


Association of maternal polycystic ovary syndrome and diabetes with preterm birth and offspring birth size: a population-based cohort study

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STUDY QUESTION: Is the presence of polycystic ovary syndrome (PCOS) associated with more adverse infant outcomes in mothers with different types of diabetes?

SUMMARY ANSWER: The presence of PCOS implies higher risks of total (medically indicated and spontaneously combined) and spontaneous preterm birth in mothers with non-insulin-treated type 2 diabetes and gestational diabetes mellitus (GDM), and lower risk of offspring being large for gestational age (LGA) in mothers with insulin-treated diabetes.

WHAT IS KNOWN ALREADY: PCOS is suggested to be an independent risk factor for adverse infant outcomes, and it is highly prevalent in mothers with diabetes. However, the impact of PCOS on the associations of different types of maternal diabetes with preterm birth and offspring birth sizes has not been reported.

STUDY DESIGN, SIZE, DURATION: This is a population-based cohort study including all live births between 1996 and 2014 in Finland. Children with concurrent maternal diagnoses that could cause signs and symptoms similar to PCOS were excluded. A total of 1 097 753 children were included.

PARTICIPANTS/MATERIALS, SETTING, METHODS: National registries were linked to identify births with maternal PCOS ($n = 24\ 682$), stratified by diabetes types. Logistic regression was used to examine the association of maternal PCOS and comorbid insulin-treated diabetes, non-insulin-treated type 2 diabetes or GDM with offspring LGA and small for gestational age (SGA). Generalized estimating equation was used to assess the risk of preterm birth in relation to maternal PCOS and diabetes. Potential interaction between PCOS and diabetes was evaluated on both additive and multiplicative scales.

MAIN RESULTS AND THE ROLE OF CHANCE: Using mothers with no PCOS and no diabetes as the reference and adjusting for maternal and birth factors, there were higher risks of total (odds ratio (OR) 2.84, 95% CI 2.21–3.66 vs. OR 1.91, 95% CI 1.77–2.07, $P = 0.01$) and spontaneous (OR 4.02, 95% CI 2.94–5.50 vs. OR 2.35, 95% CI 2.13–2.59, $P = 0.001$) preterm birth for those with PCOS in mothers with non-insulin-treated type 2 diabetes and higher risks of total (OR 1.42, 95% CI 1.27–1.58 vs. OR 0.89, 95% CI 0.86–0.91, $P = 0.0001$) and spontaneous (OR 1.80, 95% CI 1.59–2.05 vs. OR 1.01, 95% CI 0.98–1.05, $P = 0.0001$) preterm birth for those with PCOS in mothers with GDM. Among mothers with type 2 diabetes, further adjusting for maternal BMI eliminated the difference in preterm birth risks between those with and those without PCOS, and adjustment for infertility treatment and pre-eclampsia also reduced the preterm risks associated with PCOS significantly. For mothers with GDM, however, the risks of total and spontaneous preterm birth remained higher for those with PCOS following these aforementioned adjustments or stratified analysis. The risk of offspring being LGA was lower for those with PCOS than those without PCOS among mothers with insulin-treated diabetes (OR 18.90, 95% CI 14.21–25.14 vs. OR 32.04, 95% CI 29.79–34.46, $P = 0.0001$), showing departure from additivity (relative excess risk due to interaction -11.74 , 95% CI -16.17 to -7.31 , $P < 0.001$) and multiplicativity ($P < 0.001$). PCOS did not alter the risk estimate of preterm birth in mothers with insulin-treated diabetes or offspring LGA and SGA in mothers with type 2 diabetes or GDM.

LIMITATIONS, REASONS FOR CAUTION: The register-based diagnoses used in this study captured only women with PCOS seeking medical care and having live births. Including female infertility associated with anovulation as PCOS exposure was a risk for misclassification. Sample sizes for pregestational diabetes were small. Insulin purchase during pregnancy in those without a diabetes diagnosis was not accounted for in the analysis. For patients treated with insulin or other medications, we were unable to assess how they complied with such prescriptions. Also, maternal BMI was recorded only once in early pregnancy, thus the potential influence of gestational weight gain on birth outcomes could not be examined. Data on the causes for preterm birth were not available from the registers.

WIDER IMPLICATIONS OF THE FINDINGS: The presence of PCOS implied higher risks of total and spontaneous preterm birth in mothers with type 2 diabetes or GDM, and lower risk of offspring being LGA in mothers with insulin-treated diabetes. The higher risks of preterm birth added by PCOS could be explained by prepregnancy BMI or in part by infertility treatment and pre-eclampsia in maternal non-insulin-treated type 2 diabetes, but not in maternal GDM. The differential effects of PCOS on the associations of different types of maternal diabetes with infant outcomes have implications for preventative strategies and clinical counseling for affected pregnancies.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women (Escobar-Morreale, 2018), with a prevalence ranging from 6% to 10% depending on the criteria used (Bozdag et al., 2016). PCOS is associated with adverse infant outcomes, in which features characteristic of PCOS, such as hyperandrogenism and insulin resistance, PCOS-associated infertility treatment and comorbidities, such as obesity, may all be involved (Palomba et al., 2015; Bahri Khomami et al., 2019). Importantly, recent studies imply that PCOS in itself is an independent risk factor for worsened birth outcomes. A large population-based cohort study including 9.1 million births reported 37% increased risk of total preterm birth (medically indicated and spontaneous deliveries combined; odds ratio (OR) 1.37, 95% CI 1.24–1.53) in women with PCOS, after controlling for obesity, IVF use and other confounders (Mills et al., 2020a). Another register-based cohort study extended these findings by showing that the PCOS association with preterm birth persisted for extremely preterm birth and particularly for spontaneous delivery (Valgeirsdottir et al., 2021).

Recent years have witnessed a significant increase in the number of women entering pregnancy with pre-existing diabetes (Mackin et al., 2018; Thong et al., 2020). Diabetes in pregnancy, either type 1 or type 2, is associated with adverse maternal and neonatal outcomes, such as pre-eclampsia, preterm delivery and higher birthweight, which could not be explained by obesity (Mattsson et al., 2021; Murphy et al., 2021). In particular, the rates of preterm birth and infants being large for gestational age (LGA) were much higher in mothers with type 1 diabetes than that in type 2 diabetes (Murphy et al., 2021). Notably, we reported that among women with insulin-treated pre-existing diabetes, the OR was up to 11 for preterm birth, and 44 for offspring being LGA, much higher than in mothers with non-insulin-treated type 2 diabetes (Kong et al., 2019), indicating that there might

be an important role of the growth hormone insulin. PCOS is identified in up to one in four women with type 1 diabetes (Escobar-Morreale et al., 2021) and highly prevalent among women with type 2 diabetes (Peppard et al., 2001). A prior study revealed a higher miscarriage rate and delayed conception for type 2 diabetes patients with PCOS than those without (Sim et al., 2016), indicating subfertility for this population. However, the association of PCOS with infant outcomes in the setting of pre-existing diabetes remains unknown.

Furthermore, women with PCOS often have gestational diabetes mellitus (GDM; Palomba et al., 2015; Mills et al., 2020b). The associations of PCOS with infant outcomes among mothers with GDM have been investigated in several case-control studies (Alshammari et al., 2010; Li et al., 2010; Palomba et al., 2012; Foroozanfard et al., 2014; Aktun et al., 2016; Manoharan and Wong, 2020). However, the results were inconsistent: women with PCOS and comorbid GDM were reported to have higher risks of preterm birth rate or lower birthweight than GDM alone in some studies (Alshammari et al., 2010; Palomba et al., 2012) but not in others (Li et al., 2010; Foroozanfard et al., 2014; Aktun et al., 2016; Manoharan and Wong, 2020). In addition, none of the studies has examined the association of PCOS with spontaneous preterm birth among mothers with GDM. Also, all the studies had relatively small sample sizes (<326 for PCOS with comorbid GDM) and were hospital based.

Therefore, this study aimed to examine the associations of maternal PCOS and comorbid insulin-treated diabetes, non-insulin-treated type 2 diabetes or GDM with preterm birth, offspring LGA and small for gestational age (SGA) using a nationwide birth cohort from Finland. Differently adjusted models and stratified analyses were applied to test whether risk factors in the general population, such as increased BMI, multiple gestations, infertility treatment and pre-eclampsia, could influence the associations.

Materials and methods

Data source and study population

The Drugs and Pregnancy database steering committee and the data protection authority in Finland provided ethical approval for this study (THL/1662/5.05.00/2015, THL/1853/5.05.00/2016 and THL/1496/5.05.00/2019), with waiver of individual informed consent for this type of study according to Finnish legislation. The data analysis was conducted from 1 June 2019 to 31 August 2021. This study included all live births during 1996–2014 in Finland ($n = 1\,097\,753$), identified from the Drugs and Pregnancy Database (Supplementary Data), originally registered in the Medical Birth Register (MBR; Artama *et al.*, 2011). Medical diagnoses for mothers were identified from the Finnish Care Register for Health Care (HILMO), which covers patients from all hospital inpatient care and outpatient clinics in Finland with high accuracy (Sund, 2012). Medication purchases were retrieved from the Finnish Register on Reimbursement Drugs (Supplementary Data). Information from different registers was linked by the unique personal identification number assigned to Finnish citizens and permanent residents.

To ensure specificity of PCOS diagnosis, women were excluded if they had any of the following medical conditions ($n = 8244$): pituitary adenoma (ICD-9: 227.3; ICD-10: D35.2), pituitary gland disorders (ICD-9: 253; ICD-10: E22, E23), adrenal gland disorders including Cushing's syndrome and congenital adrenal hyperplasia (ICD-9: 255; ICD-10: E24/E25/E27), suparenal tumor (ICD-9: 194; ICD-10: C74), galactorrhea (ICD-9: 611.6; ICD-10: N64.3) and Turner syndrome (ICD-9: 758.6; ICD-10: Q96).

Exposures

Maternal diagnosis of PCOS was determined by PCOS or anovulatory infertility (ICD-9: 256.4 and 628.0, and ICD-10: E28.2 and N97.0), given that PCOS was the most common cause for anovulatory infertility. The cases were diagnosed by specialist doctors from hospitals. Before 2003, PCOS was diagnosed following the National Institutes of Health (NIH) criteria based on the presence of oligomenorrhea or amenorrhea, and hyperandrogenism (clinical or biochemical). From 2004, the Rotterdam criteria for PCOS diagnosis were recommended, requiring two out of three of the following symptoms: oligo- or anovulation, hyperandrogenism (clinical or biochemical) and polycystic ovary morphology on ultrasound, with exclusion of related disorders (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Tymi *et al.*, 2022). PCOS diagnosis at any time was defined as exposure because the hormonal and metabolic disturbances persist through women's lifespan.

In Finland, there is specialized care for patients with diabetes to achieve a normal blood glucose level, with high accuracy on diabetes in the registries. Mothers with insulin-treated diabetes were those with confirmed insulin purchase for diabetes before pregnancy, identified from the Finnish Register on Reimbursement Drugs. In the mothers without pregestational insulin treatment, type 2 diabetes and GDM diagnoses were identified from HILMO and the Finnish Register on Reimbursement Drugs. Non-insulin-treated type 2 diabetes was determined based on at least one of the ICD-10 diagnoses: E11, E14 and O24.1, and/or by purchases of oral antidiabetic drugs Anatomical Therapeutic Chemical (ATC) A10B (blood glucose-lowering drugs other than insulin) before pregnancy. Almost all non-insulin-treated type 2

diabetes cases were identified based on an ICD-10 diagnosis before pregnancy (8138/8185, 99.4% in non-PCOS; 533/537, 99.3% in PCOS), and at the end of the year they gave birth, all mothers categorized as having non-insulin-treated type 2 diabetes in this study had received a type 2 diabetes ICD-10 diagnosis. GDM was identified based on ICD-10 O24.4. Over the study period, GDM was diagnosed based on a standard 2-h 75-g oral glucose tolerance test, which was mainly performed at gestational weeks 24–28. After overnight fast, venous plasma glucose concentrations were measured at fasting, and 1 and 2 h after the glucose dose, with a value ≥ 5.3 , 10.0 and 8.6 mmol/l considered abnormal, respectively. GDM was diagnosed if at least one abnormal value was present. In 2008, the risk factor-based GDM screening was replaced by nearly comprehensive screening in Finland, with the latter including ~80% of pregnant women (Koivunen *et al.*, 2017). Mothers without insulin-treated diabetes, type 2 diabetes and GDM were grouped as having no diabetes. If a woman had more than one diabetes diagnosis, she would be classified in the following order: insulin-treated diabetes before pregnancy, non-insulin-treated type 2 diabetes and GDM.

Preterm birth and birth size in offspring

Information on gestational age and birth size in offspring was extracted from the MBR. Gestational age at birth for each infant is estimated based on multiple ultrasound examinations, of which the first one is at 11–13 gestational weeks. The MBR also collects information on last menstrual period, which is cross-referenced in cases of suspected error in gestational age. Preterm birth was birth before 37 gestational weeks, which was further stratified as moderately (32–36 weeks), very (28–31 weeks) and extremely (22–27 weeks) preterm birth. Spontaneous preterm birth was defined as all preterm deliveries excluding induced vaginal deliveries and planned cesarean deliveries.

LGA and SGA are birthweight and/or length more than 2 SDs above or below the sex- and gestational age-specific mean in the Finnish population (Sankilampi *et al.*, 2013), based on the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society (Clayton *et al.*, 2007).

Covariates

A directed acyclic graph was used to assist in selecting potential variables for adjustment (Supplementary Fig. S1; Textor *et al.*, 2016). The following perinatal and maternal characteristics reported to be associated with PCOS and offspring birth outcomes were retrieved from the MBR and used as covariates: birth year (continuous), parity (0 or ≥ 1), maternal age (continuous), maternal birth country (Finland or not), maternal smoking during pregnancy (yes/no), mother married at delivery (yes/no), maternal BMI (continuous), number of fetuses (1 or ≥ 2), pre-eclampsia (yes/no) and infertility treatment (yes/no). Maternal BMI was weight (kilograms) divided by height (meters) squared, recorded at the first prenatal visit around 7–10 gestational weeks, available for 95% of mothers from 2004 from the MBR. Normal BMI was defined as 18.5–24.9 kg/m². Pre-eclampsia was identified based on ICD-10 codes O11 and O14. Infertility treatment referred to IVF/ICSI (checkbox in the MBR).

Statistical analysis

All included offspring were categorized into two categories based on exposure of maternal PCOS, and then both categories were further

classified for maternal diabetes into four groups: no diabetes, GDM, type 2 diabetes and insulin-treated diabetes. The distributions of covariates were examined for each group. First, using non-diabetic non-PCOS mothers as reference, the risk estimates of total preterm birth (medically indicated and spontaneous combined) were examined, adjusting for offspring birth year, parity, mother's age at delivery, maternal country of birth, smoking and marital status (Model 1). Second, differently adjusted models and subgroup analysis were applied to assess how risk factors for preterm birth in the general population could explain the association. Thus, in Model 2, maternal prepregnancy BMI was further adjusting for; in Model 3, all singleton births were identified to test whether the association remained. In Model 4, infertility treatment and pre-eclampsia were further adjusted for to assess whether and to what extent these two factors could explain the higher risk of preterm birth. Third, a second round of analysis was performed after excluding all planned cesarean section and induced vaginal deliveries, to examine the associations of PCOS and diabetes with spontaneous preterm birth. Because maternal prepregnancy BMI was available from 2004, the analyses of total and spontaneous preterm birth involving maternal BMI (Model 2) were restricted to birth cohort 2004–2014.

Fourth, the risk estimates of LGA and SGA in relation to maternal PCOS and comorbid diabetes were examined, adjusting for offspring birth year, parity, mother's age at delivery, maternal country of birth, smoking, marital status and maternal prepregnancy BMI. As maternal BMI is an established key factor affecting birthweight and the availability of data on prepregnancy BMI, birth cohort 2004–2014 was used.

Finally, sensitivity analyses among mothers with PCOS diagnosis, i.e. excluding those with only diagnosis of anovulatory infertility, were performed.

Logistic regression models were used to estimate the associations of PCOS and diabetes with offspring being LGA and SGA. Given that a history of preterm birth is an important risk factor for preterm birth, generalized estimating equation was applied to assess the risk of preterm birth in relation to maternal PCOS and diabetes. OR and 95% CIs were reported as measures of effect sizes. Potential additive interactions between PCOS and diabetes on birth outcomes were investigated by calculating the relative excess risk due to interaction (RERI) and corresponding 95% CI, which quantifies departure from additivity between the two exposures. Generally, RERI equal to 0 means no interaction, RERI > 0 means positive interaction and RERI < 0 means negative interaction (Knol et al., 2011). We also tested departure from multiplicity between PCOS and diabetes using the product term in logistic regression. Missing data for parity (0.1%), mother's country of birth (0.4%), marital status (1.9%), smoking during pregnancy (2.6%), mode of delivery (0.1%) and prepregnancy BMI (from the year 2004, 5.2%; Kong et al., 2019) was handled as separate groups. SAS, version 9.3 and 9.4 (SAS Institute, Inc, Cary, NC, USA) were used to perform the analyses. A value of $P < 0.05$ was considered to be statistically significant.

Results

Study population characteristics

Of the 1 097 753 children included, 60 545 were born preterm, 32 373 were LGA and 34 975 were SGA. A total of 24 682 offspring were exposed to mothers with PCOS. Mothers with PCOS were

more likely to have higher prepregnancy BMI, use IVF/ICSI treatment, and deliver at older ages, and were less likely to smoke during pregnancy. Of PCOS-exposed offspring, 311 (1.3%) had maternal prepregnancy insulin-treated diabetes, 537 (2.2%) had non-insulin-treated maternal type 2 diabetes and 5218 (21.1%) had maternal GDM (Table I and Supplementary Table S1). Modes of delivery for preterm births were presented in Supplementary Table S2.

Total preterm birth in relation to maternal PCOS and diabetes

Following adjustment for birth year, parity, maternal age, country of birth, smoking and marital status (Model 1), mothers with PCOS and no diabetes were at increased risk of delivering preterm across all gestational ages, using mothers with no PCOS and no diabetes as the reference (Table II). Among mothers with GDM or non-insulin-treated type 2 diabetes, there was a higher risk of preterm birth across all gestational ages for those with PCOS. The effect of PCOS seemed stronger for earlier preterm births. For example, for type 2 diabetes PCOS implied 180% higher risks of preterm birth before 28 weeks, but only 25% higher at 32–36 weeks. PCOS did not affect the risk estimates of preterm birth at any stage among mothers with insulin-treated diabetes (Table II). Sensitivity analysis in mothers with only PCOS diagnosis (excluding those with anovulatory infertility) also revealed higher risks of preterm birth across all stages for PCOS with no diabetes, and that PCOS implied higher risks of preterm birth before 37 weeks in maternal GDM and higher risks of preterm birth before 32 weeks in type 2 diabetes (Supplementary Table S3).

To explore factors contributing to preterm birth, differently adjusted models were constructed and subgroup analyses were performed (Fig. 1). Among mothers with GDM, the risk of preterm birth remained higher for those with PCOS after further adjusting for prepregnancy BMI (OR_{GDM+PCOS} 1.44, 95% CI 1.26–1.63 vs. OR_{GDM+no PCOS} 0.91, 95% CI 0.88–0.94; Model 2) or restricting to singleton children (OR_{GDM+PCOS} 1.67, 95% CI 1.48–1.88 vs. OR_{GDM+no PCOS} 1.07, 95% CI 1.04–1.10; Model 3). The observed associations were slightly attenuated but remained higher for those with PCOS after further adjusting for pre-eclampsia and infertility treatment (OR_{GDM+PCOS} 1.10, 95% CI 0.98–1.24 vs. OR_{GDM+no PCOS} 0.84, 95% CI 0.82–0.86; Model 4). By contrast, among mothers with type 2 diabetes, PCOS did not imply additional risk of preterm birth following further adjustments for maternal BMI, or pre-eclampsia and infertility treatment, indicating that in the setting of type 2 diabetes, the additional preterm birth risk implied by PCOS was related to prepregnancy BMI, or pre-eclampsia and infertility treatment, but not multiple pregnancies. Among mothers with insulin-treated diabetes, the risk estimate of total preterm birth was comparable between those with and without PCOS across the aforementioned adjustments and stratified analysis (Fig. 1).

Spontaneous preterm birth in relation to maternal PCOS and comorbid diabetes

Mothers with PCOS and no diabetes were associated with increased risk of spontaneous preterm birth, higher at earlier gestational ages (Table III). Among mothers with GDM, there was a higher risk of spontaneous preterm birth for those with PCOS following adjusting for birth year, parity, maternal age, country of birth, smoking and

Table 1 Demographic characteristic of offspring and their mothers in Finnish birth cohort 1996–2014.

	Maternal PCOS					No maternal PCOS				
	Total (n = 24 682)	No DM (n = 18 616)	GDM (n = 5218)	T2DM (n = 537)	DM-IT (n = 311)	Total (n = 1 073 071)	No DM (n = 913 348)	GDM (n = 145 922)	T2DM (n = 8185)	DM-IT (n = 5616)
Offspring birth year										
1996–2000	4255 (17.2)	3408 (18.3)	650 (12.5)	147 (27.4)	50 (16.1)	283 112 (26.4)	249 633 (27.3)	28 838 (19.8)	3423 (41.8)	1218 (21.7)
2001–2005	5540 (22.4)	4156 (22.3)	1181 (22.6)	150 (27.9)	53 (17.0)	274 431 (25.6)	230 435 (25.2)	40 554 (27.8)	2159 (26.4)	1283 (22.8)
2006–2010	7602 (30.8)	5725 (30.8)	1627 (31.2)	152 (28.3)	98 (31.5)	288 828 (26.9)	244 681 (26.8)	40 834 (28.0)	1678 (20.5)	1635 (29.1)
2011–2014	7285 (29.5)	5327 (28.6)	1760 (33.7)	88 (16.4)	110 (35.4)	226 700 (21.1)	188 599 (20.6)	35 696 (24.5)	925 (11.3)	1480 (26.4)
Maternal age at delivery, years										
<25	3335 (13.5)	2617 (14.1)	627 (12.0)	67 (12.5)	24 (7.7)	199 627 (18.6)	173 150 (19.0)	24 241 (16.6)	1191 (14.6)	1045 (18.6)
25–29	7622 (30.9)	5786 (31.1)	1586 (30.4)	152 (28.3)	98 (31.5)	340 611 (31.7)	293 215 (32.1)	43 464 (29.8)	2117 (25.9)	1815 (32.3)
30–34	8541 (34.6)	6495 (34.9)	1767 (33.9)	175 (32.6)	104 (33.4)	334 348 (31.2)	285 001 (31.2)	45 095 (30.9)	2523 (30.8)	1729 (30.8)
≥35	5184 (21.0)	3718 (20.0)	1238 (23.7)	143 (26.6)	85 (27.3)	198 484 (18.5)	161 981 (17.7)	33 122 (22.7)	2354 (28.8)	1027 (18.3)
Prepregnancy BMI, kg/m²										
<18.5	419 (1.7)	380 (2.0)	35 (0.7)	2 (0.4)	2 (0.6)	22 471 (2.1)	21 279 (2.3)	1105 (0.8)	27 (0.3)	60 (1.1)
18.5–24.9	8656 (35.1)	7531 (40.5)	1016 (19.5)	42 (7.8)	67 (21.5)	373 050 (34.8)	339 273 (37.1)	31 229 (21.4)	820 (10.0)	1728 (30.8)
25.0–29.9	3897 (15.8)	2679 (14.4)	1100 (21.1)	60 (11.2)	58 (18.6)	129 421 (12.1)	98 237 (10.8)	29 411 (20.2)	785 (9.6)	988 (17.6)
30.0–34.9	2216 (9.0)	1164 (6.3)	925 (17.7)	76 (14.2)	51 (16.4)	47 180 (4.4)	29 280 (3.2)	16 772 (11.5)	714 (8.7)	414 (7.4)
≥35	1301 (5.3)	514 (2.8)	637 (12.2)	104 (19.4)	46 (14.8)	22 210 (2.1)	10 344 (1.1)	10 762 (7.4)	810 (9.9)	294 (5.2)
Missing	8193 (33.2)	6348 (34.1)	1505 (28.8)	253 (47.1)	87 (28.0)	478 739 (44.6)	414 935 (45.4)	56 643 (38.8)	5029 (61.4)	2132 (38.0)
Parity										
0	12 147 (49.2)	9330 (50.1)	2421 (46.4)	248 (46.2)	148 (47.6)	441 121 (41.1)	380 817 (41.7)	55 257 (37.9)	2545 (31.1)	2502 (44.6)
≥1	12 518 (50.7)	9271 (49.8)	2795 (53.6)	289 (53.8)	163 (52.4)	630 781 (58.8)	531 471 (58.2)	90 572 (62.1)	5628 (68.8)	3110 (55.4)
Missing	17 (0.1)	15 (0.1)	2 (0.0)	0 (0.0)	0 (0.0)	1169 (0.1)	1060 (0.1)	93 (0.1)	12 (0.1)	4 (0.1)
Mother's country of birth										
Finland	22 670 (91.8)	17 179 (92.3)	4727 (90.6)	471 (87.7)	293 (94.2)	987 139 (92.0)	841 286 (92.1)	133 046 (91.2)	7415 (90.6)	5392 (96.0)
Other country	1999 (8.1)	1424 (7.6)	491 (9.4)	66 (12.3)	18 (5.8)	81 942 (7.6)	68 286 (7.5)	12 685 (8.7)	754 (9.2)	217 (3.9)
Missing	13 (0.1)	13 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3990 (0.4)	3776 (0.4)	191 (0.1)	16 (0.2)	7 (0.1)
Mother's marital status										
Married	16 554 (67.1)	12 497 (67.1)	3489 (66.9)	362 (67.4)	206 (66.2)	6 363 044 (59.3)	540 452 (59.2)	87 466 (59.9)	4923 (60.1)	3203 (57.0)
Cohabiting	6028 (24.4)	4555 (24.5)	1286 (24.6)	112 (20.9)	75 (24.1)	313 006 (29.2)	267 087 (29.2)	42 165 (28.9)	2064 (25.2)	1690 (30.1)
Unmarried	1769 (7.2)	1314 (7.1)	375 (7.2)	51 (9.5)	29 (9.3)	103 245 (9.6)	87 827 (9.6)	13 848 (9.5)	951 (11.6)	619 (11.0)
Missing	331 (1.3)	250 (1.3)	68 (1.3)	12 (2.2)	1 (0.3)	20 776 (1.9)	17 982 (2.0)	2443 (1.7)	247 (3.0)	104 (1.9)

(continued)

Table 1 Continued

	Maternal PCOS					No maternal PCOS				
	Total (n = 24 682)	No DM (n = 18 616)	GDM (n = 5218)	T2DM (n = 537)	DM-IT (n = 311)	Total (n = 1 073 071)	No DM (n = 913 348)	GDM (n = 145 922)	T2DM (n = 8185)	DM-IT (n = 5616)
Smoking during pregnancy										
Yes	3225 (13.1)	2273 (12.2)	809 (15.5)	94 (9.9)	49 (15.8)	160 602 (15.0)	134 601 (14.7)	23 414 (16.0)	1661 (20.3)	926 (16.5)
No	20 865 (84.5)	15 913 (85.5)	4270 (81.8)	429 (45.1)	253 (81.4)	885 129 (82.5)	755 566 (82.7)	118 770 (81.4)	6257 (76.4)	4536 (80.8)
Missing	1007 (4.1)	430 (2.3)	139 (2.7)	429 (45.1)	9 (2.9)	27 340 (2.5)	23 181 (2.5)	3738 (2.6)	267 (3.3)	154 (2.7)
IVF/ICSI treatment										
Yes	3466 (14.0)	2710 (14.6)	669 (12.8)	58 (10.8)	29 (9.3)	22 706 (2.1)	19 509 (2.1)	2969 (2.0)	131 (1.6)	97 (1.7)
No	21 216 (86.0)	15 906 (85.4)	4549 (87.2)	479 (89.2)	282 (90.7)	1 050 365 (97.9)	893 839 (97.9)	142 953 (98.0)	8054 (98.4)	5519 (98.3)
Multiple gestation										
Yes	1143 (4.6)	932 (5.0)	177 (3.4)	19 (3.5)	15 (4.8)	31 339 (2.9)	29 048 (3.2)	2010 (1.4)	115 (1.4)	166 (3.0)
No	23 539 (95.4)	17 684 (95.0)	5041 (96.6)	518 (96.5)	296 (5.2)	1 041 732 (97.1)	884 300 (96.8)	143 912 (98.6)	8070 (98.6)	5450 (97.0)
Pre-eclampsia										
Yes	1037 (4.2)	643 (3.5)	308 (5.9)	44 (8.2)	42 (13.5)	28 962 (2.7)	22 307 (2.4)	5439 (3.7)	459 (5.6)	757 (13.5)
No	23 643 (95.8)	17 971 (96.5)	4910 (94.1)	493 (91.8)	269 (86.5)	1 044 106 (97.3)	891 038 (97.6)	140 483 (96.3)	7726 (94.4)	4859 (86.5)
Delivery mode										
S-vaginal	16 758 (67.9)	12 892 (69.3)	3480 (66.7)	306 (57.0)	80 (25.7)	816 020 (76.0)	702 313 (76.9)	106 358 (73.0)	5445 (66.5)	1724 (30.7)
I-vaginal	2209 (8.9)	1697 (9.1)	449 (8.6)	45 (8.4)	18 (5.8)	78 025 (7.3)	66 822 (7.3)	10 395 (7.1)	463 (5.7)	345 (6.1)
Planned CS	2279 (9.2)	1607 (8.6)	478 (9.2)	86 (16.0)	108 (34.7)	76 928 (7.2)	61 734 (6.8)	12 187 (8.4)	1036 (12.7)	1971 (35.1)
Urgent CS	3419 (13.9)	2406 (12.9)	808 (15.5)	100 (18.6)	105 (33.8)	100 701 (9.4)	81 214 (8.9)	16 694 (11.4)	1222 (14.9)	1571 (28.0)
Missing	17 (0.1)	14 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	1397 (0.1)	1265 (0.1)	108 (0.1)	19 (0.2)	5 (0.1)

Data are expressed as n (%). PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes. Mothers without DM-IT, T2DM, or GDM were grouped as having no DM. Mothers with DM-IT were excluded from the groups of T2DM and GDM, and likewise, mothers with T2DM were excluded from the GDM group. IVF/ICSI, including frozen embryo transfer (FET) was checkbox in the MBR (Medical Birth Register). CS, cesarean section; S-vaginal, spontaneous vaginal delivery; I-vaginal, induced vaginal labor.

Table II Adjusted odds ratio for total preterm birth according to maternal PCOS and diabetes.

	<37 weeks (n = 60 545)	32–36 weeks (n = 52 756)	28–31 weeks (n = 5664)	<28 weeks (n = 2125)
No maternal PCOS				
No DM	1.00	1.00	1.00	1.00
GDM	0.89 (0.86 – 0.91)	0.93 (0.90 – 0.96)	0.68 (0.62 – 0.75)	0.59 (0.50 – 0.69)
T2 DM	1.91 (1.77 – 2.07)	1.95 (1.79 – 2.12)	1.50 (1.16 – 1.92)	1.58 (1.07 – 2.34)
DM-IT	10.21 (9.59 – 10.88)	10.51 (9.86 – 11.20)	4.55 (3.72 – 5.56)	2.46 (1.61 – 3.75)
Maternal PCOS				
No DM	1.48 (1.39 – 1.57)	1.41 (1.32 – 1.50)	1.66 (1.40 – 1.96)	2.46 (1.92 – 3.14)
GDM	1.42 (1.27 – 1.58)	1.46 (1.30 – 1.64)	1.22 (0.86 – 1.74)	1.38 (0.83 – 2.28)
T2 DM	2.84 (2.21 – 3.66)	2.45 (1.85 – 3.26)	3.99 (2.19 – 7.27)	4.53 (1.88 – 10.94)
DM-IT	9.17 (7.10 – 11.85)	9.13 (7.01 – 11.90)	4.89 (2.31 – 10.34)	4.37 (1.41 – 13.59)

GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes mellitus; PCOS, polycystic ovary syndrome. Mothers without DM-IT, T2DM or GDM were grouped as having no DM. Mothers with DM-IT were excluded from the groups of T2DM and GDM, and likewise, mothers with T2DM were excluded from the GDM group. Values are odds ratio (95% CI).

The analysis was adjusted for offspring birth year, parity (0 or ≥ 1), maternal age at delivery, country of birth (Finland or not), smoking during pregnancy (yes/no) and mother married at delivery (yes/no).

marital status ($OR_{GDM+PCOS}$ 1.80, 95% CI 1.59–2.05 vs. $OR_{GDM+no\ PCOS}$ 1.01, 95% CI 0.98–1.05; Model 1); further, the risk remained higher for those with PCOS after further adjusting for prepregnancy BMI ($OR_{GDM+PCOS}$ 1.81, 95% CI 1.56–2.10 vs. $OR_{GDM+no\ PCOS}$ 1.02, 95% CI 0.98–1.06; Model 2), restricting to singleton children ($OR_{GDM+PCOS}$ 2.05, 95% CI 1.78–2.35 vs. $OR_{GDM+no\ PCOS}$ 1.19, 95% CI 1.15–1.23; Model 3) or further adjusting for pre-eclampsia and infertility treatment ($OR_{GDM+PCOS}$ 1.42, 95% CI 1.24–1.62 vs. $OR_{GDM+no\ PCOS}$ 0.96, 95% CI 0.93–0.99; Model 4). Among mothers with type 2 diabetes, there was also a higher risk of spontaneous preterm birth with the presence of PCOS (Model 1), which was attenuated to be comparable to that without PCOS after further adjusting for prepregnancy BMI (Model 2). The PCOS-associated spontaneous preterm birth in maternal type 2 diabetes was also significantly reduced in magnitude after further adjusting for infertility treatment and pre-eclampsia (Model 4). In contrast, among mothers with insulin-treated diabetes, the risk estimate of spontaneous preterm birth was comparable between those with and without PCOS (Fig. 2).

Sensitivity analysis in mothers with only PCOS diagnosis (excluding those with anovulatory infertility) revealed similar results (Supplementary Table SIV).

Maternal PCOS and diabetes with offspring LGA and SGA

Given the established effect of maternal obesity on offspring birth size, the analysis of PCOS association with offspring LGA and SGA was performed in birth cohort 2004–2014, for which data on maternal prepregnancy BMI was available. Using non-diabetic non-PCOS mothers as the reference, mothers with PCOS and no diabetes were not associated with either offspring LGA or SGA. Among mothers with type 2 diabetes or GDM, PCOS did not alter the ORs for offspring LGA or SGA (Table IV). Notably, the OR of insulin-treated diabetes with offspring LGA was significantly smaller with the presence of PCOS ($OR_{insulin-treated\ diabetes+PCOS}$ 18.90, 95% CI 14.21–25.14 vs.

$OR_{insulin-treated\ diabetes+no\ PCOS}$ 32.04, 95% CI 29.79–34.46), showing departure from additivity (RERI –11.74, 95% CI –16.17 to –7.31, $P < 0.001$) and multiplicativity ($P < 0.001$) between the two exposures. Sensitivity analysis among mothers with only PCOS diagnosis (excluding those with anovulatory infertility) revealed similar results, though the risk estimate for offspring LGA in mothers with insulin-treated diabetes overlapped between those with and without PCOS, probably because of limited samples (Supplementary Table SV).

Discussion

To our knowledge, this is the first study to investigate the associations of maternal PCOS with preterm birth and offspring extreme birth sizes among different types of diabetes. With this population-based cohort of over 1 million births, we found that PCOS implied higher risks of total and spontaneous preterm birth among mothers with non-insulin-treated type 2 diabetes and GDM, and lower risk of offspring LGA among mothers with insulin-treated diabetes compared to among mothers with diabetes only. Maternal BMI, pre-eclampsia and infertility treatment could explain, at least in part, the PCOS-associated preterm birth in mothers with type 2 diabetes but not in those with GDM.

For the first time, we reported higher risks of total and spontaneous preterm birth for women with PCOS among type 2 diabetes patients. In addition, our differently adjusted models demonstrated that maternal BMI, infertility treatment and pre-eclampsia could explain, at least in part the higher risks of preterm birth conferred by PCOS among mothers with type 2 diabetes. In line with this, a prior study found that a history of PCOS represented a metabolically unfavorable phenotype of type 2 diabetes, with earlier onset of type 2 diabetes, higher BMI and more pregnancy complications (Sim *et al.*, 2016).

Notably, our study showed that PCOS conferred higher risks of total and spontaneous preterm birth among mothers with GDM. This was the first study to assess spontaneous preterm birth in relation to maternal PCOS and GDM. Our data on total preterm birth, however,

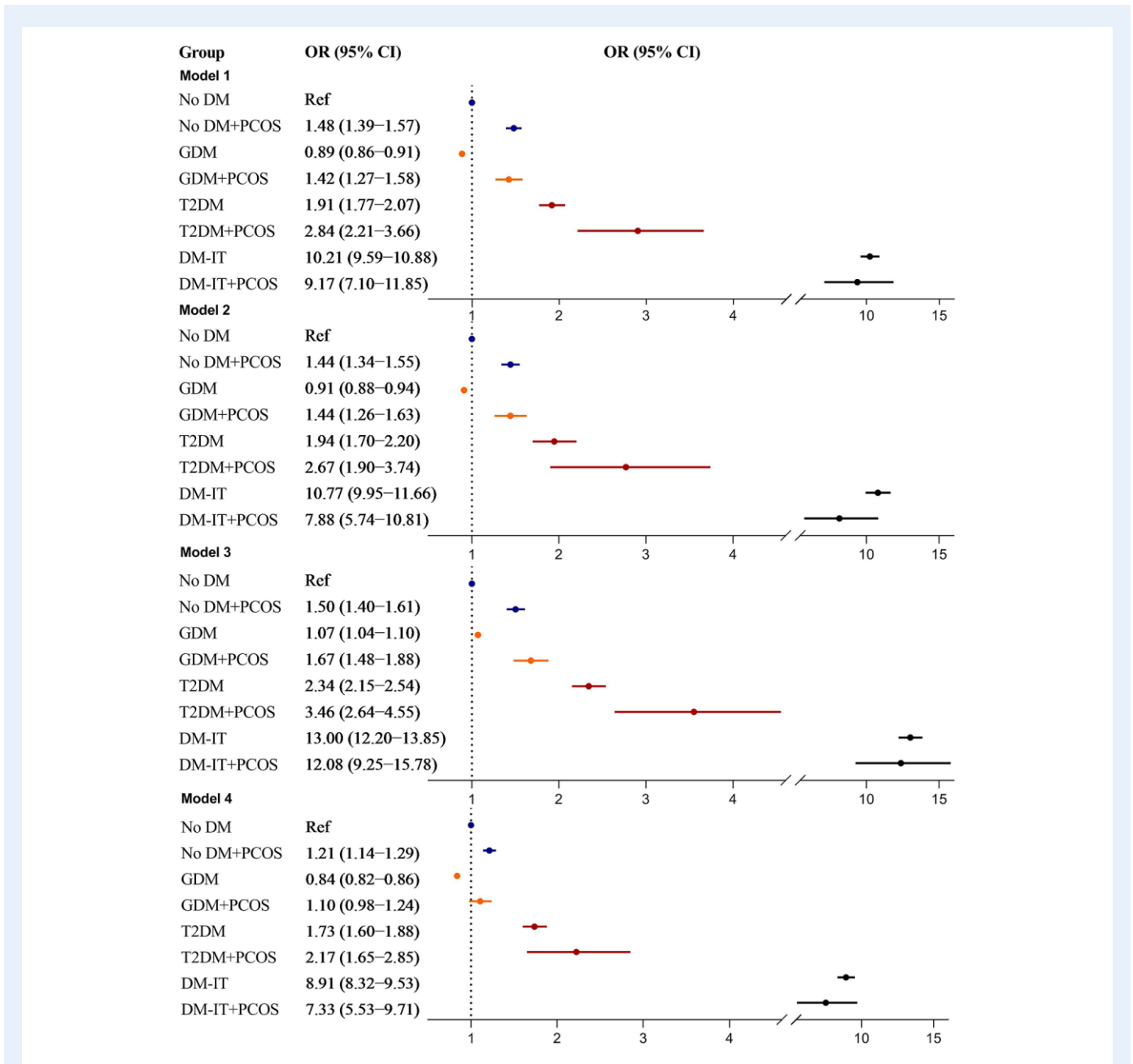


Figure 1. Adjusted odds ratio for total preterm birth in relation to maternal PCOS and diabetes. Model 1: birth cohort 1996–2014 was used, adjusting for offspring birth year, parity, maternal age at delivery, country of birth, smoking during pregnancy and mother married at delivery. Model 2: birth cohort 2004–2014 was used, adjusting for covariates in Model 1 plus maternal BMI. Model 3: birth cohort 1996–2014 was used, including singleton births only, adjusting for covariates in Model 1. Model 4: birth cohort 1996–2014 was used, adjusting for covariates in Model 1 plus infertility treatment and pre-eclampsia. PCOS, polycystic ovary syndrome; OR, odds ratio; GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes mellitus; No DM, mothers without DM-IT, T2DM or GDM; Ref, reference group.

were in agreement with that of [Palomba et al. \(2012\)](#), who reported a shorter gestational age for infants born to mothers with PCOS and GDM than those to maternal GDM alone. Other studies failed to detect differences in risk of total preterm birth between mothers with and without PCOS among GDM, probably because of insufficient power (PCOS with GDM: $n = 34\text{--}326$ vs. 5218 in our study;

[Alshammari et al., 2010](#); [Li et al., 2010](#); [Foroozanfard et al., 2014](#); [Aktun et al., 2016](#); [Manoharan and Wong, 2020](#)). Following adjusting for maternal BMI, we found that in mothers with GDM the risks of total and spontaneous preterm birth remained higher with the presence of PCOS. Moreover, the higher risks persisted after adjusting for infertility treatment and pre-eclampsia, or removing multiple pregnancies,

Table III Adjusted odds ratio for spontaneous preterm birth according to maternal PCOS and diabetes.

	< 37 weeks (n = 44 681)	32–36 weeks (n = 38 101)	28–32 weeks (n = 4714)	<28 weeks (n = 1866)
No maternal PCOS				
No DM	1.00	1.00	1.00	1.00
GDM	1.01 (0.98 – 1.05)	1.07 (1.03 – 1.11)	0.76 (0.69 – 0.85)	0.65 (0.55 – 0.77)
T2DM	2.35 (2.13 – 2.59)	2.37 (2.14 – 2.63)	1.91 (1.45 – 2.53)	2.04 (1.32 – 3.14)
DM-IT	17.80 (16.15 – 19.62)	16.74 (15.19 – 18.45)	8.53 (6.74 – 10.79)	5.18 (3.28 – 8.16)
Maternal PCOS				
No DM	1.54 (1.44 – 1.65)	1.47 (1.37 – 1.59)	1.70 (1.42 – 2.04)	2.29 (1.70 – 3.09)
GDM	1.80 (1.59 – 2.05)	1.88 (1.65 – 2.15)	1.36 (0.91 – 2.05)	1.59 (0.90 – 2.79)
T2DM	4.02 (2.94 – 5.50)	3.20 (2.22 – 4.61)	6.02 (3.10 – 11.70)	6.81 (2.54 – 18.20)
DM-IT	19.25 (13.05 – 28.40)	17.48 (11.79 – 25.93)	9.96 (4.46 – 22.25)	5.96 (1.46 – 24.39)

Spontaneous preterm births were all preterm births after excluding planned cesarean sections and induced vaginal labor. GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes mellitus; PCOS, polycystic ovary syndrome. Mothers without DM-IT, T2DM or GDM were grouped as having no DM. Mothers with DM-IT were excluded from the groups of T2DM and GDM, and likewise, mothers with T2DM were excluded from the GDM group. Values are odds ratio (95% CI).

The analysis was adjusted for offspring birth year, parity (0 or ≥ 1), maternal age at delivery, country of birth (Finland or not), smoking during pregnancy (yes/no) and mother married at delivery (yes/no).

suggesting that obesity, ART and its associated complications could not fully explain the association between PCOS and preterm birth in the setting of maternal GDM.

We noticed that the risk estimate for total preterm birth among mothers with PCOS and GDM was comparable to that among mothers with PCOS and no diabetes, suggesting a major role of PCOS rather than GDM in total preterm birth. Akin to our study, [Fougnier et al. \(2021\)](#) found no impact of GDM on preterm birth in women with PCOS. Key features of PCOS, such as hyperandrogenism and increased anti-Müllerian hormone (AMH) levels might contribute to PCOS-associated preterm birth ([Li et al., 2018](#); [Kaing et al., 2021](#)). Rapid suppression of serum AMH levels between 13th and 15th gestational weeks, resulting from physiologic cross-talk between the placenta and ovary, is essential for pregnancy ([Stegmann et al., 2015](#)). The speed and timing of AMH decreasing are linked to the increase in progesterone production during pregnancy. Persistent high levels of AMH in women with PCOS might suggest disrupted placentation and thus predict preterm delivery ([Kaing et al., 2021](#)). In addition, chronic subclinical inflammation may help account for PCOS-associated preterm birth ([Stokkeland et al., 2022](#)). Treatment with metformin, which seemed to have anti-inflammatory effects, decreased the risk of preterm delivery in women with PCOS with or without hyperandrogenism ([Løvvik et al., 2019](#)).

Our study found that the association of insulin-treated diabetes with preterm birth was not strengthened by the presence of PCOS. Given that the group insulin-treated diabetes comprised mostly type 1 diabetes (n = 5504, 92.9%), the results implied no effects of PCOS on preterm birth in mothers with type 1 diabetes, distinct to that in type 2 diabetes and GDM. In support of our findings, pathophysiology of hyperandrogenism in non-diabetic PCOS patients appeared to be different from that in women with type 1 diabetes and PCOS, with increased AMH levels in the former but normal in the latter ([Codner et al., 2007](#)). Moreover, sex hormone-binding globulin levels were increased in women with

non-diabetic PCOS but normal in those with type 1 diabetes and PCOS, which might reduce the delivery of ovarian androgens to other tissues, consequently protecting against androgen excess in these patients ([Roldan et al., 2001](#)). Future studies are warranted to validate our findings and elucidate underlying mechanisms for the differential associations of PCOS with preterm birth in the setting of different types of diabetes.

A recent systematic review reported no increased risks of LGA or SGA in mothers with PCOS when taking into account maternal BMI ([Bahri Khomami et al., 2019](#)), also supported by a large cohort study ([Mills et al., 2020a](#)). We extended this knowledge by demonstrating that the presence of PCOS did not alter the effect sizes of either LGA or SGA in mothers with type 2 diabetes, GDM or no diabetes, but significantly reduced the risk estimate of offspring LGA in mothers with insulin-treated diabetes. No studies exist, to our knowledge, on the association of maternal type 2 or type 1 diabetes and PCOS with offspring birth sizes. However, our effect sizes of PCOS on offspring LGA in maternal GDM was largely in agreement with previous studies ([Alshammari et al., 2010](#); [Li et al., 2010](#); [Palomba et al., 2012](#); [Foroozanfard et al., 2014](#); [Aktun et al., 2016](#); [Manoharan and Wong, 2020](#)). Hyperglycemia and BMI are proposed as main contributing factors to LGA for diabetes in pregnancy. Conversely, hyperandrogenism restricts fetal growth, an effect that could be prevented by intact placenta ([Carlsen et al., 2006](#); [Abbott et al., 2008](#)). Less offspring LGA in the presence of PCOS than in those without PCOS in the setting of insulin-treated diabetes might indicate impaired placental function, which affects nutrient transportation and exposes the fetus to high androgens in type 1 diabetes.

Strengths and limitations

Our main strength is the nationwide registers with prospectively collected data and large sample sizes. This allowed us to analyze the associations of maternal PCOS with comorbid different types of diabetes

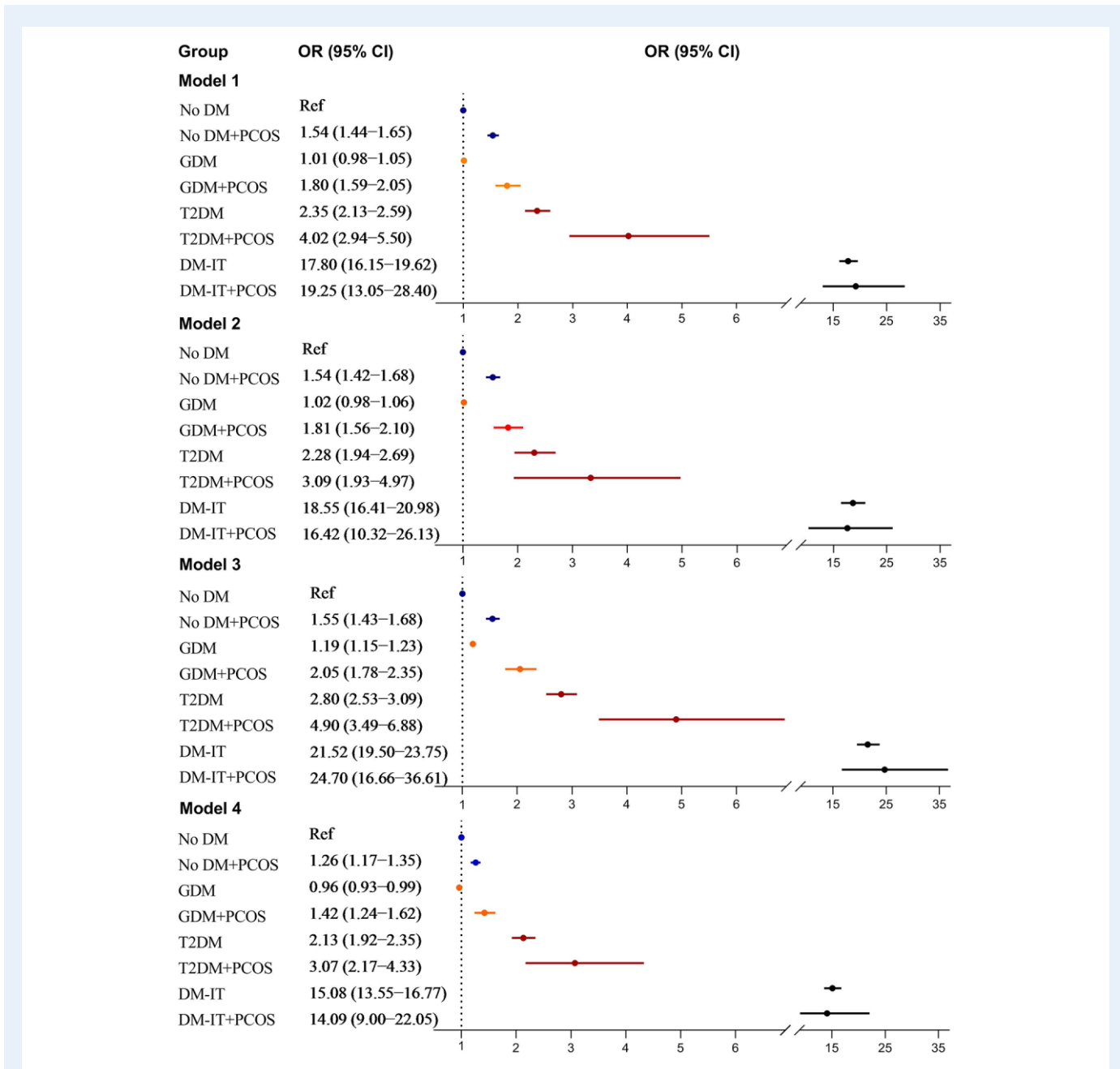


Figure 2. Adjusted odds ratio for spontaneous preterm birth in relation to maternal PCOS and diabetes. Model 1: birth cohort 1996–2014 was used, adjusting for offspring birth year, parity, maternal age at delivery, country of birth, smoking during pregnancy and mother married at delivery. Model 2: birth cohort 2004–2014 was used, adjusting for covariates in Model 1 plus maternal BMI. Model 3: birth cohort 1996–2014 was used, including singleton births only, adjusting for covariates in Model 1. Model 4: birth cohort 1996–2014 was used, adjusting for covariates in Model 1 plus infertility treatment and pre-eclampsia. PCOS, polycystic ovary syndrome; OR, odds ratio; GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes mellitus; No DM, mothers without DM-IT, T2DM or GDM; Ref, reference group.

to preterm birth at the full range of gestational ages and offspring birth sizes.

The limitations in this study should be recognized. First, PCOS is potentially underestimated because the prevalence (2.2%) is lower than previously reported (Escobar-Morreale, 2018). Women with PCOS

who did not have children were not included in our study. Also, PCOS is known to often be under-recognized. Those with milder PCOS not seeking medical care might be included in the reference group, which reduces the ability to detect potential associations. Meanwhile, by identifying cases based on ICD codes, this study might

Table IV Adjusted odds ratio for offspring that were large or small for gestational age in relation to maternal PCOS and diabetes in Finnish birth cohort 2004–2014.

	LGA (n = 17 433)		SGA (n = 20 821)	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
No maternal PCOS				
No DM	10 952 (1.9)	1.00	19 404 (3.4)	1.00
GDM	5540 (5.4)	2.10 (2.02–2.19)	2396 (2.4)	0.79 (0.75–0.83)
T2DM	491 (13.0)	4.38 (3.92–4.89)	111 (2.9)	1.07 (0.87–1.32)
DM-IT	1582 (40.3)	32.04 (29.79–34.46)	58 (1.5)	0.45 (0.34–0.59)
Maternal PCOS				
No DM	287 (2.1)	1.00 (0.88–1.14)	480 (3.5)	1.03 (0.93–1.13)
GDM	259 (6.3)	2.33 (2.04–2.68)	116 (2.8)	0.95 (0.78–1.15)
T2DM	37 (11.1)	3.52 (2.44–5.08)	11 (3.3)	1.26 (0.67–2.38)
DM-IT	83 (34.0)	18.90 (14.21–25.14)	4 (1.6)	0.57 (0.21–1.52)

LGA, large for gestational age; SGA, small for gestational age; GDM, gestational diabetes mellitus; T2DM, non-insulin-treated type 2 diabetes mellitus; DM-IT, prepregnancy insulin-treated diabetes mellitus; PCOS, polycystic ovary syndrome. Mothers without DM-IT, T2DM or GDM were grouped as having no DM. Mothers with DM-IT were excluded from the groups of T2DM and GDM, and likewise mothers with T2DM were excluded from the GDM group. Non-PCOS mothers with no diabetes were used as reference. Offspring birth year, parity (0 or ≥ 1), maternal age at delivery, maternal country of birth (Finland or not), smoking during pregnancy (yes/no), mother married at delivery (yes/no) and prepregnancy BMI were adjusted for. The analyses were performed in birth cohort 2004–2014 because maternal BMI was available from 1 January 2004.

include more severe PCOS that required medical interventions, overestimating the effect sizes of associations and making our results less generalizable. Moreover, including female infertility associated with anovulation as PCOS exposure was at risk for misclassification. Although PCOS has been reported to constitute 80% of anovulatory infertility (Balen *et al.*, 2016), this could overestimate the associations for some categories and underestimate the associations for others. However, sensitivity analyses restricted to women with a PCOS diagnosis (excluding anovulatory infertility) revealed similar risk estimates as the main analysis. Second, sample sizes for pregestational diabetes with PCOS were small. The CIs for preterm birth risks were wide, particularly at earlier gestational ages. The numbers were not powered to assess the association of PCOS with medically indicated preterm birth among mothers with type 2 or insulin-treated diabetes. Third, insulin purchase during pregnancy without diabetes diagnosis was not accounted for in the analysis; this would reduce the risk estimates as they were included in the reference group, although the number was small ($n = 5721$). For patients treated with insulin or other medications, we were unable to assess how they complied with such prescriptions. As low compliance with medications would increase glucose levels in mothers and birthweight in fetus, it might lead to overestimations of the associations with offspring LGA. Fourth, maternal BMI was recorded only once in early pregnancy, thus potential influence of gestational weight gain on birth outcomes could not be examined. Fifth, the causes for preterm birth were not available from the registers.

Conclusion

The presence of PCOS implied higher risk of total and spontaneous preterm birth in mothers with non-insulin-treated type 2 diabetes and GDM, and lower risk of offspring being LGA in mothers with

insulin-treated diabetes. Maternal obesity, infertility treatment and pre-eclampsia could explain, at least in part, the higher risks of preterm birth added by PCOS in maternal type 2 diabetes, but not in maternal GDM. The differential effects of PCOS in the associations of maternal diabetes with offspring birth outcomes have implications for preventative measures and pregnancy counseling for affected women.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The datasets underlying this article are held by the Finnish Institute for Health and Welfare. The data cannot be shared, since it has been given for this specific study, but access to similar data can be applied for through a regular permission application.

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Authors' roles

All authors met conditions for authorship. All authors met conditions for authorship. C.L., X.C. and M.G. obtained funding. X.C. conceptualized the study, interpreted the data, drafted and revised the manuscript. M.G. provided critical inputs on the study design, performed data cleaning and statistical analyses, and revised the manuscript. C.L.

conceptualized the study, acquired and interpreted the data and revised the manuscript.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

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