Paternal metformin use and risk of congenital malformations in offspring in Norway and Taiwan: population based, cross national cohort study

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ABSTRACT

OBJECTIVE

To evaluate the association between paternal metformin use and risk of congenital malformations in offspring.

DESIGN

Population based, cross national cohort study.

SETTING

Norway and Taiwan.

PARTICIPANTS

619 389 offspring with paternal data during the period of sperm development (three months before pregnancy) in the Norwegian cohort during 2010-21 and 2 563 812 in the Taiwanese cohort during 2004-18.

MAIN OUTCOME MEASURES

The primary outcome was any congenital malformation, and the secondary outcome was organ specific malformations, classified according to the European surveillance of congenital anomalies guidelines. Relative risks were estimated with an unadjusted analysis and with analyses restricted to the cohort of men with type 2 diabetes mellitus and those using overlap propensity score weighting to control for severity of diabetes and other potential confounders. Sibling matched comparisons were conducted to account for genetic and lifestyle factors. Relative risk estimates for Norwegian and Taiwanese data were pooled using a random effects meta-analytical approach.

RESULTS

Paternal data on metformin use during the period of sperm development was available for 2075 (0.3%) offspring in Norway and 15 276 (0.6%) offspring in Taiwan. Among these offspring, 104 (5.0%) in Norway and 512 (3.4%) in Taiwan had congenital malformations. Increased risks of any congenital malformation associated with paternal metformin use were observed in the unadjusted analysis and attenuated with increasing control of confounding. The relative risks of any malformations with paternal metformin use were 1.29 (95% confidence interval 1.07 to 1.55) in Norway and 1.08 (0.99 to 1.17) in Taiwan in the unadjusted analysis and 1.20 (0.94 to 1.53) and 0.93 (0.80 to 1.07), respectively, in the analysis restricted to fathers with type 2 diabetes mellitus. In the overlap propensity score weighting analysis restricted to fathers with type 2 diabetes mellitus, the relative risks were 0.98 (0.72 to 1.33) in Norway and 0.87 (0.74 to 1.02) in Taiwan, resulting in a pooled estimate of 0.89 (0.77 to 1.03). No associations were observed between paternal metformin use and any organ specific malformations. These findings were consistent in sibling matched comparisons and sensitivity analyses.

CONCLUSIONS

The findings suggest that paternal use of metformin during the period of sperm development is not associated with congenital malformations in offspring, including organ specific malformations. Metformin can therefore continue to be considered a suitable initial oral agent for managing glucose levels in men with type 2 diabetes mellitus who plan on having children.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A recent study reported an association between paternal metformin use preconception and an increased risk of major congenital malformations, particularly genital, in male infants

Type 2 diabetes mellitus in fathers, along with related health conditions and maternal factors, is known to be associated with congenital malformations in offspring, potentially providing alternative explanations for the associations

WHAT THIS STUDY ADDS

This population based, cross national cohort study found no significant association between paternal metformin use during the period of sperm development and congenital malformations in offspring

When evaluating the association between paternal drug use and risk of congenital malformations in offspring it is important to consider factors beyond the drug itself

Introduction

The global prevalence of type 2 diabetes mellitus is escalating among men of reproductive age.[1-3] This disease can have an adverse effect on fertility in men at multiple levels, including reduced sperm vitality[4 5] and the suppression of gonadal testosterone production.[6] Obesity, a condition that commonly accompanies type 2 diabetes mellitus, also poses a major risk to fertility in men by impairing spermatogenesis and consequently decreasing fecundability.[7 8] As an initial glucose lowering agent, metformin is widely used in the treatment of type 2 diabetes mellitus. Nonetheless, concerns have emerged about the potential harmful effects of metformin on the reproductive health of men.

Exposure to metformin in vitro may lead to decreased cell proliferation and altered secretory functions of testicular Sertoli cells.[9] Several animal studies have also shown that exposure to metformin results in reduced testicular weight and sperm production.[10 11] In men with type 2 diabetes mellitus, the use of metformin may interfere with testicular steroidogenesis as a result

of its antiandrogenic properties,[10] leading to lower testosterone levels.[12 13] This reduction in testosterone can further diminish sperm quality,[14] which in turn may negatively affect embryogenesis and the early development of offspring from the time of conception, including an increased potential risk of congenital malformations.[15 16] As metformin is considered non-mutagenic, epigenetic rather than genetic alterations to the sperm DNA have been proposed.[17] A recent Danish study found preconception metformin use in men to be associated with a 40% increased risk of major congenital malformations in offspring (adjusted odds ratio 1.40, 95% confidence interval (CI) 1.08 to 1.82),[18] particularly genital birth defects in male infants (3.39, 1.82 to 6.30). A reanalysis of Danish data also indicated a 1.4-fold increase in the risk of major congenital malformations associated with paternal metformin use.[19]

Although fathers contribute half of their offspring's DNA, understanding the safety of metformin use in men for offspring is limited. While previous studies have shown an association between paternal metformin use and risk of congenital malformations in offspring,[18 19] the biological plausibility in humans remains unclear. Furthermore, owing to the narrow national focus and inadequate control of confounding factors, including type 2 diabetes mellitus, severity of hyperglycaemia, and other diabetes related conditions, questions about the causality between paternal metformin use and risk of congenital malformations in offspring remain unresolved. To provide further guidance for the treatment of diabetes in men of reproductive age, we conducted a cross national cohort study leveraging national databases from Norway and Taiwan to assess the association between paternal metformin use and risk of congenital malformations in offspring, taking into account potential confounding by underlying indications and associated factors.

Methods

Data source and study population

This cross national cohort study was conducted using population based data from Norway and Taiwan. The Norwegian cohort included data from the Medical Birth Registry of Norway, the Norwegian Prescription Database, the Norwegian Patient Registry, and the Norwegian control and payment of health reimbursements. The Taiwanese cohort used information from the National Birth Certificate Application database, the National Health Insurance database, and the Maternal and Child Health Database. Supplementary appendix 1 provides detailed descriptions of the data sources used in the analysis, and both data sources have been used extensively to study drug safety in pregnancy.[20-22] We performed data linkage deterministically by assigning encrypted and unique identification numbers to newborns and parents to generate data for further analysis. The requirement for informed consent was waived owing to the use of deidentified patient data. This study followed the STROBE (strengthening the reporting of observational studies in epidemiology) reporting guideline.

We identified all pregnancies resulting in liveborn singletons from 2010 to 2021 in the Norwegian cohort and from 2004 to 2018 in the Taiwanese cohort. From both cohorts we excluded pregnancies with missing identification numbers for offspring or either parent, unknown sex of the offspring, missing gestational age, multiple pregnancies, and pregnancies in which the mother had filled a prescription for a known teratogenic drug (see supplementary eTable 1). We determined the start of pregnancy in both cohorts as the date of delivery minus gestational age, which was based on ultrasound examination and registered in databases with a high completeness and validity in both Norway (90-98%)[23] and Taiwan (88.3%).[24]

Metformin use

The process of developing fully mature spermatozoa, including spermatogenesis and maturation in the epididymis, spans around three months.[25] We determined paternal use of metformin during this period of sperm development by utilising the dispensing date and number of days supplied. In Norway, we presumed one defined daily dose to estimate the number of days supplied, thereby calculating the end date of a prescription; in Taiwan, we used the recorded number of days supplied according to the claims databases. We considered fathers to have used metformin when the days supplied overlapped with the three months before pregnancy, the period for sperm development (see supplementary eFigure 1). A dose-effect analysis, which was only possible in the Taiwanese cohort, was estimated by the mean daily use of metformin. Mean daily use was calculated using the defined daily dose, as defined by the World Health Organization Collaborating Center for Drug Statistics Methodology,[26] and categorised as low dose (defined daily dose <1.0) and high dose (defined daily dose ≥1.0).

Outcomes of interest

The primary outcome was any congenital malformation, and the secondary outcome was organ specific malformations (see supplementary eTable 2), according to the European surveillance of congenital anomalies (EUROCAT) guideline.[27] In the Norwegian cohort, we retrieved this information from the Medical Birth Registry of Norway, which is a member of EUROCAT. In the Taiwanese cohort, we employed an algorithm based on a previous study that utilised inpatient or outpatient diagnostic codes to identify congenital malformations diagnosed within one year after birth.[28] Data on organ specific malformations were only available for the Taiwanese cohort, except for the category of congenital heart defects, which were available for both cohorts. Analysis and reporting of data were conducted only for those outcomes that were sufficiently represented in the groups for metformin use and no metformin use.

Covariates

We considered a broad range of confounders using directed acyclic graphs (see supplementary eFigure 2). In both cohorts, we identified the calendar year of the offspring's birth and paternal characteristics, which included age, proxies for severity of diabetes (number of other glucose lowering drugs used, adaptive diabetes complications severity index),[29-32] chronic comorbidities (eg, hypertension, hyperlipidaemia, mental illness) (see supplementary eTable 3), and drug use (eg, insulin, sulfonylurea, other antidiabetic drugs, antihypertensive drugs, cardiovascular drugs, psychotropic agents) as confounders (see supplementary eTable 4). Moreover, we also considered maternal characteristics and lifestyle factors as proxies for confounders or risk factors for congenital malformations.

Statistical analyses

We compared the baseline characteristics of fathers who used or did not use metformin using standardised differences to evaluate balance between covariates, with a difference >0.10 considered meaningful. Results are presented from analyses performed at three levels of adjustment: an unadjusted analysis, an analysis restricted to fathers with a diagnosis of type 2 diabetes mellitus to control for the potential effects of the underlying illness or associated factors, and an analysis restricted to fathers with a diagnosis of type 2 diabetes mellitus, utilising overlap propensity score weighting to further control for proxies of diabetes severity and other potential confounders. The propensity score was calculated using a logistic regression model that incorporated all variables listed in the covariates section, followed by the calculation of overlap weights. This method upweighted individuals in the overlapping portion of the propensity score distribution (see supplementary eFigure 3) by assigning each a weight reflective of the probability of being assigned to the opposite group.[33 34] Generalised linear models were used to estimate relative risks with 95% confidence intervals (CIs) for any congenital malformation, employing a robust variance estimator to account for the weighting and data clustering because of multiple offspring for each father. Relative risk estimates for the two countries were pooled using random effects meta-analytical models, with heterogeneity assessed by the I^2 statistic. Random effects were applied in the meta-analysis owing to the potential heterogeneity in patient characteristics across countries, even though the same protocol was used. This approach assumes a normal distribution of effects, weighted by both within study and between study variances, resulting in a conservative estimate with a wider CI. In the Norwegian cohort, we dealt with missing data using multiple imputation by chained equations with 10 replications, based on the assumption that the data were missing at random (see supplementary appendix 2).[35 36] For the Taiwanese cohort, we used healthcare utilisation databases, which contained complete information on all recorded diagnoses, as well as all procedures and drugs administered. No adjustments were made for multiple testing, so the CI widths should not be interpreted as substitutes for hypothesis testing. Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata/MP version 17.0 (StataCorp).

To control for shared genetic factors, we compared siblings in both cohorts. Sibling comparisons, by design, can account for time fixed confounders shared by siblings.[37] All sibling pairs of each father were identified in the study, and only those pairs discordant for both metformin use and outcomes contributed to the estimated within pair association. Conditional logistic regression models, adjusted for calendar year of the offspring's birth and both paternal and maternal characteristics—including age, type 2 diabetes mellitus, proxies for diabetes severity, chronic comorbidities, and drug use—were employed for within family comparisons.

We performed several sensitivity analyses to test the robustness of the findings. Firstly, the definition of type 2 diabetes mellitus was revised to include both diagnosis codes and antidiabetic drug use. Secondly, to reduce the possibility of misclassifying metformin use, we revised the definition of use to require at least one filled prescription for metformin during the period of sperm development. Thirdly, to minimise the effect of maternal risk factors, we excluded mothers who used diabetes drugs, had a diabetes diagnosis, had a hypertension diagnosis, or were prescribed cardiovascular drugs during the six months before the start of pregnancy to the end of the first trimester. Fourthly, we restricted the cohort to both fathers younger than 45 years and mothers younger than 35 years to diminish the effect of advancing age on risk of congenital malformations.[38 39] Fifthly, as the cohorts were initially limited to pregnancies resulting in live births, we included stillbirths, spontaneous abortions, and terminations after pregnancy week 12 in the Norwegian cohort. Sixthly, we used methods that have previously been adopted to evaluate the potential impact of varying frequencies of stillbirths, miscarriages, or terminations between exposure and non-exposure to metformin (see supplementary appendix 3).[40 41] Seventhly, to address potential outcome misclassification in the Taiwanese cohort, we applied a quantitative bias analysis using a probabilistic method to simulate outcome misclassification (see supplementary appendix 4).[41 42] Furthermore, we used probabilistic bias analyses to account for unmeasured paternal overweight or obesity in both cohorts (see supplementary appendix 5).[43] Finally, we conducted prespecified exploratory analyses to assess the association between sulfonylurea, insulin, and dipeptidyl peptidase-4 inhibitors and risk of any malformations.

Patient and public involvement

Although we support the involvement of patients and the public, no funding was available for such undertakings in this project. As a result, no patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this research.

Results

Cohort characteristics

We identified 619 389 offspring with paternal data in the Norwegian cohort during 2010-21 and 2 563 812 in the Taiwanese cohort during 2004-18 (see supplementary eFigure 4). Paternal linkage to pregnancies was possible in 91.0% of the Norwegian

	Norwegian overall cohort			Taiwanese overall cohort		
	No (%)			No (%)		
	Metformin	No metformin	Standardised difference	Metformin	No metformin	Standardised difference
Total	2075	617 314		15 276	2 548 536	
Year of delivery						
2004-06	-	-		1570 (10.3)	520 007 (20.4)	
2007-09	-	-		2112 (13.8)	506 246 (19.9)	
2010-12	509 (24.5)	171 652 (27.8)		2954 (19.3)	481 338 (18.9)	
2013-15	522 (25.2)	166 536 (27.0)		4120 (27.0)	535 210 (21.0)	
2016-18	546 (26.3)	155 457 (25.2)		4520 (29.6)	505 735 (19.8)	
2019-21	498 (24.0)	123 669 (20.0)		-	-	
Paternal characteristics						
Mean (SD) age at delivery	41.6 (7.9)	32.9 (6.2)		39.4 (6.6)	33.4 (5.4)	
Type 2 diabetes mellitus	1848 (89.1)	4764 (0.8)		12 734 (83.4)	8759 (0.3)	
No of other glucose lowering agents						
0	1007 (48.5)	613 021 (99.3)		3656 (23.9)	2 542 091 (99.7)	
1	702 (33.8)	4151 (0.7)		5763 (37.7)	4780 (0.2)	
≥2	366 (17.6)	142 (0.0)		5857 (38.3)	1665 (0.1)	
aDCSI*						
0	1866 (89.9)	600 639 (97.3)		11 882 (77.8)	2 519 272 (98.9)	
1	209 (10.1)	16 675 (2.7)		2929 (19.2)	28 221 (1.1)	
≥2				465 (3.0)	1043 (0.04)	
Chronic comorbidities*						
Hypertension	483 (23.3)	13 163 (2.1)		5479 (35.9)	45 878 (1.8)	
Hyperlipidaemia	257 (12.4)	12 204 (3.0)		8302 (54.3)	44 878 (1.8)	
Mental illness	529 (25.5)	96 100 (15.6)		510 (3.3)	40 010 (1.6)	
Drug use						
Insulin	303 (14.6)	4027 (0.7)		2111 (13.8)	2253 (0.1)	
Sulfonylurea	442 (21.3)	187 (0.0)		9676 (63.3)	4045 (0.2)	
Other antidiabetic drugs	639 (30.8)	221 (0.0)		6251 (40.9)	1963 (0.1)	
Lipid modifying agents	701 (33.8)	7340 (1.2)		8039 (52.6)	32 085 (1.3)	
Beta blockers	183 (8.8)	4484 (0.7)		2441 (16.0)	65 679 (2.6)	
Calcium channel blockers	182 (8.8)	2651 (0.4)		2828 (18.5)	38 606 (1.5)	
RAAS agents	588 (28.3)	8090 (1.3)		5198 (34.0)	35 812 (1.4)	
Diuretics	67 (3.2)	1194 (0.2)		1003 (6.6)	22 815 (0.9)	
Antithrombotic agents	137 (9.6)	345 (8.5)		1808 (11.8)	19 029 (0.8)	
Antidepressants	161 (7.8)	17 784 (2.9)		624 (4.1)	40 206 (1.6)	
Antipsychotics	43 (2.1)	6019 (1.0)		842 (5.5)	94 711 (3.7)	
Other hypnotic agents	170 (8.2)	24 167 (3.9)		3439 (22.5)	341 487 (13.4)	

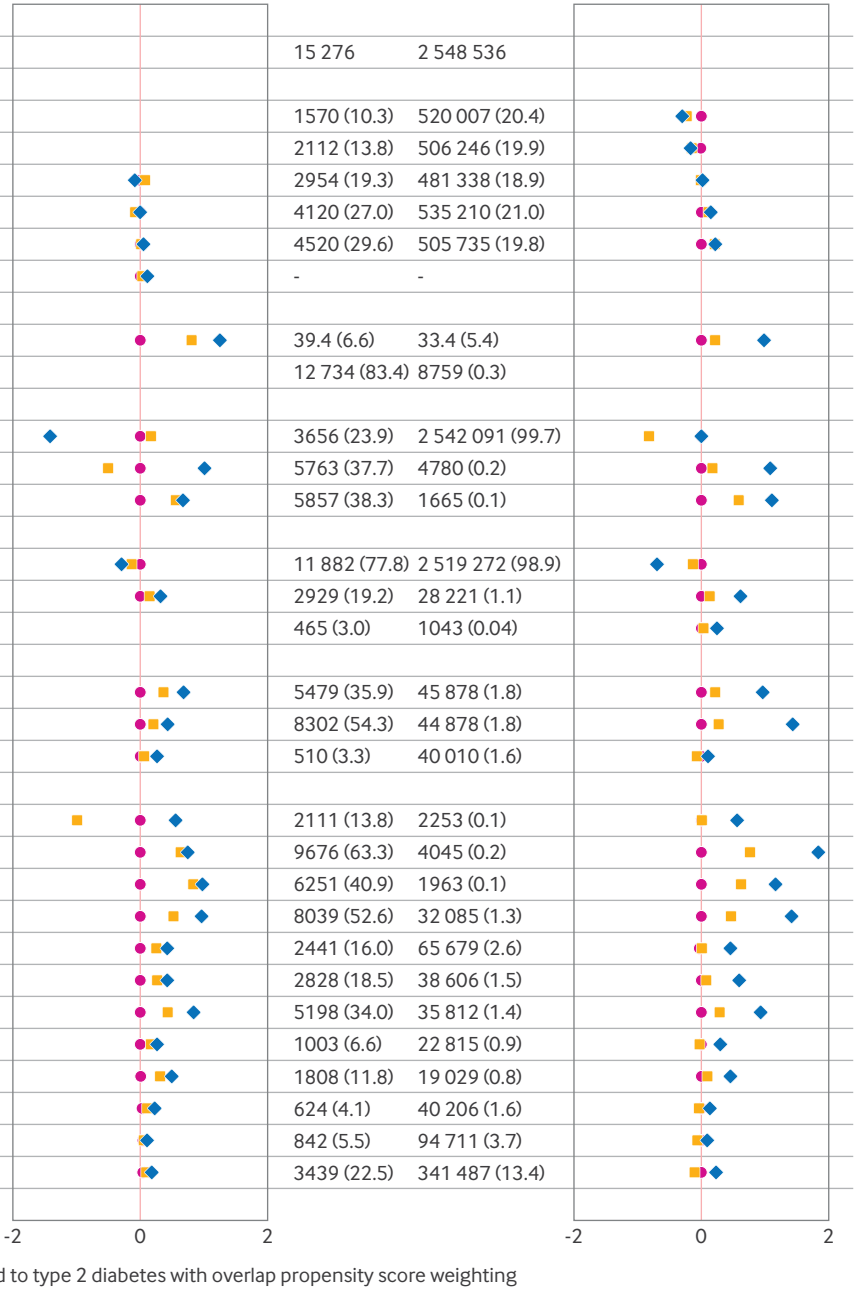

Fig 1 | Baseline characteristic of pregnancies with and without paternal metformin use during the period of sperm development by paternal characteristics. Standardised differences illustrate the balance in baseline characteristics across the overall cohort and the cohort restricted to fathers with type 2 diabetes mellitus before and after adjustment for overlap propensity score weight. *As availability of diagnostic codes differed between the data sources in Norway and Taiwan, the aDCSI and comorbidities are not directly comparable. SD=standard deviation; aDCSI=adaptive diabetes complications severity index; RAAS=renin-angiotensin-aldosterone system

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cohort and 95.6% of the Taiwanese cohort. Among these, fathers of 2075 (0.3%) offspring in Norway and 15 276 (0.6%) offspring in Taiwan used metformin during the period of sperm development. Compared with fathers who did not use metformin, those who used metformin were older and had a higher prevalence of diabetes and other chronic illnesses, notably hypertension, hyperlipidaemia, and mental illness (fig 1, supplementary eTable 5). These fathers were also more likely to use other types of glucose lowering drugs, cardiovascular drugs, and psychotropic agents. Their female partners were also more likely to be older and to have conditions such as diabetes and obesity (fig 2).

In the cohort restricted to fathers with type 2 diabetes mellitus, baseline characteristics were generally balanced between those who used and did not use metformin. However, fathers who used metformin were still observed to be older, have more severe diabetes, and be more likely to use cardiovascular drugs (see supplementary eTable 6). After applying overlap weights, a perfect balance of mean values of covariates included in the propensity score was achieved between fathers who used and did not use metformin in both cohorts (see supplementary eTable 7).

Risk of congenital malformations

In the Norwegian cohort, congenital malformations were observed in 24 041 (3.9%) offspring of fathers who did not use metformin during the period of sperm development, compared with 104 (5.0%) offspring of fathers who used metformin (fig 3). Paternal metformin

	Norwegian overall cohort			Taiwanese overall cohort		
	No (%)			No (%)		
	Metformin	No metformin	Standardised difference	Metformin	No metformin	Standardised difference
Total	2075	617 314		15 276	2 548 536	
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2016-18	546 (26.3)	155 457 (25.2)		4520 (29.6)	505 735 (19.8)	
2019-21	498 (24.0)	123 669 (20.0)		-	-	
Maternal characteristics during pregnancy						
Mean (SD) age at delivery	33.6 (5.0)	30.3 (5.0)		33.5 (4.9)	30.7 (4.8)	
Type 2 diabetes mellitus	62 (3.0)	5061 (0.8)		179 (1.2)	7214 (0.3)	
No of other glucose lowering agents						
0	2008 (96.8)	608 474 (98.6)		14 996 (98.2)	2 532 617 (99.4)	
1	48 (2.3)	8165 (1.3)		166 (1.1)	12 303 (0.5)	
≥2	19 (0.9)	675 (0.1)		114 (0.7)	3616 (0.1)	
aDCSI*						
0	2008 (96.8)	597 585 (96.8)		15 116 (99.0)	2 535 099 (99.5)	
1	67 (3.2)	19 729 (3.2)		150 (1.0)	13 077 (0.5)	
≥2				10 (0.1)	360 (0.0)	
Drug use						
Metformin	56 (2.7)	5790 (0.9)		239 (1.6)	12 793 (0.5)	
Insulin	26 (1.3)	3475 (0.6)		121 (0.8)	5083 (0.2)	
Sulfonylurea	<5 (0.1)	126 (0.1)		73 (0.5)	2505 (0.1)	
Other antidiabetic drugs	8 (0.4)	289 (0.1)		76 (0.5)	2042 (0.1)	
Folic acid	1310 (63.1)	477 661 (77.4)		909 (6.0)	139.541 (5.5)	
Lifestyle factors						
Smoking	109 (5.3)	37 478 (6.1)		26 (0.2)	3073 (0.1)	
Obesity or overweight	1201 (57.9)	214 019 (34.7)		37 (0.2)	1908 (0.1)	

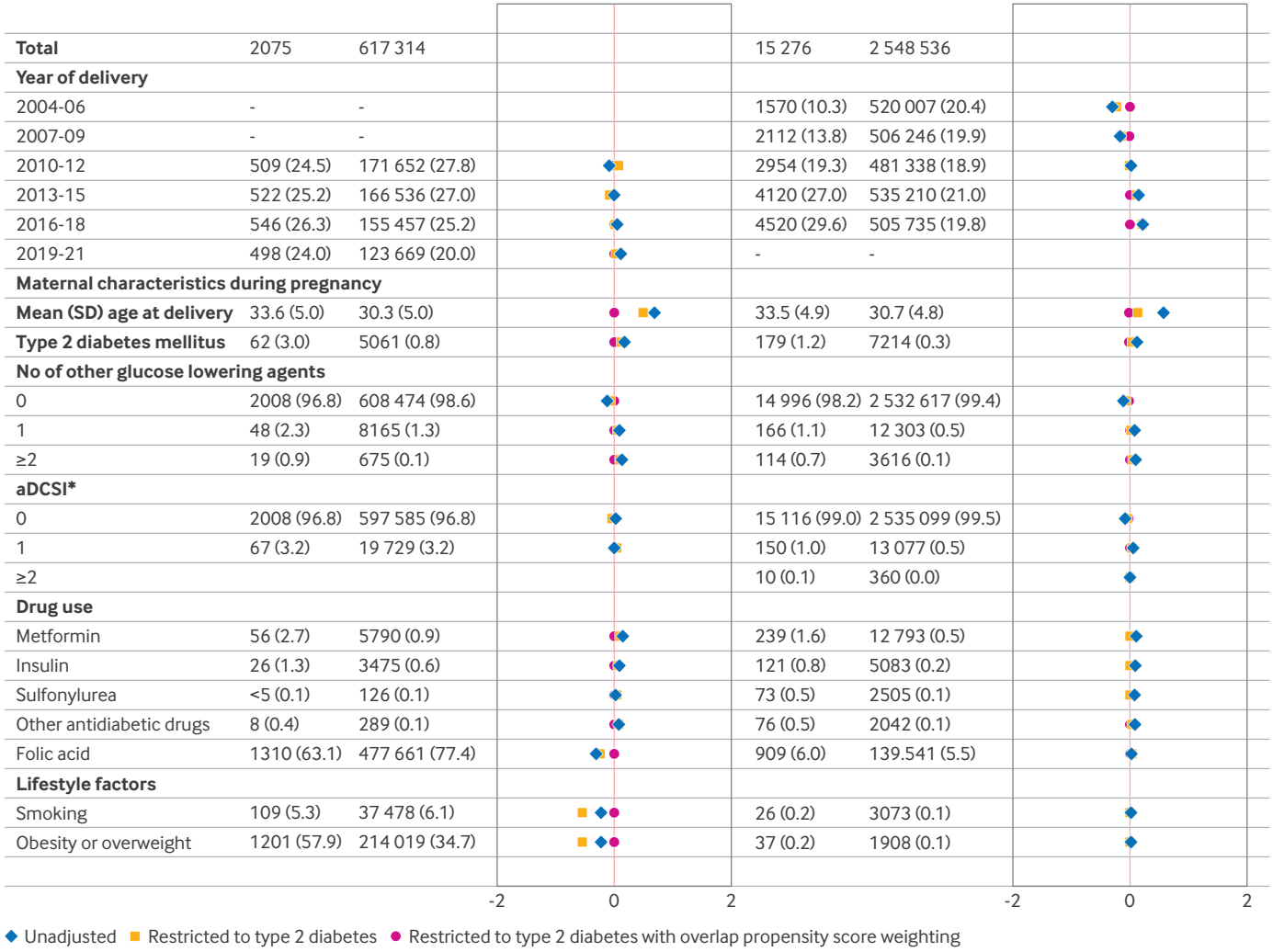

Fig 2 | Baseline characteristic of pregnancies with and without paternal metformin use during the period of sperm development by maternal characteristics during pregnancy. Standardised differences illustrate the balance in baseline characteristics across the overall cohort and the cohort restricted to fathers with type 2 diabetes mellitus before and after adjustment for overlap propensity score weight. *As availability of diagnostic codes differed between the data sources in Norway and Taiwan, the aDCSI and comorbidities are not directly comparable. SD=standard deviation; aDCSI=adaptive diabetes complications severity index

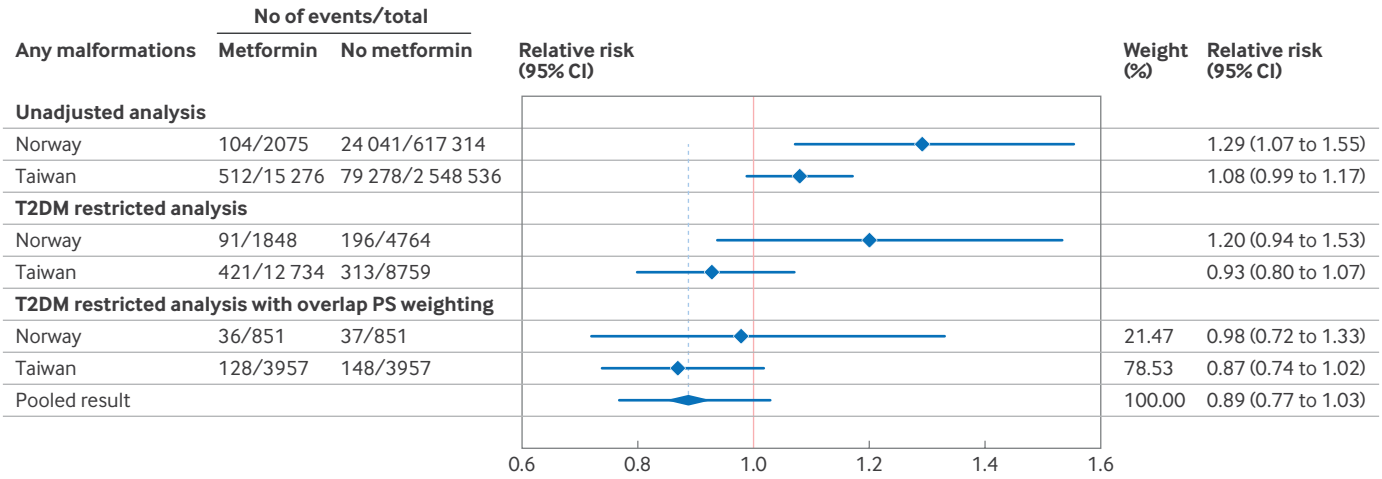

Fig 3 | Associations between paternal metformin use during the period of sperm development and risk of any congenital malformation. CI=confidence interval; PS=propensity score; T2DM=type 2 diabetes mellitus

use was associated with an increased risk of congenital malformations (unadjusted relative risk 1.29, 95% CI 1.07 to 1.55). Similarly, in the Taiwanese cohort, congenital malformations were diagnosed in 79 278 (3.1%) offspring of fathers who did not use metformin, compared with 512 (3.4%) offspring of fathers who used metformin, producing a slightly increased unadjusted relative risk of 1.08 (0.99 to 1.17).

When the cohort was restricted to fathers with type 2 diabetes mellitus, the risk estimates in the Norwegian cohort were not noticeably attenuated, but precision decreased (restricted relative risk 1.20, 95% CI 0.94 to 1.53). In the Taiwanese cohort, the restricted relative risk of 0.93 (0.80 to 1.07) indicated no association between paternal metformin use and congenital malformations when confounding by indication was considered.

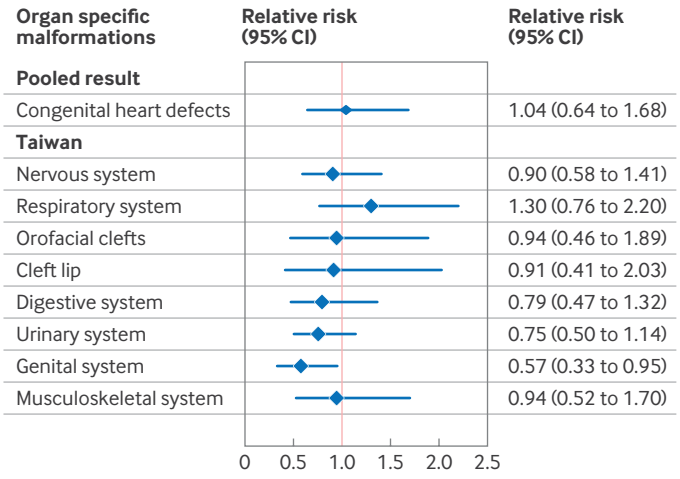

Fig 4 | Associations between paternal metformin use and risk of specific congenital malformations in cohort restricted to fathers with type 2 diabetes mellitus and overlap propensity score weighting. Only categories with enough numbers were reported. CI=confidence interval

After full adjustment for all measured confounders using overlap propensity score weighting in the restricted analysis, the risk estimate shifted towards the null in the Norwegian cohort (weighted relative risk 0.98, 95% CI 0.72 to 1.33). For the Taiwanese cohort, the adjusted risk estimate remained similar to that obtained after restricting the cohort to fathers with type 2 diabetes mellitus (0.87, 0.74 to 1.02). Pooling the adjusted estimates for paternal metformin use from both the Norwegian and the Taiwanese cohorts resulted in a weighted relative risk of 0.89 (0.77 to 1.03; I^2=0.0%). When exploring the risk of organ specific malformations associated with paternal metformin use, no increased associations were found (fig 4), and no dose effects were observed across the various types of malformations (see supplementary eTable 8).

Sibling matched comparison

In the sibling matched comparison, 76 sibling pairs were included from the Norwegian cohort and 581 pairs from the Taiwanese cohort (table 1). After adjusting for potential confounders shared between siblings, paternal metformin use during the period of sperm development was not associated with risk of congenital malformations in offspring in either the Norwegian cohort (adjusted odds ratio 0.83, 0.43 to 1.59) or the Taiwanese cohort (0.84, 0.68 to 1.04).

Sensitivity and exploratory analyses

Consistent results were observed in both the Norwegian cohort and the Taiwanese cohort when modifying the definition of type 2 diabetes mellitus, redefining metformin use as at least one prescription dispensed during the period of sperm development, excluding mothers with risk factors, restricting the analysis to fathers younger than 45 years or mothers younger than 35 years, and including stillbirths, miscarriages, or terminations in the Norwegian cohort (fig 5). Under the

Table 1 Associations between paternal metformin use during the period of sperm development and risk of overall congenital malformations in offspring: sibling matched comparison

Cohort	No of sibling pairs	No of offspring		Odds ratio (95% CI)	
		Paternal metformin	No paternal metformin	Unadjusted	Adjusted
Norwegian	76	111	78	1.04 (0.60 to 1.80)	0.83 (0.43 to 1.59)
Taiwanese	581	619	716	0.89 (0.75 to 1.05)	0.84 (0.68 to 1.04)

CI=confidence interval.

strongest assumptions tested for potential selection bias owing to restriction to live births, the relative risk estimates remained below 1.30 for any congenital malformations in both the Norwegian cohort and the Taiwanese cohort (see supplementary eFigure 5). Additionally, using probabilistic bias analyses to examine potential outcome misclassification in the Taiwanese cohort (see supplementary eTable 9) and to address unmeasured paternal overweight and obesity in both cohorts (see supplementary eTable 10) yielded similar findings to the main analysis.

In the exploratory analyses, we evaluated the association between paternal use of sulfonylurea, insulin, or dipeptidyl peptidase-4 inhibitor before pregnancy and risk of any congenital malformations in the type 2 diabetes mellitus restricted cohort (see supplementary eTable 11). We found no substantial increase in risk associated with the use of any of these drugs.

Discussion

In this population based, cross national study including about 3.2 million pregnancies with paternal data from Norway and Taiwan, after adjustment for type 2 diabetes mellitus and other potential confounding factors, we found no increase in the risk of any congenital malformations among infants born to fathers who used metformin during the period of sperm development. Additionally, no associations with organ specific malformations were observed, including genital malformations, which were previously reported to be associated with metformin use.[18] Furthermore, findings were consistent across sibling matched comparisons, accounting for time invariant confounders such as genetic or familial environmental factors, as well as in several prespecified sensitivity analyses.

Comparison with other studies

A previous study conducted in Denmark observed an association between paternal metformin use before pregnancy and congenital malformations.[18] Additionally, a reanalysis of Danish data revealed a 1.4-fold higher risk of major congenital malformations linked to paternal metformin use.[19] Our results, however, do not support those findings and point to confounding rather than a causal association. In general, paternal use of medicines can influence the

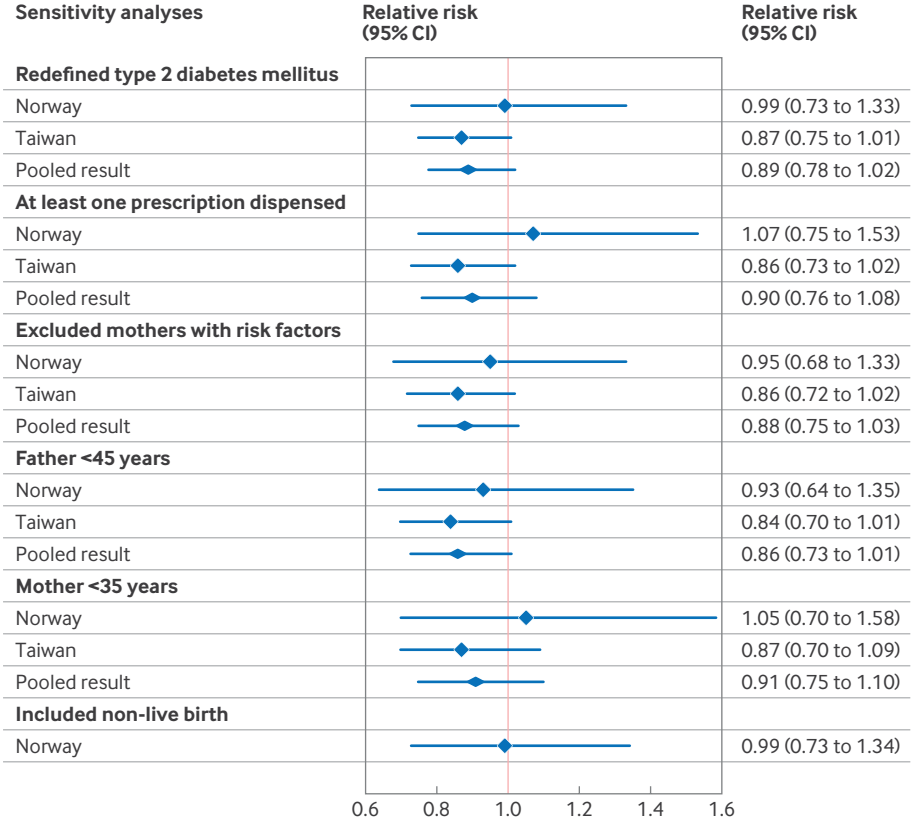

Fig 5 | Associations between paternal metformin use before pregnancy and risk of any congenital malformation after type 2 diabetes mellitus restricted with overlap propensity score weighting: sensitivity analyses. CI=confidence interval

risk of congenital malformations in offspring in two ways: firstly, through a direct effect on sperm DNA, and, secondly, indirectly, through the transmission of agents in the seminal fluid, leading to maternal exposure. Given that metformin has shown no recombinogenic or mutagenic activity at pharmacological concentrations,[44] the first mechanistic pathway is unlikely, and the drug use window selected in the present study does not allow for assessment of the second pathway. Although the mechanism behind the increased risk of malformations in offspring from paternal metformin use has been proposed to be due to an epigenetic mechanism of action, our findings do not support a biological causal mechanism in humans.

In contrast with analyses in the Danish study, our adjusted analyses restricted the cohort to fathers with type 2 diabetes mellitus to mitigate potential confounding by indication, associated conditions, and lifestyle behaviours. Without this restriction, we observed notable differences in age, prevalence of diabetes, other chronic comorbidities, and drug use between the exposed and non-exposed groups, suggesting lack of exchangeability between the two groups. Notably, advancing father's age,[45] as well as paternal metabolic syndrome related diseases,[46] are well known risk factors for congenital malformations. Although the Danish study reported a high E-value of 2.15,[18] unobserved confounding in their study, including type 2 diabetes mellitus related conditions, obesity, and codrug use, may explain away the observed association.

A potential concern raised in the previous Danish study was the confounding effect of blood glucose levels on the increased risk of malformations associated with paternal metformin use.[18] People treated with glucose lowering drugs generally have higher average glucose levels compared with healthy individuals before treatment. Nevertheless, our analysis suggests that the direct effect of mean glucose levels is unlikely to significantly confound these findings. In the Norwegian cohort, when we restricted our analysis to fathers with type 2 diabetes mellitus, we found no substantial shift in the risk estimate towards the null. This finding aligns with the results from earlier studies.[18 47 48] Specifically, the Danish study found no significant associations in the group that used insulin (adjusted odds ratio 0.98, 95% CI 0.85 to 1.14).[18] This may highlight the minimal impact of average glucose levels on the risk of malformation. Therefore, the differences between our findings and those of the Danish study may be due to the more extensive control of confounders, including severity of diabetes, metabolic syndrome associated conditions, chronic diseases, codrug use, and maternal characteristics, other than solely blood glucose levels.

In our study, we also observed that offspring of fathers who used metformin more often tend to have spouses with type 2 diabetes mellitus and obesity. Previous research has similarly reported spousal concordance for diabetes,[49] often attributed to shared lifestyle and environmental factors.[50] Maternal pre-existing diabetes is associated with several subtypes of congenital anomalies in newborns.[51] Furthermore, both the overall risk of major congenital malformations and the risk of malformations in specific organ groups increase progressively with severity of maternal overweight and obesity.[52] Hence, maternal characteristics may also serve as important confounders in studies assessing the safety of paternal drug use on outcomes in their offspring. To address this, we adjusted for a broad range of paternal and maternal potential confounding variables using propensity scores. While this method cannot eliminate all potential confounding, it has resulted in the unexposed and exposed groups with nearly identical measured parental characteristics and has tended to further lower the risk estimates.

An increased risk of genital birth defects in male offspring after paternal metformin use reported in the Danish study[18] was not observed in our study, which instead showed a reduction in the risk. Hypospadias, the most prevalent major male genital malformation, has a global incidence of 20.9 per 10 000 births.[53] A recent study indicated a potential link between paternal health, particularly components of metabolic syndrome, and the occurrence of hypospadias in sons.[54] Notably, between 70% and 80% of people with type 2 diabetes mellitus are estimated to have metabolic syndrome.[55] In addition to restricting the analyses to fathers with a diagnosis of type 2 diabetes mellitus, we adjusted for metabolic syndrome associated conditions such as hypertension, hyperlipidaemia, and proxies of the severity of diabetes. This comprehensive consideration of metabolic syndrome related confounders offers a possible explanation for the discrepancies between our findings and those of the Danish study regarding male genital malformations.[18] It is therefore reassuring that metformin was not associated with an altered risk of genital malformations. However, since only the Taiwanese cohort in the present study was available to assess genital malformations, future research with larger sample sizes is warranted to verify these results.

The crude estimates in both the Norwegian cohort (relative risk 1.29, 95% CI 1.07 to 1.55) and the Taiwanese cohort (1.08, 0.99 to 1.17) were lower than the adjusted association reported in the Danish study (adjusted odds ratio 1.40, 95% CI 1.08 to 1.82).[18] One potential concern is misclassification of either drug use or outcome, as both differential and non-differential misclassification may bias results towards the null.[56] Similar to the Danish study, however, the Norwegian cohort utilised high quality registry data, and therefore the likelihood of misclassification is considered to be low. We also conducted several sensitivity analyses in both the Norwegian cohort and the Taiwanese cohort to quantify the impact of misclassification, with no substantial alteration to the main findings. On the other hand, the differences in crude relative risks between Norway and Taiwan could be attributed to heterogeneity in patient characteristics, such as body mass index. In probabilistic analyses that accounted for paternal overweight and obesity, we found that paternal overweight and obesity had a greater impact on the Norwegian cohort compared with the

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Taiwanese cohort. Nonetheless, after full adjustments, we achieved homogeneous findings, which were then pooled using a random effects meta-analysis.

Limitations of this study

The high paternal linkage rate of more than 90% in both cohorts makes these data sources extremely valuable for studying the safety of paternal drug use, and the findings from the present study could inform future drug safety communications about the use of metformin among men before pregnancy. Our study is, however, also subject to certain limitations. Metformin use was determined based on filled prescriptions, and we were unable to confirm actual drug intake by participants, which may lead to misclassification of drug use. To enhance reliability, we revised the definition for metformin use to require at least one filled prescription during the period of sperm development in our sensitivity analyses, which gave similar results. Another potential limitation is residual and unmeasured confounding, as with all observational studies. Although we accounted for a broad range of confounders using multiple statistical methods, including sibling matched comparisons, we cannot completely eliminate the impact of residual and unmeasured confounders, such as lifestyle factors, dietary habits, body mass index, and genetic factors. Moreover, our databases do not include laboratory data, such as haemoglobin A_{1c} levels. As a result, we were constrained to using diagnosis codes to identify type 2 diabetes mellitus and had limited ability to account for glycaemic control. However, we implemented comprehensive measures to deal with this issue, incorporating the adaptive diabetes complications severity index and the use of glucose lowering agents within the propensity score to align diabetes severity across the study comparators to the greatest extent possible. Additionally, the present study excluded women taking teratogenic drugs from the analysis. Many pregnant women may choose to terminate a pregnancy using teratogenic drugs; however, owing to data limitations, we are unable to explore the impact of this situation on our study. Furthermore, despite utilising large national cohorts, estimating the risks for most organ specific malformations remains challenging. Future well designed studies are needed to more accurately assess the risk of paternal metformin use, diabetes, and obesity on specific malformations.

Clinical implications

Metformin is a cornerstone in the drug treatment of type 2 diabetes mellitus. Recently, concerns have emerged about the risk of congenital malformations in offspring associated with paternal use of metformin,[18] primarily owing to its potential to cause epigenetic alterations to the sperm DNA.[17] This concern raises questions about the clinical use of metformin for men of reproductive age considering fatherhood. The findings of our cross national study, which includes data from Norway and Taiwan, suggest that metformin keeps its current clinical profile as an initial oral agent for managing glucose levels in men with type 2 diabetes mellitus who are planning a family. The study also underscores the necessity of considering factors beyond the drug itself, such as the underlying indication, related health conditions, and maternal risk factors, when evaluating the association between paternal drug use and risk of congenital malformations in offspring.

Conclusion

Our results indicate that paternal use of metformin during the period of sperm development is not associated with an increased risk of any congenital malformations in offspring. Additionally, we found no notable increases in risk for any specific organ malformations, including genital malformations. These results provide reassurance and can assist clinicians in making informed treatment decisions when selecting metformin in the treatment of type 2 diabetes mellitus among men who are planning a family.

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Contributors: All authors drafted the article, revised it critically for important intellectual content, and approved the final version for publication. FYH and HMEN are the guarantors. LCM, MMHJG, HMC, LKC, FYH, and HMEN designed the research. LCM, MMHJG, FYH, and HMEN drafted and prepared the manuscript. LCM and MMHJG prepared the data. LCM analysed the data. LCM, MMHJG, HMC, Chen LK, FYH, and HMEN provided critical methodological and statistical input. LCM, MMHJG, FYH, and HMEN contributed to the clinical interpretation.

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Ethical approval: This study was approved by the Regional Committee for Research Ethics in South-eastern Norway (2018/140/REK Sør-Øst) and the Data Protection Officer at the University of Oslo (58033), and by the Institutional Review Board of the National Taiwan University Hospital (202101129RINC). The requirement for informed consent was waived owing to the use of deidentified patient data.

Data sharing: All potentially identifiable data were encrypted to protect anonymity. Access to data is restricted to investigators whose proposal is approved and who have signed a data access agreement.

Transparency: LCM, FYH, and HMEN affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The study results will be disseminated to the public through press releases, social media, and presentations at conferences.

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Supplementary information: Appendices 1-5, eTables 1-11, and eFigures 1-5