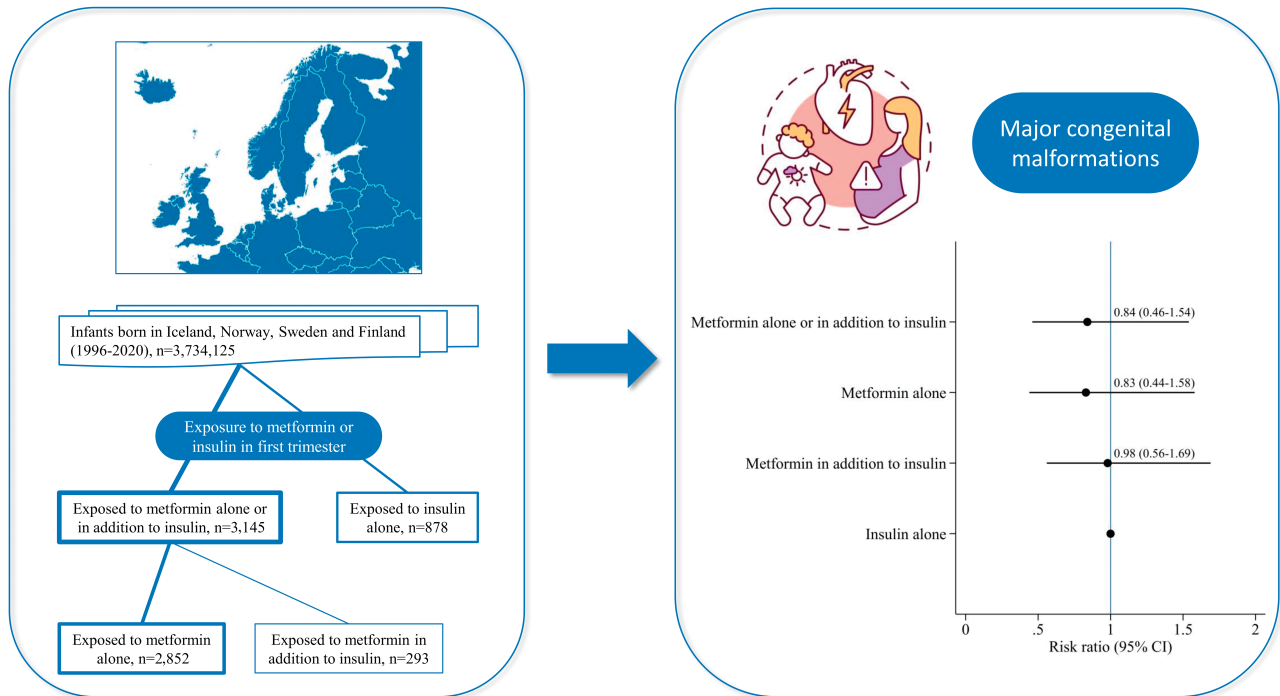# Metformin Versus Insulin and Risk of Major Congenital Malformations in Pregnancies With Type 2 Diabetes: A Nordic Register-Based Cohort Study

Lars J. Kjerpeseth, Carolyn E. Cesta, Kari Furu, Anders Engeland, Mika Gissler, Hanne L. Gulseth, Øystein Karlstad, Maarit K. Leinonen, Laura Pazzagli, Helga Zoega, and Jacqueline M. Cohen

Metformin versus insulin and risk of major congenital malformations in pregnancies with type 2 diabetes

Ill.: Mostphotos

## ARTICLE HIGHLIGHTS

- Unlike insulin, metformin crosses the placenta, raising concern about its fetal safety.
- This cohort study assesses the risk of major congenital malformations with metformin versus insulin in pregnancies with type 2 diabetes since trials have been too small to give precise estimates of this risk.
- In the study comprising four Nordic countries, evidence of an increased risk of any or cardiac malformations was not found for early pregnancy exposure to metformin (alone or in addition to insulin) versus insulin alone.
- The findings can guide prescribers and patients who are considering metformin treatment for type 2 diabetes in pregnancy.

# Metformin Versus Insulin and Risk of Major Congenital Malformations in Pregnancies With Type 2 Diabetes: A Nordic Register-Based Cohort Study

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## OBJECTIVE

**To assess the risk of major congenital malformations with metformin versus insulin in pregnancies with type 2 diabetes.**

## RESEARCH DESIGN AND METHODS

**This cohort study used four Nordic countries' nationwide registers of live and stillborn infants exposed to metformin or insulin during first trimester organogenesis. Main exclusion criteria were type 1 diabetes, polycystic ovary syndrome, fertility treatment, and exposure to other diabetes drugs. Adjusted risk ratios (RRs) and 95% CIs were estimated for any and cardiac malformations.**

## RESULTS

**Of 3,734,125 infants in the source population, 25,956 were exposed to metformin or insulin in the first trimester, and 4,023 singleton infants were included. A malformation was diagnosed in 147 (4.7%) of 3,145 infants with exposure to any metformin (alone or in addition to insulin) and 50 (5.7%) of 878 infants with exposure to insulin alone (RR 0.84, 95% CI 0.46–1.54). Among 2,852 infants exposed to metformin alone and 293 infants exposed to metformin in addition to insulin 127 (4.4%) and 20 (6.8%), respectively, had a malformation. The adjusted risk was not increased for either metformin alone (0.83, 0.44–1.58) or both metformin and insulin (0.98, 0.56–1.69) versus insulin alone. Corresponding RRs for cardiac malformations were 1.01 (0.55–1.84) for any metformin, 0.92 (0.47–1.81) for metformin alone, and 1.72 (0.76–3.91) for both metformin and insulin.**

## CONCLUSIONS

**No evidence of an increased malformation risk with metformin versus insulin in the first trimester was found. Results should be interpreted with caution since information on glycemic control was missing.**

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The prevalence of type 2 diabetes in reproductive-age women and, consequently, during pregnancy has grown rapidly in past decades (1–3). Type 2 diabetes is associated with several adverse birth outcomes, including an up to threefold increased risk of nonchromosomal major congenital malformations (4). This risk, however, can be substantially mitigated by appropriate glycemic control (2,4,5).

Insulin has traditionally been the recommended glucose-lowering drug in pregnancy since it has well-established efficacy and safety (6). However, insulin is costly, is cumbersome to administer, and requires frequent glucose measurements. Metformin, the first-line drug for type 2 diabetes outside of pregnancy, is increasingly being used during pregnancy (7).

Unlike insulin, metformin crosses the placenta, raising concerns of potential teratogenicity (6,8). Randomized controlled trials (RCTs) have not been able to adequately investigate this risk because of small sample sizes and because randomization to metformin typically occurs after the first trimester, when major organs are formed and are most sensitive to the development of congenital malformations (6,9). Observational studies on metformin exposure in early pregnancy have been reassuring but scarce, especially for type 2 diabetes (10,11). The evidence on specific malformations is even more limited because of small study sizes (11). While the American Diabetes Association guidelines recommend insulin before metformin for type 2 diabetes in pregnancy (8), the prescribing advice is not consistent among guidelines, product labels, and other drug information sources (8). Thus, larger studies are needed to explore the safety of first trimester metformin exposure in pregnant women with type 2 diabetes and particularly to assess specific concerns, such as cardiac malformations, the organ system most often affected by malformations (6,11).

To generate evidence, we pooled individually linked register data from four Nordic countries. The nationwide registers in Nordic countries provide complete coverage of live births and stillbirths with accurate measurement of gestational age, dispensed prescription drugs, and recorded diagnoses in mothers and infants (12). We compared the risk of any and cardiac major congenital malformations with prenatal exposure to metformin (alone or in addition to insulin) versus insulin alone in the first trimester in pregnant women with type 2 diabetes. We excluded those with other indications, such as polycystic ovary syndrome and assisted reproductive treatment, to minimize confounding by indication.

## RESEARCH DESIGN AND METHODS
### Study Setting and Data Sources
This cohort study was based on data from the nationwide medical birth registers of Finland (1996–2016), Iceland (2004–2017), Norway (2005–2020), and Sweden (July 2006–2019). Using personal identity numbers unique to all residents, mother and infant pairs were linked to nationwide registers on filled prescriptions and specialist health care in all countries. We also linked to registers on cause of death (all countries except for Finland and mothers in Iceland) and educational attainment (all countries except Finland), to primary care data registers in Norway and Finland, and to the Finnish Register of Congenital Anomalies. In the Nordic health registers, the sex assigned at birth is reported, while gender identity is not available. Thus, in this article, we define women as human females of any gender identity. Further details of the registers are available in the Supplementary Material.

### Study Population
We included singleton, live-born or stillborn infants with prenatal exposure to insulin or metformin in first trimester (Fig. 1). Exposure was defined as at least one recorded dispensing, meaning a filled prescription at the pharmacy, of metformin (Anatomical Therapeutic Chemical code A10BA02) or insulin (Anatomical Therapeutic Chemical codes starting with A10A) during the period. First trimester was defined as the start date of last menstrual period before pregnancy to 97 days after last menstrual period. It was calculated by subtracting the gestational age (as recorded in the medical birth registers, assessed primarily by ultrasound) from the delivery date. Infants were not included if the recorded gestational age of the pregnancy was missing, <22 weeks, >44 weeks, or implausible based on birth weight (sex-specific birth weight $z$ score >4 SDs and gestational age <35 weeks) because of uncertainty regarding the timing of the first trimester (13). Terminations were excluded since we only had information on induced abortions from 12 weeks onward for Norway.

To focus on outcomes associated with metformin or insulin, we excluded infants diagnosed with a teratogenic infection (i.e., rubella, cytomegalovirus, toxoplasmosis), chromosomal anomaly, microdeletion, or genetic syndrome within 1 year of birth. We also excluded infants with potential exposure to other glucose-lowering drugs or known teratogenic drugs in the first trimester (Supplementary Table 1).

Since the intent of the study was to estimate the effect of metformin on major congenital malformations using insulin as an active comparator, we focused on infants born to mothers with type 2 diabetes, thereby reducing the influence of confounding by indication. Because of underrecording of the diagnosis in the register data, we defined type 2 diabetes in mothers as the absence of type 1 diabetes or other chronic diabetes than type 2 diabetes, polycystic ovary syndrome, and assisted reproductive treatment, conditions for which only one drug is indicated. Thus, infants were excluded if their mother had been dispensed insulin between 90 days before last menstrual period and end of first trimester and had a recorded diagnosis of type 1 diabetes in specialist health care or in the Norwegian medical birth register before delivery. Similarly, infants born to mothers with other types of chronic diabetes (except type 2 diabetes), polycystic ovary syndrome, or assisted reproductive treatment were excluded using diagnoses recorded in specialist (mainly) and primary health care before delivery. Assisted reproductive treatment was additionally identified from the medical birth registers, diagnoses or procedures from 90 days before last menstrual period to delivery, or the dispensing of all three of the following drug classes from 90 days before last menstrual period and end of first trimester: gonadotropin-releasing hormone analogs, gonadotropins, and human chorionic gonadotropin.

### Definition of Exposure and Comparison Groups
We compared infants with prenatal exposure to metformin in the first trimester with those exposed to insulin alone. Infants with prenatal exposure to both metformin and insulin during the first trimester were allocated to the metformin group, which was then divided into three exposure groups compared with insulin alone in the primary analyses: exposure to any metformin (alone or in addition to insulin), metformin in addition to insulin, and metformin alone.

### Definition of Outcomes
The outcome was major congenital malformations in the infant, diagnosed within 1 year of birth and recorded in medical birth, patient, malformation, or cause of death registers. The definition was aligned as closely as possible with the classification

```
┌─────────────────────────┐
│ Total number of infants │
│ in dataset,             │
│ n=3,734,125             │
└─────────────────────────┘
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Exclusion:
- Not singleton, n=111,486
- Terminations, n=10,191
- Missing birthweight, n=3,377
- Missing sex, n=99
- Gestational age missing or outside valid range, n=3,443
- Gestational age implausible based on birthweight, n=247

Exposed to metformin or insulin in first trimester, n=25,956

Exposed to metformin alone or in addition to insulin, n=8,526

Exposed to insulin alone, n=17,430

Exclusion:
- Prenatal exposure to other antidiabetics, n=376
- Prenatal exposure to known teratogenic drugs, n=15
- Genetic MCM or congenital infection, n=36
- Type 1 diabetes recorded in mother, n=804
- Other types of chronic diabetes in mother, n=61
- Polycystic ovary syndrome in mother, n=2,868
- Assisted reproductive therapy in mother, n=1,221

Exclusion:
- Prenatal exposure to other antidiabetics, n=371
- Prenatal exposure to known teratogenic drugs, n=50
- Genetic MCM or congenital infection, n=45
- Type 1 diabetes in mother, n=15,962
- Other types of chronic diabetes in mother, n=26
- Polycystic ovary syndrome in mother, n=65
- Assisted reproductive therapy in mother, n=33

Exposed to metformin alone or in addition to insulin, n=3,145

Exposed to insulin alone, n=878
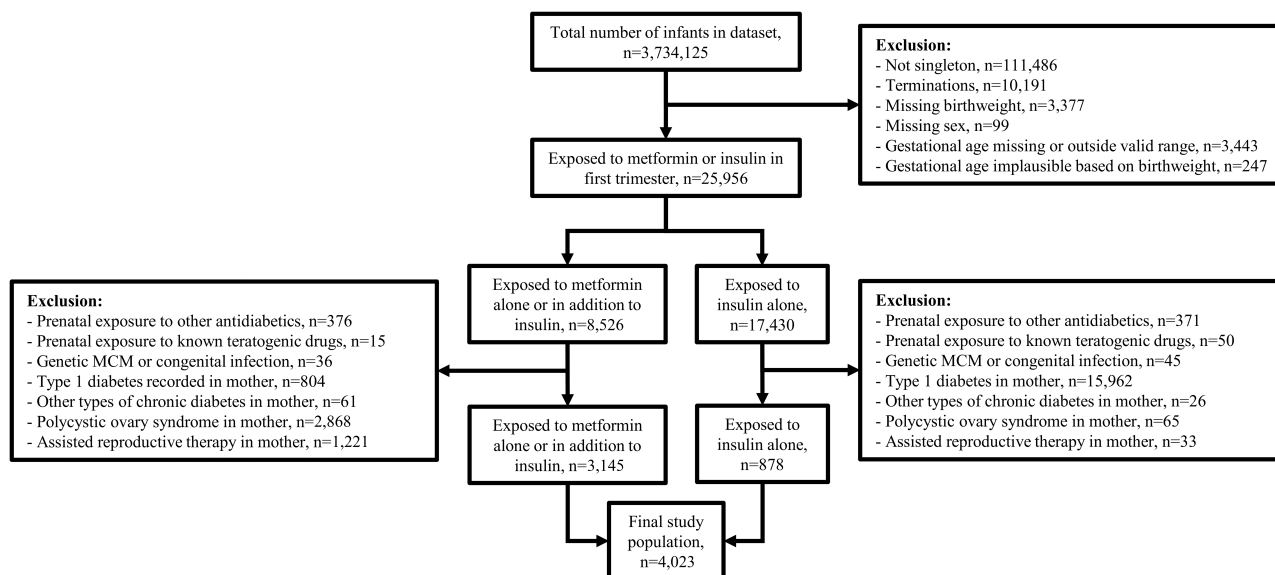
Final study population, n=4,023

Figure 1—Selection of the study population of infants from nationwide medical birth registers of Finland (1996–2016), Iceland (2004–2017), Norway (2005–2020), and Sweden (July 2006–2019). Exclusions are sequential in the order listed. The metformin group included infants with prenatal exposure to metformin alone or in addition to insulin. MCM, major congenital malformation.

in the European Commission's network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT Guide 1.4) (14) (Supplementary Table 2). We considered any major congenital malformation as the primary outcome and the subgroup of major cardiac malformations as the secondary outcome. For Finland, we only considered validated diagnoses from the Finnish Register of Congenital Malformations. To increase diagnostic validity for Iceland, Norway, and Sweden, we required at least two diagnosis codes from the same subgroup to be recorded on separate visit dates if the malformation was only diagnosed in outpatient specialist care.

### Covariates

To reduce confounding, we adjusted for country and year of birth and maternal characteristics including age at delivery, country of birth (Nordic/non-Nordic or Finnish/non-Finnish citizenship), and cohabitation with a partner. Potential exposure in the first trimester to suspected teratogenic drugs, glucocorticoids, lipid-modifying drugs, and antihypertensive drugs was also adjusted for. Furthermore, we adjusted for maternal BMI at the start of pregnancy; maternal comorbidities; potential complications of type 2 diabetes, such as chronic hypertension, cardiovascular disease, and other diabetes complications; epilepsy; and severe mental illness. Comorbidities were defined by

diagnosis codes recorded from 1 year before last menstrual period to end of pregnancy, except for skin and vaginal infections, which were identified from 1 year before last menstrual period to end of first trimester. For Norway and Finland, comorbidities were also defined using drug reimbursement indication codes within the same time window. See Supplementary Table 3 for the definitions of the covariates.

### Statistical Analyses

Data from the four countries were harmonized in a common data model and individually pooled into one cohort before the analyses were performed (15). To adjust for differences in baseline covariates between comparison groups, we used propensity score fine stratification with up to 50 strata and at least 3 exposed and nonexposed in each stratum. After stratification, Mantel-Haenszel pooling was used to estimate relative risks (risk ratios [RRs]) with 95% CIs for prenatal exposure to metformin versus insulin. This method performs better than traditional propensity score methods when the prevalence of the exposure is low (16). All covariates previously listed were included in the propensity score model. Maternal country of birth, cohabitation with a partner, and BMI had missing values (0.6%, 4.3%, and 24.0%, respectively) and were imputed 100 times using predicted mean matching and

included in a propensity score analysis that was conducted in each imputed data set. The estimates were then combined using Rubin's rules (17). We used Stata SE 17 for Windows statistical software (StataCorp, College Station, TX) to analyze the data.

### Sensitivity Analyses

We conducted several sensitivity analyses, each for both the primary and secondary outcomes. First, a new-user design was implemented by including only infants born to mothers with no dispensing of metformin or insulin from 90 days before last menstrual period to end of gestational week 6 (18). The aim of this approach was to further exclude infants born to mothers dispensed metformin for polycystic ovary syndrome or assisted reproductive treatment or insulin for type 1 diabetes. The resulting study population thus included infants born to mothers with type 2 diabetes who did not receive pharmacological treatment until after gestational week 6 or if type 2 diabetes in the mother was first diagnosed during prenatal care. Second, the study population was restricted to women with at least one diagnosis of type 2 diabetes recorded at any time in the available look-back period before or on the date of birth. Third, we conducted a sensitivity analysis requiring at least two dispensations of the drugs of interest to reduce the impact of potential exposure misclassification, since infants of mothers

with only a single dispensing of metformin and/or insulin in first trimester may have had limited or no prenatal exposure. Fourth, a complete case analysis was conducted to check the consistency with the results obtained from the multiple imputation approach used in the primary analyses. Fifth, smoking in early pregnancy, folic acid use before and during pregnancy, and maternal education were not included in the primary analyses, since information on each variable was unavailable for at least one of the included countries. In a sensitivity analysis, missing values of these variables were imputed 100 times using the same approach as in the primary analyses. Sixth, high-dimensional propensity score analyses were undertaken to identify potential proxies for unmeasured confounders, such as glycemic control in mothers, and to explore the impact of these on the observed associations (19). The model included the top 100 empirically selected covariates and the following predefined covariates: country and year of birth, maternal age, country of birth, cohabitation with a partner, and BMI. The empirically selected covariates were identified from inpatient and outpatient diagnosis codes, inpatient and outpatient procedure codes, primary care codes, and drug codes recorded before pregnancy. Seventh, to further disentangle the potential teratogenic effect of metformin from that of diabetes, we selected a different study population of mothers with a diagnosis of polycystic ovary syndrome and no pregestational diabetes before delivery. The exclusion criteria were the same as for the primary study population except that we also excluded mothers with a diagnosis of type 2 diabetes but not mothers who received assisted reproductive treatment. We compared the malformation risk with and without metformin exposure after adjusting for the same covariates as in the primary analyses.

### Ethics Statement

The research was approved by applicable ethics review boards and/or register controllers in all study countries (Supplementary Table 4).

### Data and Resource Availability

The data that support the findings of this study are available from the data custodians of the Nordic health registers, but restrictions apply to the availability of these data, which were used under license for the current study and, therefore, are not publicly available.

## RESULTS

In total, the source population included 3,734,125 infants. We identified 25,956 singleton, live-born or stillborn infants with prenatal exposure to metformin or insulin in the first trimester. After exclusions, 4,023 infants remained in the final study population: 878 (21.8%) were exposed to insulin alone, while 3,145 (78.2%) pregnancies were exposed to any metformin, either alone (2,852 infants) or in addition to insulin (293 infants). The most prevalent reasons for exclusion were polycystic ovary syndrome and assisted reproductive treatment in the mother among those exposed to metformin and maternal type 1 diabetes among those exposed to insulin alone. Of note, Finland was the only country contributing to the study population before 2004 (152 infants).

Mothers of infants with prenatal exposure to insulin were generally older, more often multiparous, and more often born in a non-Nordic country than mothers of infants with prenatal exposure to metformin (Table 1). All maternal comorbidities and comedications were generally more common in the insulin group, especially chronic hypertension. BMI $\geq 30$ kg/m$^2$, lower education, and no use of folic acid before or during pregnancy were also more prevalent in the insulin group. Information on BMI, education, and folate use, as well as smoking, was missing for many mothers.

A major congenital malformation occurred in 147 (4.7%) infants with prenatal exposure to metformin (alone or in addition to insulin) and 50 (5.7%) infants with prenatal exposure to insulin alone. The crude RR was 0.82 (95% CI 0.60–1.12) for metformin versus insulin, and, after adjustment for confounders, the estimated RR was 0.84 (0.46–1.54) (Table 2).

Among the 2,852 infants prenatally exposed to metformin alone, 127 (4.4%) had a malformation, and among 293 infants exposed to metformin and insulin, 20 (6.8%) had a malformation. The relative risk for the comparison with insulin alone did not suggest an increased risk associated with metformin after adjusting for confounders (Table 2).

The malformations were most common in the cardiac organ system. Major cardiac malformations occurred in 63 (2.0%) and 18 (2.1%) infants exposed to any metformin and insulin, respectively. After adjustment, neither any metformin (RR 1.01, 95% CI 0.55–1.84) nor metformin alone (0.92, 0.47–1.81) was associated with an increased risk of cardiac malformations compared with insulin alone (Table 2). In a corresponding analysis, an increased risk was observed for exposure to both metformin and insulin; however, the estimate was uncertain (1.72, 0.76–3.91).

For both any and cardiac malformations, the sensitivity analyses were mostly in line with the primary analyses (Table 3). In infants of mothers with polycystic ovary syndrome, the risk of any (RR 1.12, 95% CI 0.92–1.36) and cardiac (1.12, 0.82–1.53) malformations did not differ significantly with and without metformin exposure. However, among infants of mothers with a recorded type 2 diabetes diagnosis, metformin (alone or in addition to insulin) was associated with an increased risk for cardiac malformations versus insulin alone. Again, the estimate was uncertain (2.03, 0.89–4.62).

To elucidate the two results suggesting a potential increased risk of cardiac malformations with exposure to metformin, we performed a supplementary exploratory analysis. The distribution of subgroups of cardiac malformations among infants exposed to insulin alone and those exposed to any metformin was investigated. Right ventricular outflow obstruction defects were relatively more common in the latter group, but this may be explained by a lower number of cases overall in the insulin group because of its smaller size compared with metformin (Supplementary Fig. 1).

## CONCLUSIONS

Among the 4,023 infants included in this large Nordic cohort study, we found no evidence of an increased risk of either any or major cardiac malformations with prenatal exposure to metformin compared with insulin alone in pregnancies affected by type 2 diabetes. These null findings are in line with other observational studies (11,20–25). One of the largest previous studies comparing first trimester exposure to metformin with insulin was a Taiwanese population-based cohort study of 1,166 infants born to mothers with type 2 diabetes. The results

**Table 1—Maternal and pregnancy characteristics in the study population of infants with prenatal exposure to metformin alone or in addition to insulin or insulin alone**

| | Metformin alone or in addition to insulin, n (%) | Insulin alone, n (%) |
|---|---|---|
| Total | 3,145 (100) | 878 (100) |
| Infant's country of birth | | |
| Finland | 1,169 (37.2) | 242 (27.6) |
| Iceland | 275 (8.7) | 32 (3.6) |
| Norway | 960 (30.5) | 168 (19.1) |
| Sweden | 741 (23.6) | 436 (49.7) |
| Infant's year of birth* | | |
| 1996–2006 | 351 (11.2) | 226 (25.7) |
| 2007–2009 | 617 (19.6) | 137 (15.6) |
| 2010–2012 | 578 (18.4) | 118 (13.4) |
| 2013–2015 | 670 (21.3) | 184 (21.0) |
| 2016–2020 | 929 (29.5) | 213 (24.3) |
| Maternal age (years) | | |
| <25 | 218 (6.9) | 43 (4.9) |
| 25–29 | 910 (28.9) | 166 (18.9) |
| 30–34 | 1,106 (35.2) | 295 (33.6) |
| 35–39 | 707 (22.5) | 276 (31.4) |
| ≥40 | 204 (6.5) | 98 (11.2) |
| Parity | | |
| Nulliparous | 1,461 (46.9) | 178 (20.6) |
| Primiparous | 965 (30.9) | 298 (34.5) |
| Multiparous | 692 (22.2) | 387 (44.8) |
| Missing, n | 27 | 15 |
| Maternal education† | | |
| Compulsory | 275 (16.7) | 96 (18.3) |
| Preuniversity | 714 (43.5) | 271 (51.5) |
| University | 653 (39.8) | 159 (30.2) |
| Missing, n | 1,503 | 352 |
| Married/cohabitation with partner‡ | 2,899 (92.6) | 756 (87.0) |
| Missing, n | 16 | 9 |
| Non-Nordic birth country of mother§ | 663 (22.1) | 345 (40.3) |
| Missing, n | 150 | 22 |
| BMI in early pregnancy (kg/m$^2$)‖ | | |
| <18.5 | 27 (1.1) | <5‡‡ |
| 18.5–24 | 569 (23.2) | 83 (13.8) |
| 25–29 | 620 (25.2) | 152 (25.2) |
| ≥30 | 1,240 (50.5) | 366 (60.7) |
| Missing, n | 689 | <277 |
| Smoking in early pregnancy¶ | 225 (8.3) | 83 (10.5) |
| Missing, n | 448 | 84 |
| Folate use before/during pregnancy# | 797 (40.3) | 126 (19.8) |
| Missing, n | 1,169 | 242 |
| Maternal comorbidities** | | |
| Skin/vaginal infection | 91 (2.9) | 19 (2.2) |
| Diabetic complication | 77 (2.4) | 25 (2.8) |
| Chronic hypertension | 248 (7.9) | 85 (9.7) |
| Cardiovascular disease | 7 (0.2) | 6 (0.7) |
| Epilepsy | 23 (0.7) | 8 (0.9) |
| Severe mental illness | 31 (1.0) | 14 (1.6) |
| Maternal comedication†† | | |
| Suspected teratogenic drugs | 190 (6.0) | 57 (6.5) |
| Antihypertensive drugs | 144 (4.6) | 59 (6.7) |
| Lipid-modifying agents | 57 (1.8) | 17 (1.9) |
| Glucocorticoids | 68 (2.2) | 26 (3.0) |

*Finland contributed births from 1996 to 2016, Iceland from 2004 to 2017, Norway from 2005 to 2020, and Sweden from July 2006 to 2019. †Education was not available for Finland and missing for 21% in Norway and 17% in Sweden in the study population. ‡Married/cohabitation status was missing for 0.6% of the study population. §Non-Nordic birth country of mother was missing for 4.3% of the study population, including 12% in Finland (for which only Finnish/non-Finnish maternal citizenship was available in the research material). ‖BMI was missing for

### Table 1—Continued

55% in Iceland, 48% in Norway, 6% in Sweden, and 13% in Finland. ¶Smoking status was not available for Iceland and missing for 13% in Norway, 4% in Sweden, and 3% in Finland in the study population. #Folate use before pregnancy was not available for Finland and Sweden. Folate use during pregnancy was not available for Finland and was assumed missing for Iceland since we were not able to adequately capture use from prescribed drug dispensations. **The look-back period for maternal comorbidities was from 365 days before last menstrual period to end of first trimester (97 days after last menstrual period) for skin/vaginal infections and from 365 days before last menstrual period to birth for the other comorbidities. Comorbidities are defined in Supplementary Table 3. ††The look-back period for maternal comedication was 90 days before last menstrual period to end of first trimester. Comedications are defined in Supplementary Table 3. ‡‡Numbers between 1 and 4 are not shown to protect confidentiality.

were comparable to ours regarding any congenital malformations. However, the authors did not analyze more specific malformations, such as the cardiac subgroup, possibly because of a small sample size (20).

An even larger Finnish nationwide cohort study by Brand et al. (26) of 10,129 infants also compared metformin with insulin in pregnancy but was not exclusive to type 2 diabetes and had median exposure after the first trimester. Their point estimates suggested a somewhat more protective effect of metformin than ours. We excluded infants born to mothers with other indications than type 2 diabetes to make the comparison arms more similar regarding indication and glycemic control, which may explain why our point estimates are closer to null.

The results of RCTs are similarly reassuring that there is no strong teratogenic effect of metformin. A 2021 meta-analysis of nine RCTs comparing metformin alone or in combination with insulin with insulin alone in pregnancies affected by gestational diabetes mellitus or type 2 diabetes did not find a difference in the risk of congenital malformations in infants (9). The results were in large part driven by the Metformin in Women With Type 2 Diabetes in Pregnancy (MiTy) trial comparing metformin with placebo, in addition to insulin, among pregnant patients with type 2 diabetes (27). However, on average, the randomization occurred after the first trimester in this and the other trials (9).

Our study has a cohort design based on pooled register data from the full population of infants and mothers across four Nordic countries with universal and tax-funded health care. Personal identity numbers unique to all residents enable individual-level linkage of the registers to provide long and complete follow-up of both mother and infant (12). Unlike many other studies, we focused on prenatal exposure during organogenesis in the first trimester. Our data include better measurement of gestational age than most large data sets since the information is primarily based on ultrasound routinely offered during pregnancy. To avoid selection bias, we included stillbirths in addition to live births, which is rarely done by other studies. In total, >3,000 infants with prenatal exposure to metformin were included in the study. To our knowledge, this study is the largest to date to investigate the risk of major congenital malformations associated with metformin use in the first trimester generally and in type 2 diabetes specifically. Because of the large sample size, we were able to include analyses on cardiac malformations, which have not been well captured in the existing evidence (11).

An exception is a European population-based case-control study that reported a signal for an increased risk of pulmonary valve atresia associated with prenatal metformin exposure (21). The authors suggested that the finding might be by chance because of multiple testing of many congenital malformations. We did not have a sufficient sample size to test for single malformations. However, for prenatal exposure to metformin in addition to insulin, the point estimate suggested a moderately increased risk of cardiac malformations compared with insulin alone. Similarly, in the sensitivity analysis restricted to infants of mothers with recorded type 2 diabetes, exposure to any metformin was associated with twice the risk of cardiac malformations compared with insulin alone. However, there were only seven cases in the insulin comparison group, and the result was not statistically significant. The other analyses on cardiac malformations did not suggest a significant harmful effect of metformin.

### Table 2—Risk of any and cardiac major congenital malformations in infants with prenatal exposure to metformin alone or in addition to insulin compared with insulin alone

|  | Outcome prevalence, n (%) | | RR (95% CI) | |
|---|---|---|---|---|
|  | Exposure to metformin | Exposure to insulin alone | Crude | Adjusted* |
| Any major congenital malformation |  |  |  |  |
| Metformin alone or in addition to insulin | 147 of 3,145 (4.7) | 50 of 878 (5.7) | 0.82 (0.60–1.12) | 0.84 (0.46–1.54) |
| Metformin alone | 127 of 2,852 (4.4) | 50 of 878 (5.7) | 0.78 (0.57–1.08) | 0.83 (0.44–1.58) |
| Metformin and insulin | 20 of 293 (6.8) | 50 of 878 (5.7) | 1.20 (0.73–1.98) | 0.98 (0.56–1.69) |
| Cardiac major congenital malformation |  |  |  |  |
| Metformin alone or in addition to insulin | 63 of 3,145 (2.0) | 18 of 878 (2.1) | 0.98 (0.58–1.64) | 1.01 (0.55–1.84) |
| Metformin alone | 52 of 2,852 (1.8) | 18 of 878 (2.1) | 0.89 (0.52–1.51) | 0.92 (0.47–1.81) |
| Metformin and insulin | 11 of 293 (3.8) | 18 of 878 (2.1) | 1.83 (0.88–3.83) | 1.72 (0.76–3.91) |

*Adjusted for country and year of birth of infant; maternal characteristics, including age, country of birth, cohabitation with a partner, BMI, epilepsy, severe mental illness, chronic hypertension, cardiovascular disease, skin/vaginal infections, and other diabetic complications; and prenatal exposure to suspected teratogenic drugs, glucocorticoids, lipid-modifying drugs, and antihypertensive drugs.

**Table 3—Sensitivity analyses for the risk of any and cardiac major congenital malformations in infants with prenatal exposure to metformin alone or in addition to insulin compared with insulin alone**

| | Outcome prevalence, *n* (%) | | RR (95% CI) | |
| --- | --- | --- | --- | --- |
| | Exposure to metformin alone or in addition to insulin | Exposure to insulin alone (or no metformin#) | Crude | Adjusted** |
| **Any major congenital malformation** | | | | |
| New-user design* | 24 of 361 (6.7) | 35 of 569 (6.2) | 1.08 (0.65–1.79) | 1.07 (0.53–2.13) |
| Recorded type 2 diabetes† | 53 of 915 (5.8) | 27 of 406 (6.7) | 0.87 (0.56–1.36) | 0.93 (0.55–1.57) |
| ≥2 dispensations in pregnancy‡ | 58 of 1,248 (4.7) | 50 of 829 (6.0) | 0.77 (0.53–1.11) | 0.83 (0.42–1.64) |
| Complete case analysis§ | 115 of 2,302 (5.0) | 37 of 580 (6.4) | 0.78 (0.55–1.12) | 0.88 (0.59–1.32) |
| Education, folate use, and smoking included as covariates‖ | 147 of 3,145 (4.7) | 50 of 878 (5.7) | 0.82 (0.60–1.12) | 0.85 (0.47–1.53) |
| High-dimensional propensity score¶ | 147 of 3,145 (4.7) | 50 of 878 (5.7) | 0.82 (0.60–1.12) | 0.88 (0.52–1.49) |
| Polycystic ovary syndrome (metformin vs. no metformin)# | 104 of 2,554 (4.1) | 1,813 of 51,912 (3.5) | 1.17 (0.96–1.42) | 1.12 (0.92–1.36) |
| **Cardiac major congenital malformation** | | | | |
| New-user design* | 8 of 361 (2.2) | 13 of 569 (2.3) | 0.97 (0.41–2.32) | 0.94 (0.33–2.73) |
| Recorded type 2 diabetes† | 26 of 915 (2.8) | 7 of 406 (1.7) | 1.65 (0.72–3.77) | 2.03 (0.89–4.62) |
| ≥2 dispensations in pregnancy‡ | 25 of 1,248 (2.0) | 18 of 829 (2.2) | 0.92 (0.51–1.68) | 1.08 (0.54–2.16) |
| Complete case analysis§ | 44 of 2,302 (1.9) | 12 of 580 (2.1) | 0.92 (0.49–1.74) | 1.04 (0.51–2.11) |
| Education, folate use, and smoking included as covariates‖ | 63 of 3,145 (2.0) | 18 of 878 (2.0) | 0.98 (0.58–1.64) | 1.00 (0.55–1.83) |
| High-dimensional propensity score¶ | 63 of 3,145 (2.0) | 18 of 878 (2.0) | 0.98 (0.58–1.64) | 1.04 (0.56–1.93) |
| Polycystic ovary syndrome (metformin vs. no metformin)# | 44 of 2,554 (1.7) | 758 of 51,912 (1.5) | 1.18 (0.87–1.59) | 1.12 (0.82–1.53) |

*New use was defined as no dispensing of metformin or insulin from 90 days before to 48 days after last menstrual period. †Including infants born to mothers with at least one diagnosis of type 2 diabetes recorded at any time in the available look-back period before or on delivery date. In the metformin group, 260 (28%) of the infants were also exposed to insulin. ‡Infants born to mothers with one dispensing of metformin (alone or in addition to insulin) in the first trimester and at least one other dispensing of metformin at any time during pregnancy were compared with infants born to mothers with one dispensing of insulin alone in the first trimester and at least one other dispensing of insulin at any time during pregnancy. §Only mother-child pairs with complete information on covariates were included in the analysis. ‖Maternal education level at delivery, folate use before pregnancy, folate use during pregnancy, and smoking in early pregnancy were added as covariates in the model used in the primary analyses. Missing values were imputed 100 times as in the primary analyses. ¶High-dimensional propensity score with predefined plus top 100 empirically selected covariates. The 200 most prevalent codes were identified in six dimensions of codes recorded within 1 year of the start of pregnancy: inpatient and outpatient diagnosis codes, inpatient and outpatient procedure codes, primary care codes, and drug codes. We selected the top 100 binary empirical codes for inclusion in the propensity score model in addition to country and year of childbirth and maternal age, BMI, cohabitation with a partner, and country of birth (non-Nordic country/non-Finnish citizen). Missing values were imputed 100 times as in the primary analyses. #Infants born to mothers with a diagnosis of polycystic ovary syndrome and no pregestational diabetes before delivery. We compared the malformation risk with and without metformin exposure after adjusting for the same covariates as in the primary analyses. **Adjusted for country and year of birth of infant; maternal characteristics including age, country of birth, cohabitation with a partner, BMI, epilepsy, severe mental illness, chronic hypertension, cardiovascular disease, skin/vaginal infections, and other diabetic complications; and prenatal exposure to suspected teratogenic drugs, glucocorticoids, lipid-modifying drugs, and antihypertensive drugs.

In our study population, none had pulmonary valve atresia. However, right ventricular malformations were relatively more common among infants with prenatal exposure to metformin (Supplementary Fig. 1). This group of malformations has been found to be associated with pregestational diabetes (28). Since the increase was only seen in those with both metformin and insulin exposure or those with type 2 diabetes recorded, but not in other analyses, we suggest that this result may be due to residual confounding. The findings might also have been caused by prevalent maternal use of insulin analogs in the insulin group, which are associated with a lower risk of cardiac malformations than human insulin (29).

Like other observational studies, a limitation of our study is that information on glycemic control in the mother, an important risk factor for congenital malformations, was not available. However, we adjusted for several comorbidities and comedications likely related to poor glycemic control, such as cardiovascular disease and diabetes complications, although these might not have been sufficient proxies for glycemic control in the pregnancy (30). We excluded infants of women with other indications for metformin and insulin than type 2 diabetes and used insulin as an active comparator to metformin, thereby reducing the risk of confounding by indication and disease severity (18,31). To test the robustness of this approach, we

conducted a sensitivity analysis using the high-dimensional propensity score method, which aims to capture proxies for unmeasured confounders (19). This yielded a result comparable to the primary analyses, suggesting no increased risk of malformations overall associated with metformin.

Another limitation is the inadequate recording of type 2 diabetes. Initial diagnosis and follow-up of type 2 diabetes outside of pregnancy usually occurs in primary care in the study countries. We had primary care data for Finland and Norway but not Iceland and Sweden. Furthermore, the International Classification of Primary Care codes used in primary care were not specific to type 2 diabetes before 2014. Even after typical

referral to specialist care during pregnancy, physicians may only use a non-specific diabetes code. Therefore, we decided not to limit the study population to pregnancies of mothers with type 2 diabetes based on recorded diagnosis codes. Instead, women with other indications for metformin or insulin were excluded. Reassuringly, the sensitivity analysis limiting the study population to pregnancies with a recorded diagnosis of type 2 diabetes gave a point estimate close to 1. An analysis with a new-user design was conducted to further exclude women with other indications than type 2 diabetes. This analysis also suggested no clinically relevant increase in the risk of malformations.

A further limitation is that information on potentially important confounders, such as maternal BMI, education, folate use, and smoking, were partially or completely missing for some of the study countries. Still, the sensitivity analysis with multiple imputation of maternal education, folate use, and smoking and the one using complete cases gave similar results close to null. Although we know that metformin and insulin were dispensed at the pharmacies, we cannot be sure that the mothers actually used the drugs. The null finding for the sensitivity analysis requiring at least two dispensations of metformin or insulin during the pregnancy was reassuring in this regard.

Our findings could support policymakers, prescribers, and patients weighing the benefits and disadvantages of metformin compared with insulin for glycemic control in pregnancy. The null finding for the sensitivity analysis restricted to mothers with polycystic ovary syndrome suggests that the results are generalizable to other conditions as well. Future studies should investigate the reproductive safety of other noninsulin glucose-lowering drugs that are increasingly used in type 2 diabetes.

In summary, in this cohort study of four Nordic countries, we found no evidence of an increased risk of major congenital malformations in the offspring of mothers with type 2 diabetes treated with metformin compared with insulin during organogenesis in early pregnancy. The results should be interpreted with caution because of missing information on glycemic control, which is an important risk factor for congenital malformations.

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