described in more detail in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-project.org/doc/R-FDA.pdf, accessed 23 March 2017). Full audit trail starting from raw data obtained from register holders and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results. The study may be inspected by the Sponsor's independent representative(s), scientific committee, or by the competent authorities.

EPID Research will maintain information on the study individuals securely on site according to up-to-date standard operating procedures. EPID Research will also maintain appropriate data storage, including periodic backup of files, and archiving procedures (see 9.10.4). EPID Research will comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all programs. The study Sponsor or other parties outside EPID Research cannot receive access to individual-level data. Only aggregated results will be presented to the Sponsor or otherwise published.

9.7 Data analysis

All data received from the registers will be investigated for potential inconsistencies or errors. At minimum, data investigation will include controlling that all data are available as requested, checking the type and format of received variables, the proportion of missingness and investigation of value ranges for potential outliers or erroneous recordings. Issues related to data not being available as requested will be resolved with the data holders. Other issues will be

resolved internally by the study statistician together with the study team, when necessary. All actions related to these data investigations and corrections made for erroneous recordings and other inconsistencies will be documented.

This protocol describes statistical methods on a general level. A detailed statistical analysis plan (SAP) will be written with more detailed description of the performed analyses and illustration of study result outputs as template tables and/or figures.

9.7.1 Analysis sets

In the analyses of children born from 1996 onwards, the analysis population will consist of the three cohorts described in Section 9.2, with PCOS being analysed exclusively among girls:

1. Children with in utero exposure to metformin only

2. Children with in utero exposure to a combination of metformin and insulin (subsequently or in combination)

3. Children with in utero exposure to insulin only.

Analyses for the secondary objectives of prevalence and risk of abnormal growth outcomes at birth and continuous growth outcomes at birth will be stratified by sex.

In analyses of children born from 2004 onwards, the analysis population will include an additional fourth cohort of children described in Section 9.2, with PCOS being analysed exclusively among girls:

4. Children of women with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment.

In all regression analyses, the children with in utero exposure to insulin only will be considered as the reference group.

9.7.2 Derived and transformed data

If a variable is completely missing from a database, it will be excluded from the analysis. If a variable is missing for only some of the patients, a missing data category will be added and used in the analysis. Imputation will not be used.

In general, variables recorded at clinical practice level are automatically included in the Finnish national registers. Thus, for most study variables little to no missing data are anticipated. Moreover, the risk of possible bias related to missing data is expected to be minimal, because the reasons for missing data are expected to be independent of the study objectives, for example due to the database management systems or lack of recording at practice level.

With regard to variables used in this study, diagnoses are recorded at healthcare visits and a lacking observation will be considered as a non-case. It remains unknown, however, whether a lacking diagnosis was due to patient not having a visit or if a diagnosis was not recorded in the

national registers due to e.g. lack of recording at practice level. Relatively common and less-severe conditions, such a hypertension among adults, are anticipated to be unrecorded more often than severe conditions. The diagnoses to be detected in the current study are, however, anticipated to be well-recorded, because the diagnoses concern pregnant women and children.

Although little to no missing data are anticipated for most study variables, there are some exceptions. The growth data are anticipated to be missing for approximately 35% and the regional laboratory data for approximately 32% of the population, as described in 9.4 and further elaborated in 0.

9.7.3 Statistical methods

9.7.3.1 Population baseline characteristics

The baseline characteristics (Table 3) of the pregnant women and the children will be summarised at birth. For the pregnant women, all pregnancy-related variables, maternal comorbidities during pregnancy, mother's demographic factors and other variables of interest will be described. For children, characteristics at birth will be described. These characteristics will be described in the total population and separately in each study cohort by exposure status. Continuous variables will be described by mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum. Categorical variables and continuous variables that were also categorised will be described by proportion and frequency in each category.

9.7.3.2 Primary objective: Long-term diagnoses

Descriptive analyses

The prevalence and incidence of children having a long-term diagnosis listed as an outcome in the primary objective will be estimated with 95% confidence intervals (CI) separately within each study cohort by exposure status and in the total population. The prevalence and incidence will be presented annually starting from birth (1 week) up to 20 years as long as data are available as specified below (Figure 3).

For permanent effects (Figure 3), the prevalence will be counted among children who are still followed-up when reaching a given age (separately for 0, 1, 2, …, 20 years) and the prevalent cases are those who have ever been diagnosed between birth and the given age. The number of new cases between each yearly age period (yearly incidence) will also be reported together with the proportion counted among those who were at risk (in follow-up without the diagnosis) at the beginning of each the specific age period. The cumulative risk of permanent effects will also be characterised using the Kaplan-Meier estimator.

For temporary effects (Figure 3), the cases between each yearly age period (yearly incidence) will be reported as the number and proportion among those who were at risk (followed-up) at the beginning of each age period. For temporary effects, cases will be counted if a child had a recorded diagnosis within the yearly age period regardless of diagnoses recorded prior to that age period.

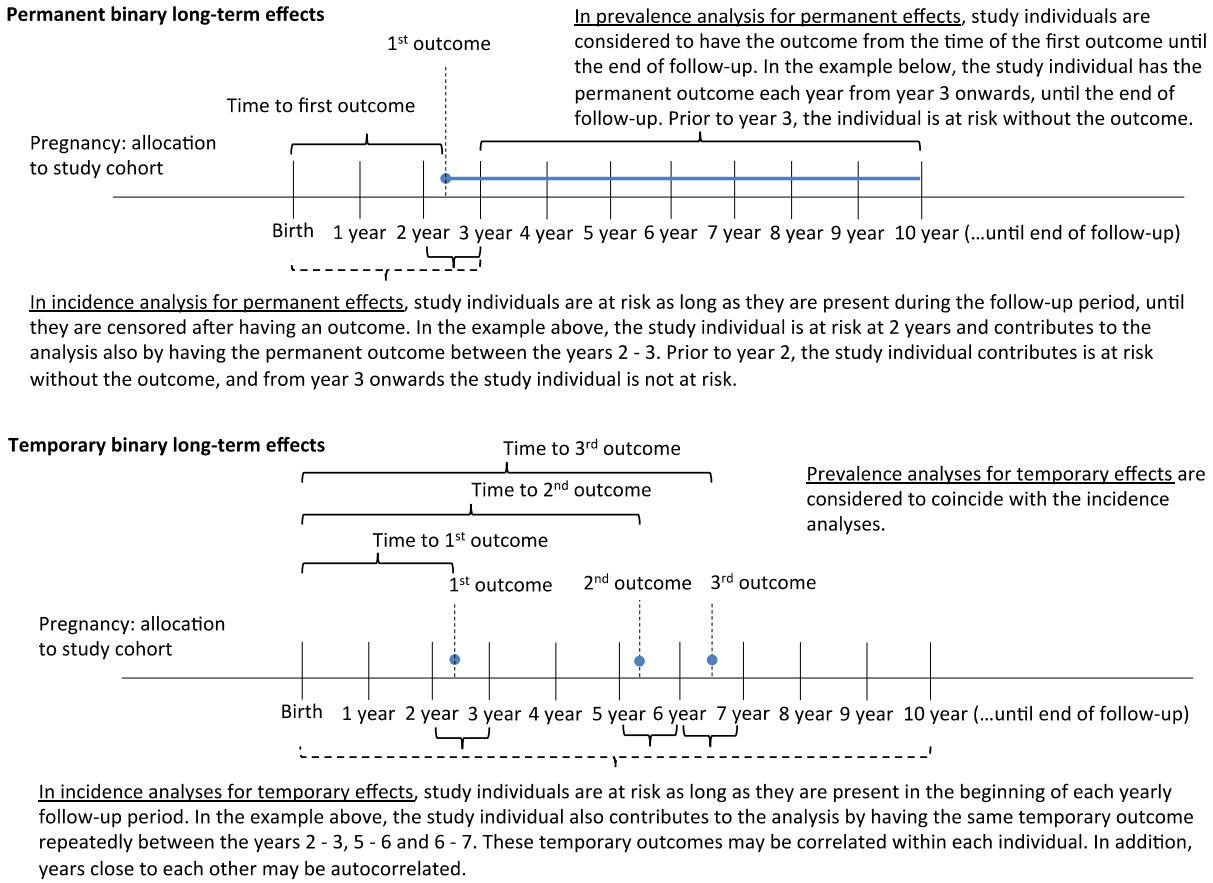


Figure 3. Illustration of analyses of permanent and temporary binary long-term effects (for primary objectives and secondary objectives B).

Formal main analyses

As the main analyses for the primary objective, the risk of each permanent and temporary long-term effect will be investigated as a time-to-event variable where the start time is at birth. For permanent outcomes the event time will be the first indication of the given long-term diagnosis. For temporary effects, multiple event times will be allowed per child and in the analyses temporal and within subject correlations will be considered, using e.g. random effects or a marginal model approach (details will be specified in the SAP). In the analyses, three different Cox proportional hazards models will be used. The first Cox model will only include the exposure status as the investigated outcome and will generate a crude unadjusted HR estimate. The second model will generate an estimate adjusted for potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders as in model 2 and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

Formal subsidiary analyses

As subsidiary analyses for the primary objective, the yearly prevalence of each permanent long-term effect will be compared as a binary outcome (each year separately) using three different logistic regression models. The first regression model will only include the exposure status and the investigated outcome and will generate a crude unadjusted OR estimate. The second model will generate an estimate adjusted for potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders as in model 2 and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

Furthermore, the yearly incidences of each permanent and temporary effect will be compared as a binary outcome i) using all years together as a repeated binary outcome and ii) using each yearly variable as a separate outcome. Three different logistic regression models will be considered and in case i) temporal and within subject correlations will be considered, using e.g. random effects or a marginal model approach (details will be specified in the SAP). The first regression model will only include the exposure status and the investigated outcome and will generate a crude unadjusted OR estimate. The second model will generate an estimate adjusted for potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

9.7.3.3 Secondary objective A: Immediate effects

Descriptive analyses

The number and prevalence (proportion) of children having any of the binary birth outcomes listed in the secondary objective A will be estimated with 95% CI, separately within each study cohort by exposure status and in the total population. Similarly, continuous outcomes listed in the secondary objective A will be presented with relevant summary statistics including: mean with 95% CI, SD, median, 25^{th} and 75^{th} percentiles, minimum, and maximum.

Formal analyses

The immediate binary birth outcomes will be investigated using three different logistic regression models. The first regression model will only include the exposure status and the investigated variable and will generate a crude unadjusted OR estimate. The second model will generate an estimate adjusted for potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders as in model 2 and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

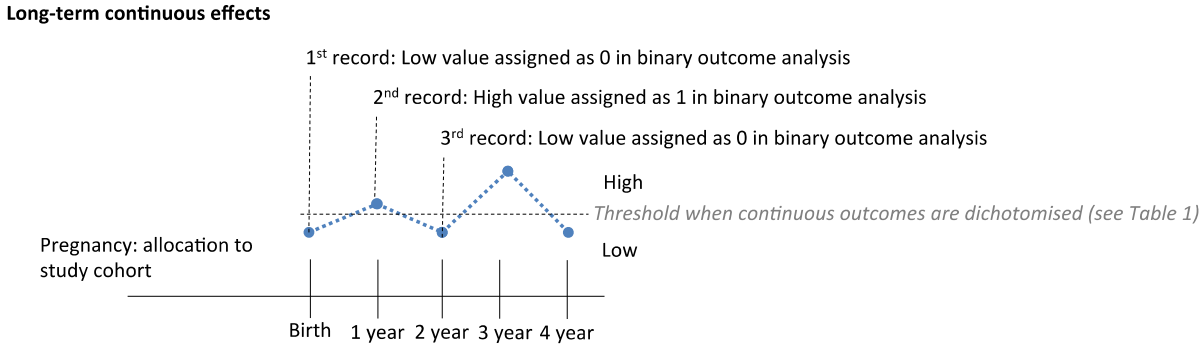
The immediate continuous birth outcomes will be investigated using three different linear regression models. The first regression model will only include the exposure status as the

investigated outcome and will generate a crude unadjusted estimate. The second model will generate an estimate adjusted for potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders as in model 2 and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

Secondary objective B: Long-term growth-related effects

Descriptive analyses

For binary temporary long-term growth-related effects, the descriptive analysis will be done as described for the long-term diagnoses in the primary objective (Figure 3). In addition, continuous outcomes will be presented yearly (Figure 4) with relevant summary statistics including min, max, median, Q1, Q3, mean with 95% CI, SD, separately within each study cohort by exposure status and in the total population. If a child has several measurements within one year, a mean value will be derived and used in the population summaries.



All long-term continuous effects are temporary. The incidence of the derived binary outcomes will be calculated as described for the temporary binary long-term outcomes. Between each yearly time period, a derived binary outcome is considered to be present when at least one record of the continuous outcome is above a pre-defined threshold (value 1 in the binary analysis). Continuous outcomes will be analysed adjusting for the year of the outcome. The outcomes may be correlated within each individual. In addition, measurements close to each other may be autocorrelated.

Figure 4. Illustration of analyses of continuous long-term effects (for secondary objectives B).

Formal analyses

For binary temporary long-term growth-related effects, the formal analysis will be done as described for long-term diagnoses in the primary objective.

Continuous outcomes will be investigated using a linear regression in which temporal and within subject correlations will be considered, using e.g. random effects or a marginal model approach (details will be specified in the SAP) and year of the outcome will be adjusted for. The first regression model will only include the exposure status and the investigated outcome and will generate a crude unadjusted estimate. The second model will generate an estimate adjusted for

potential confounders as listed in Table 3 (see 9.3). The third model will generate propensity score adjusted estimates, including potential confounders and in addition adjusting for estimated propensity of being exposed to metformin in utero, using either matching, weighting, stratification or covariate adjustment (method will be specified in the SAP).

9.7.3.4 Exploratory objectives: factors associated with outcomes

Descriptive analyses

The descriptive analyses, as listed above for the primary objective and for the secondary objectives A and B, will be re-performed stratifying by the following variables as listed in Table 3 (see 9.3): Gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative DDDs of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant).

Formal analyses

Following the formal analyses described above for the primary and for the secondary objectives A and B, the crude effect will be derived using a model having exposure status and only each of the following variables at a time: gestational week of initiating the pharmacological antidiabetic treatment, dispensed cumulative DDDs of metformin during pregnancy, maternal pre-pregnancy BMI, persistence of diabetes in the mother after birth, and gestational week of GDM diagnosis (as relevant). An adjusted estimate will be derived using by using the adjusted model that has all the potential confounders. In this analysis, adjusted models may need to be revised if the independent variables in the model are highly correlated (please see section 9.7.3.7).

9.7.3.5 Sensitivity analyses

1. To address the limitation that pregnant women with a dispensation of metformin or insulin may not actually have used the medication, one sensitivity analysis for the primary objectives will include in the cohorts exclusively children of women with at least two dispensing occasions of the exposures of interest during pregnancy. The results of this sensitivity analysis will be compared to the results of the main analysis.

2. The influence of the limitation that blood glucose measurements are unavailable for all included children will be investigated in a sensitivity analysis, in which analyses on the primary outcomes hypoglyceamia and hyperglycaemia will be stratified by region of residency, based on the availability of the laboratory data. The results with and without the laboratory data will be compared.

3. Sensitivity analyses for the primary outcomes will include analyses of the long-term diagnoses among the children of women with a diagnosis of GDM, and the results will be compared to the results of the main analysis including children of mothers treated with metformin or insulin for any indication. In this sensitivity analysis, long-term diagnoses will be compared in the four cohorts of children (including children of women with GDM and naïve to in utero exposure to pharmacological antidiabetic treatment) as described above for the primary objective. Descriptive analyses will also be stratified to two

groups: children of women with a diagnosis of GDM and without a diagnosis of GDM. In the formal analyses, this new group definition will replace the old exposure definition. The time period for studying the outcome starts from the availability of GDM diagnoses (2004).

4. A sensitivity analysis comparing women with prior T2DM diagnosis to those without will also be performed. Similarly, in this sensitivity analysis the analysis will be performed as specified for the primary objective above. The distinction is that the original exposure definition will be replaced by the new group definition of having T2DM diagnosis or not. In addition, metformin exposure, insulin exposure and GDM will be used as additional covariates in the regression models.

5. In the primary formal Cox regression analyses all yearly outcomes are analysed together and a common exposure effect will be assumed throughout time. However, it may be that the exposure effect is not constant, i.e., that the proportional hazards assumption is not valid. In order to investigate this, the analysis will be re-performed using a model in which a separate exposure effect is allowed for each age period. Details of the model used in this analysis will be defined in the SAP.

6. The influence of potential effect modifiers on the estimated exposure effects will be explored by re-performing the primary formal Cox regression analyses with further adjustments. With regard to variables identified as potential effect modifiers (variable-exposure pairs per outcome), the Cox regression will be re-performed in pre-defined strata defined by the potential effect modifier or, alternatively, an interaction term will be added into the model. Variables being potential effect modifiers and the preferred method of model adjustment (stratification or additional interaction term) will be specified in the SAP.

7. In the analysis for the primary objectives, the strength of an unmeasured confounder needed to move the estimated HR to the null will be assessed using the "rule out" method proposed by Schneeweiss [47].

8. An additional sensitivity analysis for the main and subsidiary analysis, in which highly correlated variables will be removed from the regression model, may be performed depending on if multicollinearity is detected (please see Section 9.7.3.7).

9.7.3.6 Propensity score and weight estimation

A separate model will be considered for the propensity of being exposed to metformin in utero. In the propensity model, the outcome will hence be the in utero metformin exposure. Variables listed in Table 3 (see 9.3) will be included in the propensity model as independent variables. The following steps will be performed in the propensity score and weight estimation

1. Balance analysis of potential propensity score weight variables prior to weighting. This analysis will compare standardised differences of the selected variables (prevalence or mean) between different exposure groups prior to weighting. In addition, the full

distributions of the selected variables will be compared using e.g. quantile-quantile or density plots, as will be specified in the SAP.

2. Propensity score estimation using in utero exposure to metformin as the outcome and factors affecting treatment selection as independent variables. Followed by weight estimation

3. Balance analysis of propensity score weight variables after weighting. This analysis will compare statistics of the selected variables between different exposure groups after weighting using the same methods as described in point 1 above. The results will be used to investigate how successful the weighting was.

4. Actual outcome analysis, as described above for the primary and secondary objectives, with the distinction that either propensity score matching, weighting, stratification or covariate adjustment will be used. The preferred method will be specified in the SAP.

9.7.3.7 Investigation of correlations between covariates (multicollinearity)

Multicollinearity between covariates (independent predictors) that will be adjusted for in the regression models, as listed in Table 3 (see 9.3), will be investigated by regressing (with linear regression) each independent variable against all the other independent variables and by calculating the variance inflation factor. If the variance inflation factor is greater than 4, removal of highly correlated covariates will be considered as follows. In the exploratory analysis, in which factors associated with outcomes will be investigated, the effect of each independent predictor needs to be estimated correctly and hence highly correlated variables will be removed and their effect on the outcome will be estimated in separate models. In the main and subsidiary analyses, the independent variables are adjusting variables and not of interest, *per se,* and hence they will not be removed. However, additional sensitivity analysis, in which highly correlated variables are removed, may be performed.

9.7.3.8 Multiplicity adjustment

No formal adjustment will be made. As this is a large population-based study, several results may be statistically significant, especially when considering specified p-value thresholds such as 0.05, even if the results themselves have no clinical relevance e.g. due to the estimated effect size. On the other hand, several models will be used in additional / sensitivity analyses in an exploratory manner in order to investigate how sensitive the pre-defined main approach is for further adjustments. Results and statistical significance arising from such explorative analyses should be viewed and discussed against the corresponding results from the pre-defined main approach (formal main analyses).

9.7.4 Sequence of analyses

All analyses will be performed after receiving all data from the data sources. Interim analyses will not be performed.

9.8 Quality control

The study will be conducted as specified in this protocol. The principal investigator, the co-investigators and the Sponsors of the study must approve all revisions to the protocol. All changes to the protocol shall be properly documented as protocol amendments and, when necessary, such protocol amendments are delivered to relevant ethics committees and register holders.

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [48]. The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP) by International Society for Pharmacoepidemiology [49]. EPID Research, the principal investigator, co-investigators, the Sponsors and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

EPID Research will be the register holder for the retrieved data, also in the responsibility of destroying the data after the study. Standard operating procedures of EPID Research will be used in the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All work will be subject to quality control and documentation procedures to make certain the final report is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned or if clarifying analyses are required, the missing or the additional information and results will be included in the report(s) and the corresponding explanation given. All key study documents, such as the protocol, SAP, and study reports will undergo quality-control review, senior scientific review, and editorial review.

A quality control will also be performed on the retrieved register data, including controlling the inclusion of compulsory variables, such as SID, hospitalisation, and main diagnosis, in the delivered register data. If data are missing or incorrect, the dataset is sent back to the register holder for correction.

All programs for data management and data analyses will be written by study statistician(s). Quality control check of these programs will be carried out by a statistician other than the one who writes the program. All processes from data management leading to dissemination of study results will undergo quality control checks for programs, result tables and written text. A detailed audit trail of all documents (programs, result tables, reports) along with quality control processes will be maintained.

9.9 Limitations of the research methods

In this non-interventional study, exclusively routinely collected data in the national registers and regional databases in Finland will be obtained. The advantages of using the national registers and regional databases in Finland include the recording of data independently of any study purposes and the full population coverage of the national registers. The use of these data sources enables including individuals fulfilling the inclusion criteria in the study, whereas a selection bias cannot completely be ruled out in a field study. An additional advantage is the high reliability and validity of the data sources proposed for the study (see 9.4).

Despite these advantages, the following limitations arise from the use of routinely collected data:

- In defining the study cohorts, children with in utero exposures are identified based on dispensed prescriptions recorded in the Prescription register. Although a dispensation of a medication is an indication of medication use, dispensing data may not fully reflect actual use of a medication during pregnancy and may therefore cause misclassification of the in utero exposures. This limitation will be addressed in a sensitivity analyses for the primary objectives, which will include in the cohorts exclusively children of women with at least two dispensing occasions.

- As the Finnish Prescription register excludes medications administered in hospitals, some residential facilities and other institutions, the included children do not represent children of hospitalised and institutionalised women who used the medications of interest. However, the conditions and medications of interest in the study are by large treated in primary and secondary care, and the pregnant women would collect prescriptions of interest from pharmacies with a reimbursement. All such dispensed prescriptions are included in the Prescription register, also when the prescriber represents the private sector.

- The used diagnostic information in the Finnish health registers is dependent on the coding practices in clinical practice. Thus, a potential under- or misreporting of diagnoses by practitioners may limit defining diagnoses in the study, including the primary outcomes. While the coding practices in clinical practice cannot be influenced in the current study, the limitation is minimised by using clinical experts for validating the most relevant diagnostic codes to be used in the study. The limitation is further minimised by complementing diagnostic information with laboratory data for the outcomes hypo- and hyperglycaemia and with growth data for the outcome obesity.

- Conducting analytic analyses is limited by potentially low number of children with some outcomes of interest. Particularly, PCOS among girls is diagnosed usually earliest at adolescence, requiring sufficient follow-up time. As the number of children with long follow-up is anticipated to be low and the incidence of PCOS is relatively low, the number of girls with PCOS as an outcome is expected to be insufficient for analytical interpretations. Although some analyses may lack power, all planned analyses will be run, and the potentially low power will be considered in the interpretations and the reporting of the study results. If the data do not permit an analysis as planned, the missing

results will be included in the report with an explanation and the descriptive results will still be presented.

- Based on the estimated numbers of children in each cohort by age, no children aged over 14 years exposed to metformin in utero may be present in the study. However, the children will be followed for as long as data are available, up to the age of 20 years of age, because the extrapolation used in the study size estimations may not reflect the reality, and children aged over 14 years with in utero exposure to metformin might still be observed. Nonetheless, the number of older children exposed to metformin in utero is anticipated to be low, limiting analytical analyses.

- Growth-related follow-up data are available in Finland only from 2011 onwards. Hence secondary outcomes relating to growth (except birth weight and height) will only be available for every year of life since birth for children born in 2011-2016 and for a maximum follow-up period of six years. For children born between 1996-2010, growth data are not available for the time period between birth and 2011.

- Growth outcomes cannot be assessed in the entire population of children, because the data in 2011-2016 are missing for approximately 35% of children, these. As these missing data are random, independent of the study and the research question, this limitation is unlikely to influence the results, beyond weakening the power of these analyses.

- Data on blood glucose measurements are not feasible to obtain from the regional databases of all regions in Finland and thus the data are not available for all study individuals. Thus, outcomes relating to hypoglyceamia and hyperglyceamia may be underestimated for the part of the total population for whom exclusively diagnostic data for these outcomes are available. To address this potential limitation in the analyses on hypoglyceamia and hyperglyceamia, stratified analyses by region of residency, based on the availability of the laboratory data, will be conducted.

- Confounding by indication (also called channelling bias) may result from selective prescribing of a specific medication to patients with a different clinical profile (e.g., more severe). This bias can also arise because of differences in the contraindications and warning and precaution sections regarding metformin or insulin. This will influence the prescribing of medications and, if related to the outcome, act as a confounding factor. In the current study, propensity score weighting will be used, as a method for observational studies to account for bias in a choice of treatment or behaviour (in utero exposures in the current study) in a non-randomised setting.

- However, the propensity score weighting is limited by the unavailability of the following potential confounders by indication: nutritional therapy during pregnancy, exercise during pregnancy, total weight gain and increase in the BMI during pregnancy, and severity of GDM (relevant only in analyses from 2004 onwards). The inability to fully consider these potential confounders by indication will be considered in the interpretation of the study results.

- In the propensity score weighting of the subgroup analyses, gestational week of GDM diagnosis will be used as a proxy for the severity of GDM. Dates for GDM diagnosis will be retrieved from HILMO (secondary care) and from AvoHILMO (primary care), because the Medical Birth Register includes no diagnosis dates. As AvoHILMO was established in 2011 and GDM is typically diagnosed in primary care, the dates of GDM diagnosis and thus the variable gestational week of GDM diagnosis are anticipated to be missing for several children born before 2011.

- In the model adjustments, also other potential confounders will be considered. However, the following potential confounders (other than the potential confounders by indication above) are not available in the Finnish data sources: mode of conception, alcohol use during pregnancy, drug abuse during pregnancy, maternal vitamin D deficiency, maternal vitamin supplement use, and information on breastfeeding and introduction of nonmilk foods. In the analyses for the primary objectives, unmeasured confounding will be assessed as part of the sensitivity analyses. In addition, the inability to consider potential confounders in the model adjustments will be considered in the interpretation of the results.

- The unavailability of breastfeeding information also hinders considering the children's potential exposure to metformin and/or insulin through breastfeeding. Treatment of gestational diabetes is usually discontinued after delivery, while women with PGDM and PCOS will continue treatment after delivery and the children might be further exposed to metformin and/or insulin through breastfeeding.

- The THL has reported administrative challenges in the maintenance of the Register of Congenital Malformations, in compiling the data for the years 2014-2016. Thus, major congenital anomalies (secondary outcome A) for the years 2014-2016 may not be available from the Register of Congenital Malformations by the end of the data collection of the current study. If the data are not available, major congenital anomalies will not be analysed after the end of 2013 and all children's follow-up will end the latest in 2013.

9.10 Other aspects

9.10.1 Independent ethics committee

Prior to commencement of the study in Finland, the protocol will be submitted together with an application form, a variable list, a summary in Finnish and the principal investigator's CV to the Ethics Committee of the Hospital District of Helsinki and Uusimaa for the committee's review and approval. The written favourable approval of the Ethics Committee, obtained in Finnish, will be filed by the investigator and a copy will be sent to the Sponsor.

The study cannot start before EPID Research has obtained the written confirmation of favourable approval from the Ethics Committee of the Hospital District of Helsinki and Uusimaa. The Ethics Committee will provide documentation of the date of the meeting at which the favourable approval was given, and of the voting members present at the meeting. Written evidence of

favourable approval that clearly identifies the study, and the protocol version reviewed will be provided by the Ethics Committee.

Amendments to the protocol will also be submitted to the concerned Ethics Committee, before implementation in case of substantial changes.

9.10.2 Health and other authorities

The protocol will be submitted to the data holders of the included data sources, according to the regulations and procedures for obtaining person-level data for scientific research.

9.10.3 Quality assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, or regulatory agencies may conduct quality assurance audits/inspections at any time during or following a study. The principal investigator must agree to allow auditors/inspectors direct access to all study-related documents, apart from patient-level data, because the register holder of the study register (EPID Research) cannot provide access to person-level data to any other parties, according to national legislation in Finland. The principal investigator must also agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual study report, will be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.10.4 Archiving

As the register holder of the study register, EPID Research is in charge of archiving and destroying the data.

The study data will be held at EPID Research's servers located in a high-quality data centre at Nebula, representing the highest industry standards. EPID Research's Standard Operating Procedure ER-10020.3 Computer System Access and Data Security describes the fundamental principles for managing, accessing and maintaining the computer systems at the company. According to this document, only programmers and statisticians have rights to files and directories that contain sensitive data.

Access to the study data cannot be given to any third parties, and the study data cannot be used for other purposes than described in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

All study data and supporting documents for the study will be retained for five years after the final study report or the first publication of study results, whichever comes later. Secure archives will be maintained for the orderly storage and retrieval of all study-related material. Access to

the archives will be controlled and limited to authorised personnel only. An index shall be prepared to identify the archived contents and their location. When the date of destroying the data and supporting documents is approaching, EPID Research shall request further instructions from the Sponsor. No destruction will be performed without the written approval of the Sponsor.

10 Protection of human subjects

This is a fully register-based study. The study does not affect the treatment of the individuals, the pregnant women or their children, and the pregnant women or their children will not be contacted in any phase of the study. The study is conducted by following the ENCePP code of conduct [48] as well as the Guidelines for GPP [49]. EPID Research, the Sponsor and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study will be registered into ENCePP's European Union electronic Register of Post-Authorisation Studies (EU PAS register).

EPID Research will receive pseudonymised data including SIDs only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the local legislation: Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the original register holders). The study registers are formed on the basis of the Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein.

The Sponsor will not have access to the patient level data at any time of the study.

The protocol will be subjected to the Ethics Committee of the Hospital District of Helsinki and Uusimaa for review and approval, as described under 9.10.1. In addition, a register notification of the forming study register will be sent to the Office of the Data Protection Ombudsman.

10.1 Subject information and informed consent

No information to the individuals, the pregnant women or their children, or informed consents from them are needed. As this non-interventional study involves analysis of secondary data, no individuals will be contacted in any phase of the study, and the study involves no risk or potential harm to the individuals beyond those involved in routine medical care.

10.2 Subject identification and privacy

This study involves analysis of secondary data and all data are pseudonymised to protect the privacy of the individuals. All data on the individuals (pregnant women and their children) will be made de-identifiable ensuring the full data protection of the individuals.

11 Management and reporting of adverse events

According to Good Pharmacovigilance Practices (GVP) Module VI.C.1.2.1 ”for non-interventional studies which are based on secondary use of data” [50], adverse reactions reporting is not required.

12 Plans for disseminating and communicating study results

12.1 Study report

EPID Research and the principal investigator will report the results in a study report. The completed study will be summarised in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings. The report will be delivered to the Sponsor and the responsible parties.

The final study report may be used for the discussions with the competent authorities as required.

Within three months following the study report, an abstract of the study findings will be made available to the public through the EU PAS register. According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. The Sponsor is entitled to view the final results and interpretations prior to submission for publication in the EU PAS register, and to comment these without unjustifiably delaying the publication. The principal investigators may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period due to pending response from the peer-review process.

12.2 Publication

Based on the study report, the principal investigator and co-investigators (members of the responsible parties and possible other contributors approved by the responsible parties) will prepare (a) scientific manuscript(s) for academic publication. The responsible parties decide the publication forums.

The principal investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by the Sponsor, prior to submission for publication. The Sponsor has the right to comment on results and the interpretation thereof. Requests on changing the interpretation of the results or their presentation must be based on sound scientific reasons. The principal investigator is free not to take the comments of the Sponsor into account and, in the event of such a refusal, the Sponsor may only require that the presentation of the results be changed to delete confidential information. The Sponsor cannot unjustifiably delay the publication. In this particular study the commenting time for the Sponsor during the review rounds is agreed to be maximum of one month.

The principal investigator and the Sponsor are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content [51]. These conditions apply equally to external investigators and to employees of the Sponsor.

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14 Appendices

14.1 List of stand-alone documents

Number	Document reference number	Date	Title
None			

14.2 ENCePP Checklist for Study Protocols

Study title:
Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a retrospective register-based cohort study

Study reference number:
Merck study number: MS200084_0011
EPID Research: ER-9550

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	6
1.1.4 Interim progress report(s)	☐	☐	☒	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7-8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7-8
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	8.1
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.1
	4.2.2 Age and sex?	☒	☐	☐	9.2.1
	4.2.3 Country of origin?	☒	☐	☐	9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication?	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7.3 9.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.2 9.7.3 9.9
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.3.2 9.7.3 9.9
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1.2 9.4
9.1.3 Covariates?	☒	☐	☐	9.3.2 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1.2 9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.2 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1 9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1.2 9.4
9.3.3 Covariates?	☒	☐	☐	9.3.2 9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4 9.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.3 Are stratified analyses included?	☒	☐	☐	9.7.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.3
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6 9.10.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8 9.10.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Company substance code **INN**
Protocol number

Comments:

Name of the main author of the protocol: Katja Hakkarainen

Date: 18/May/2017

Signature: Katja Hakkarainen

14.3 Additional information

Appendix 1. List of codes for diagnoses

Study term/condition category						
	ICD-10 (code)	**ICD-10 (text)**	**Deviation in the Finnish ICD-10 codes**	**ICPC-2 (code)**	**ICPC-2 (text)**	**Permanent/ temporary variable[a]**
1	**Obesity[b]**					**Temporary**
	E66	Obesity	No	T82 T83	Obesity Overweight	
2	**Hypoglycaemia[b]**					**Temporary**
	E16.1	Other hypoglycaemia	***Yes*** *E16.10 Hyperinsulinism* *E16.11 Hyperinsulinism NOS* *E16.17 Functional nonhyperinsulinaemic hypoglycaemia* *E16.19 Other specified hypoglycaemia*	T87	Hypoglycaemia	
	E16.2	Hypoglycaemia, unspecified	No	T87	Hypoglycaemia	
	P70.0	Syndrome of infant of mother with gestational diabetes	No	-	-	
	P70.1	Syndrome of infant of a diabetic mother	No	-	-	
	P70.3	Iatrogenic neonatal hypoglycaemia	No	-	-	
	P70.4	Other neonatal hypoglycaemia	No	-	-	
3	**Hyperglycaemia[b]**					**Temporary**
	R73	Elevated blood glucose level	No	-	-	
4	**Hypertension[b]**					**Temporary**
	I10-I15	Hypertensive diseases	No	K86 K87	Hypertension uncomplicated Hypertension complicated	
	P29.2	Neonatal hypertension	No	-	-	
5	**Diabetes mellitus[b]**					**Permanent**
	E10-E14	Diabetes Mellitus	No	F83 T89 T90	Retinopathy Diabetes insulin dependent Diabetes non-insulin dependent	
	P70.2	Neonatal diabetes mellitus	NA		-	
6	**PCOS[b,c]**					**Permanent**
	E28.2	Polycystic ovarian syndrome	No	T99	Endocrine/metab/nutrit. dis. other	
7	**Challenges in motor-social development[b]**					**Permanent**
	F80	Specific developmental disorders of speech and language	No	P24 P99	Specific learning problem Psychological disorders, other	
	F81	Specific developmental	No	P24	Specific learning problem	

Study term/condition category

ICD-10 (code)	ICD-10 (text)	Deviation in the Finnish ICD-10 codes	ICPC-2 (code)	ICPC-2 (text)	Permanent/ temporary variable[a]
	disorders of scholastic skills				
F82	Specific developmental disorder of motor function	No	P24	Specific learning problem	
F83	Mixed specific developmental disorders - meeting the criteria for two or more of F80-F82	No	P24	Specific learning problem	
F84	Pervasive developmental disorders (includes Autism)	No	P99	Psychological disorders, other	
F88	Other disorders of psychological development	No	P99	Psychological disorders, other	
F89	Unspecified disorder of psychological development	No	P99	Psychological disorders, other	
F90	Hyperkinetic disorders	No	P81	Hyperkinetic disorder	
F91	Conduct disorders	No	P22	Child behaviour symptom/complaint	
F92	Mixed disorders of conduct and emotions	No	P22	Child behaviour symptom/complaint	
F93	Emotional disorders with onset specific to childhood	No	P22	Child behaviour symptom/complaint	
F94	Disorders of social functioning with onset specific to childhood and adolescence	No	P22	Child behaviour symptom/complaint	
F95	Tic disorders	No	P10	Stammering/stuttering/tic	
F98	Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence	No	P10 P11 P12 P13 P29	Stammering/stuttering/tic Eating problem in child Bedwetting/enuresis Encopresis/bowel training problem Psychological symptom/complt other	
-	-	-	P28	Limited function/disability	
-	-	-	P85	Mental retardation	

8	Major congenital anomalies - structural anomalies[b]				Not applicable
Q00-Q07	Congenital malformations of the nervous system	No	N85	N85 Congenital anomaly neurological	
Q10-Q18	Congenital malformations of eye, ear, face and neck	No	F80 F81 H80 D81	Blocked lacrimal duct of infant Congenital anomaly eye other Congenital anomaly of ear Congenital anomaly digestive system	
Q20-Q28	Congenital malformations of the circulatory system	No	K73	Congenital anomaly cardiovascular	
Q30-Q34	Congenital malformations of the respiratory system	No	R89	Congenital anomaly respiratory	
Q35-	Cleft lip and cleft palate	No	D81	Congenital anomaly digestive	

Study term/condition category

	ICD-10 (code)	ICD-10 (text)	Deviation in the Finnish ICD-10 codes	ICPC-2 (code)	ICPC-2 (text)	Permanent/ temporary variable[a]
	Q37				system	
	Q38-Q45	Other congenital malformations of the digestive system	No	D81	Congenital anomaly digestive system	
	Q50-Q56	Congenital malformations of genital organs	No	X83	Congenital anomaly genital female	
				Y82	Hypospadias	
				Y83	Undescended testicle	
				Y84	Congenital genital anomaly (m) other	
	Q60-Q64	Congenital malformations of the urinary system	No	U85	Congenital anomaly urinary tract	
	Q65-Q79	Congenital malformations and deformations of the musculoskeletal system	No	L82	Congenital anomaly musculoskeletal	
	Q80-Q89	Other congenital malformations	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
				B79	Congenital anomaly blood/lymph other	
				S83	Congenital skin anomaly other	
				T78	Thyroglossal duct/cyst	
				T80	Congenital anom endocrine/ metab.	
				Y84	Congenital genl anomaly (m) other	
9	**Major congenital anomalies - Chromosomal defect[b]**					**Not applicable**
	Q90-Q99	Chromosomal abnormalities, not elsewhere classified (incl trisomies)	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q90	Down syndrome	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q91	Edwards syndrome and Patau syndrome	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q92	Other trisomies and partial trisomies of the autosomes, not elsewhere classified	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q93	Monosomies and deletions from the autosomes, not elsewhere classified	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q95	Balanced rearrangements and structural markers, not elsewhere classified	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q96	Turner syndrome	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q97	Other sex chromosome abnormalities, female phenotype, not elsewhere classified	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
	Q98	Other sex chromosome abnormalities, male phenotype,	No	A90[d]	Congenital anomaly not otherwise specified/multiple	

Study term/condition category						
	ICD-10 (code)	**ICD-10 (text)**	**Deviation in the Finnish ICD-10 codes**	**ICPC-2 (code)**	**ICPC-2 (text)**	**Permanent/ temporary variable[a]**
		not elsewhere classified				
	Q99	Other chromosome abnormalities, not elsewhere classified	No	A90[d]	Congenital anomaly not otherwise specified/multiple	
10	**Major congenital anomalies - Congenital hypothyroidism[b]**					**Not applicable**
	E00	Congenital iodine-deficiency syndrome	No	T80	Congenital anomaly endocrine/metabolic	
	E00.1	Congenital iodine-deficiency syndrome, myxoedematous type - Hypothyroid	No	T80	Congenital anomaly endocrine/metabolic	
	E00.2	Congenital iodine-deficiency syndrome, mixed type	No	T80	Congenital anomaly endocrine/metabolic	
	E00.9	Congenital iodine-deficiency hypothyroidism NOS, within Congenital iodine-deficiency syndrome, unspecified	No	T80	Congenital anomaly endocrine/metabolic	
	E02	Subclinical iodine-deficiency hypothyroidism	No	T86	Hypothyroidism/myxoedema	
	E03	Other hypothyroidism	No	T86	Hypothyroidism/myxoedema	
	E03.0	Congenital hypothyroidism with diffuse goitre	No	T86	Hypothyroidism/myxoedema	
	E03.1	Congenital hypothyroidism without goitre	No	T86	Hypothyroidism/myxoedema	
	E03.2	Hypothyroidism due to medicaments and other exogenous substances	No	T86	Hypothyroidism/myxoedema	
	E03.8	Other specified hypothyroidism	***Yes*** *E03.80 Hypothyroidism caused by autoimmune thyroiditis* *E03.82 Hypothyroidism caused by autoimmune thyroiditis* *E03.89 Other specified hypothyroidism*	T86	Hypothyroidism/myxoedema	
	E03.9	Hypothyroidism, unspecified	No	T86	Hypothyroidism/myxoedema	
11	**Gestational diabetes mellitus[c]**					**Not applicable**
	O24.4	Diabetes mellitus arising in pregnancy	No	W85	Gestational diabetes	
	O24.9	Diabetes mellitus in pregnancy, unspecified	No	-	-	
12	**Type 1 diabetes mellitus[c]**					**Not applicable**
	E10	Type 1 diabetes mellitus	No	T89	Diabetes insulin dependent	
	O24.0	Pre-existing type 1 diabetes mellitus	No	-	-	

Study term/condition category						
	ICD-10 (code)	**ICD-10 (text)**	**Deviation in the Finnish ICD-10 codes**	**ICPC-2 (code)**	**ICPC-2 (text)**	**Permanent/ temporary variable[a]**
13	**Preeclampsia[c]**					**Not applicable**
	O14	Pre-eclampsia	No	W81	Toxaemia of pregnancy	
14	**Type 2 diabetes mellitus[c]**					**Not applicable**
	E11	Type 2 diabetes mellitus	No	T90	Diabetes non-insulin dependent	
	O24.1	Pre-existing type 2 diabetes mellitus	No	-	-	
15	**Essential hypertension[c]**					**Not applicable**
	I10	Essential (primary) hypertension	No	K86	Hypertension uncomplicated	
16	**Gestational hypertension[c]**					**Not applicable**
	O13[e]	Gestational [pregnancy-induced] hypertension	No	W81	Toxaemia of pregnancy	
17	**Persistent diabetes mellitus in mother after birth[c]**					**Not applicable**
	E10-E14 excl E11	Diabetes mellitus, excl. type 1 diabetes mellitus	No	F83[f] T90	Retinopathy Diabetes non-insulin dependent	

ICD-10 = International Classification of Diseases, 10th revision; ICPC-2 = International Classification of Primary Care, 2nd revision; PCOS = polycystic ovary syndrome.
[a] Applicable exclusively for long-term diagnoses (evaluated throughout the childhood).
[b] Applied to the children.
[c] Applied to the mothers.
[d] Applied exclusively to define the main group "any major congenital anomaly", and not to define by type, because the code includes both major structural anomalies and chromosomal defect.
[e] O13 also includes mild preeclampsia.
[f] Type 1 diabetes mellitus already excluded as part of exclusion criteria.

Appendix 2. List of codes for medications

Medications	ATC (code)	ATC (text)
In utero exposures		
Metformin	A10BA02	Metformin
Insulins	A10A	Insulins and analogues
Exclusion		
Blood glucose lowering drugs	A10B	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
	A10BA Except for A10BA02	Biguanides
	A10BB	Sulfonylureas
	A10BC	Sulfonamides (heterocyclic)
	A10BD	Combinations of oral blood glucose lowering drugs
	A10BF	Alpha glucosidase inhibitors
	A10BG	Thiazolidinediones
	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
	A10X	OTHER DRUGS USED IN DIABETES
	A10XA	Aldose reductase inhibitors
Glucocorticoids – systemic use	H02AB	Glucocorticoids
Covariates		
Dispensation of antidiabetic medications	A10	Drugs used in diabetes

ATC = Anatomical Therapeutic Chemical.

14.4 Signature pages and responsible persons for the study

Signature Page – Protocol Lead

Study Title:	Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study
Study Protocol Date / Version:	15 May 2017/ Version 1.0

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study protocol:

Signature

16.05.2017

Date of Signature

Name, academic degree:	Dr. Kerstin Brand
Function / Title:	Pharm Med Director Diabetes
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250 64293 Darmstadt, Germany

Signature Page – EU QPPV (European Union Qualified Person Responsible for Pharmacovigilance for Merck KGaA)

Study Title:	Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study
Study Protocol Date / Version:	15 May 2017/ Version 1.0

EU QPPV, European Union Qualified Person Responsible for Pharmacovigilance:

I approve the design of the non-interventional study protocol:

Signature

16 May 2017

Date of Signature

Name, academic degree:	Dr. Berit Nautrup-Andersen
Function / Title:	European Union Qualified Person Responsible for Pharmacovigilance
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250 64293 Darmstadt, Germany

Signature Page – Principal Investigator

Study Title	Consequences for life of children with in utero exposure to metformin in Finland (CLUE) – a register-based cohort study
Study Protocol Date / Version	15 May 2017/ Version 1.0
Principal Investigator	Pasi Korhonen

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmacoepidemiology Practices (GPP) and all applicable Health Authority requirements and national laws.

Signature

16 MAY 2017

Date of Signature

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