

# research



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## ORIGINAL RESEARCH Cross sectional survey in 148 countries

### Progress of nations in the organisation of, and structures for, kidney care delivery between 2019 and 2023

Okpechi IG, Levin A, Tungsanga S, et al

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**Study question** What were the changes in key measures of kidney care globally between 2019 and 2023?

**Methods** Data were used from an international cross sectional survey of the International Society of Nephrology Global Kidney Health Atlas conducted in 2019 and in 2023. Participants were from 148 countries across the 10 regional boards of the International Society of Nephrology. Analyses compared availability of kidney replacement treatment services, access, health financing, workforce, registries, and policies for kidney care.

**Study answer and limitations** Globally from 2019 to 2023, the number of centres that provided haemodialysis (4.4 per million population (pmp) to 4.8 pmp ( $P<0.001$ )), peritoneal dialysis (1.4-1.6 pmp), and kidney transplantation (0.43-0.46 pmp) increased. Results showed that the proportions of countries that used public funding for kidney care (free at point of

delivery) increased from 27% in 2019 to 28% in 2023 for haemodialysis, 23% to 28% for peritoneal dialysis, and 31% to 36% for kidney transplantation. The survey based study design was a limitation given the potential for subjectivity in responses (eg, social desirability bias) depending on respondents' knowledge, expertise, and perceptions.

**What this study adds** Globally, key aspects that determine delivery of quality kidney care, such as availability of services and public funding for care, showed variable degrees of changes across country income levels and world regions. Countries need to develop and implement strategies for preserving and improving access to kidney care services, particularly for kidney transplantation.

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OLAF DOERING/ALAMY

# Paternal metformin use and malformations in offspring

**ORIGINAL RESEARCH** Population based, cross national cohort study

## Paternal metformin use and risk of congenital malformations in offspring in Norway and Taiwan

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**Study question** Is there any association between paternal metformin use in the period during sperm development and risk of congenital malformations in offspring?

**Methods** This cross national cohort study identified 619389 offspring with paternal data in Norway from 2010 to 2021 and 2563812 offspring in Taiwan from 2004 to 2018. Paternal metformin use during the period of sperm

development (three months before pregnancy) was assessed. The main outcome was any congenital malformation, and the secondary outcome was organ specific malformations. Relative risks were estimated through unadjusted analyses, as well as through analyses restricted to men with type 2 diabetes mellitus and those using overlap propensity score weighting to control for severity of diabetes and other potential confounders.

**Study answer and limitations** Paternal data on metformin use during the period of sperm development was available for 2075 (0.3%) offspring in Norway and 15276 (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. Although the study accounted for a broad range of confounders using multiple statistical methods, the effect of residual and unmeasured confounders cannot be excluded.

## COMMENTARY Latest big study is reassuring for potential fathers and their partners

The antidiabetic drug metformin reduces hyperglycaemia by inhibiting hepatic glucose production and increasing insulin sensitivity.<sup>1</sup> It is used as initial treatment for type 2 diabetes and off-label to manage a range of other conditions associated with metabolic dysregulation, including obesity and polycystic ovary syndrome.<sup>2</sup> More than 24 million prescriptions for metformin were issued in the UK during 2022-23.<sup>3</sup>

With widespread use comes additional concern for characterising safety at the population level. During pregnancy, metformin crosses the placenta.<sup>4</sup> A growing body of literature has consequently focused on characterising any potential effects of maternal metformin use on offspring.<sup>5-8</sup> Reassuringly, such use has not been convincingly linked with an increased risk of congenital abnormalities.<sup>5,6</sup>

By comparison, the potential effect of paternal metformin use on risk of congenital abnormalities among offspring has been understudied. The first major study to examine this association was published in 2022: using population based data from Denmark (n=1116779), the authors found that prescription

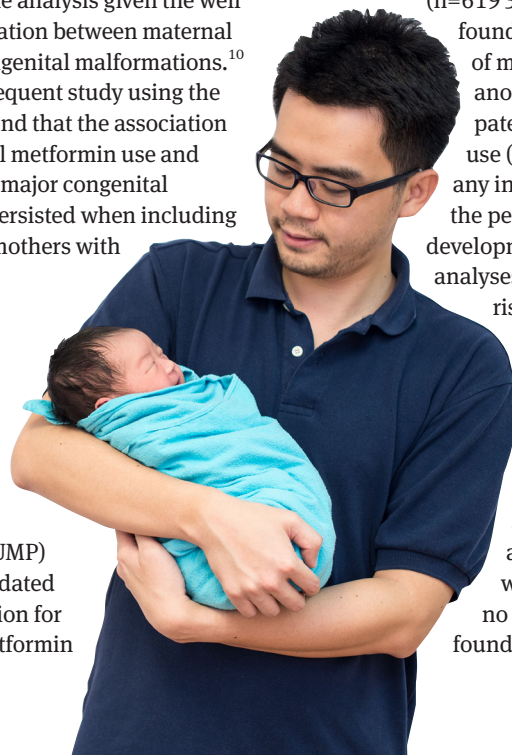
of metformin to fathers during the preconception period (for any indication) was associated with an increased risk of major congenital malformations among offspring, compared with insulin.<sup>9</sup> Specifically, this study reported a 3.3-fold increase in the likelihood of genital birth defects in male offspring (adjusted odds ratio 3.39 (95% confidence interval (CI) 1.82 to 6.30)). Offspring of mothers with pre-existing and gestational diabetes were excluded from the analysis given the well described association between maternal diabetes and congenital malformations.<sup>10</sup> However, a subsequent study using the same dataset found that the association between paternal metformin use and increased risk of major congenital malformations persisted when including the offspring of mothers with diabetes.<sup>11</sup>

These findings understandably caused concern. The UK Teratology Information Service's best use of medicine in pregnancy (BUMP) database was updated to include a caution for fathers using metformin

during the preconception period, acknowledging possible risks and the need for further research.

### Differences between countries

The paper by Meng and colleagues provides a welcome re-evaluation of paternal metformin use and risk of congenital abnormalities among offspring.<sup>12</sup> Using population based data from Taiwan (n=2563812) and Norway (n=619389), the authors found an increased risk of major congenital anomalies after paternal metformin use (prescribed for any indication) during the period of sperm development in unadjusted analyses in Norway (relative risk 1.29 (95% CI 1.07 to 1.55)) but not in Taiwan (1.08 (0.99 to 1.17)). Critically, however, after adjusting for relevant covariates and restricting analyses to fathers with type 2 diabetes, no association was found between paternal

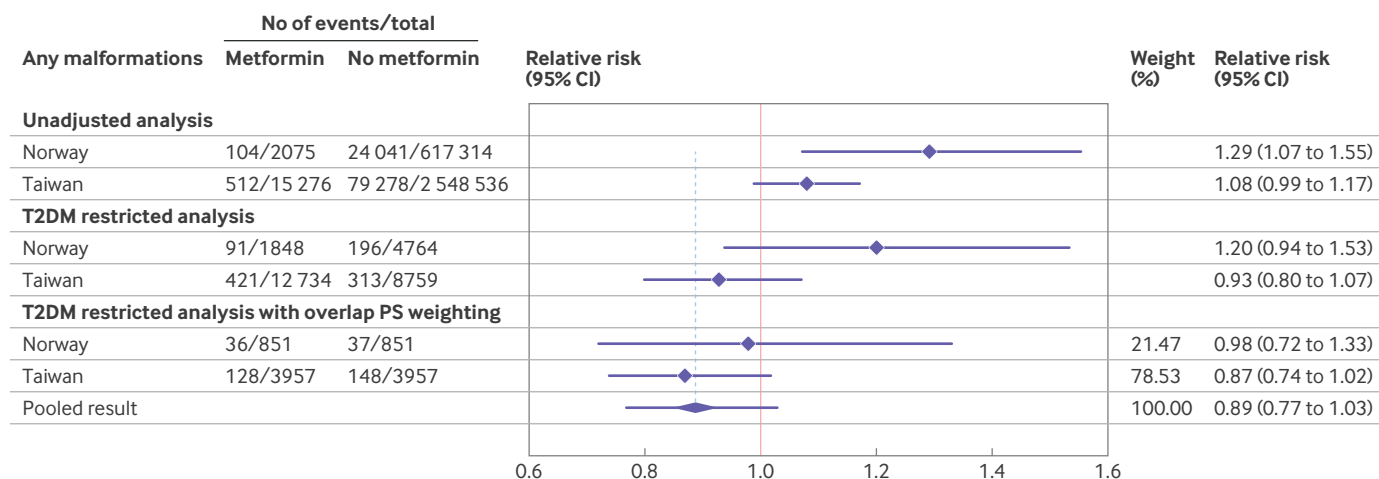


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Test for heterogeneity:  $P=0.50$ ;  $I^2=0\%$

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

**What this study adds** The findings of this study 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.

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metformin use and major congenital anomalies in offspring for either cohort alone (propensity score weighted relative risk in Norway 0.98 (95% CI 0.72 to 1.33) and in Taiwan 0.87 (0.74 to 1.02)) or combined in a meta-analysis (0.89 (0.77 to 1.03)).

This lack of association persisted across several prespecified sensitivity analyses. Data on organ specific malformations were limited in the Norwegian cohort. While these data were available in the Taiwanese cohort, evidence of an association between metformin use and risk of genital malformations in male offspring was lacking—unadjusted results actually suggested a reduced risk (0.57, 95% CI 0.33 to 0.95), but additional large studies accounting for relevant confounders are needed before further conclusions can be drawn.

In light of Meng and colleagues' publication, two large population based studies with inconsistent findings now exist. How can this inconsistency be explained? As with all retrospective cohort studies, findings depend on the quality of the data available and on the analyses conducted. The earlier Danish studies were possibly limited by the lack of descriptive data on participants' comorbidities, including diabetes. Although insulin (the comparator used in the Danish studies)



### These findings provide some reassurance for clinicians, and for fathers-to-be prescribed metformin preconception

is uniquely prescribed for diabetes, metformin is prescribed for other conditions, raising the possibility that the group using metformin might include a different population from the group using insulin.

Indeed, the cohort that used metformin were more commonly prescribed antihypertensives, cholesterol lowering drugs, and diuretics than the insulin control cohort, hinting at the presence of comorbidities associated with the metabolic syndrome.<sup>9</sup> This is highly relevant: a US study found that metabolic syndrome in fathers was associated with a 26% increased risk of hypospadias in

their offspring.<sup>13</sup> Unobserved confounders and underlying paternal disease could therefore help to explain the association observed between metformin use and major congenital malformations in the Danish cohort.

By contrast, the Taiwanese and Norwegian datasets analysed by Meng and colleagues contained detailed paternal data on comorbidities, including severity of diabetes, which were included in the adjusted model. This study also spanned two countries and included more than double the number of participants compared with the Danish cohort. Finally, lack of a known biological mechanism also adds to the case against a link between paternal metformin use and fetal malformations. Human and animal studies generally indicate a neutral or beneficial effect of metformin on steroidogenesis and spermatogenesis.<sup>14</sup>

For some, Meng and colleagues' findings may not completely lay to rest concerns raised by the Danish analyses, and further confirmatory studies are worth while. At the very least, however, these findings provide some reassurance for clinicians, and for fathers-to-be prescribed metformin preconception.

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## Intense simplified strategy for newly diagnosed type 2 diabetes in patients with severe hyperglycaemia

Liu L, Ke W, Hai Li, et al

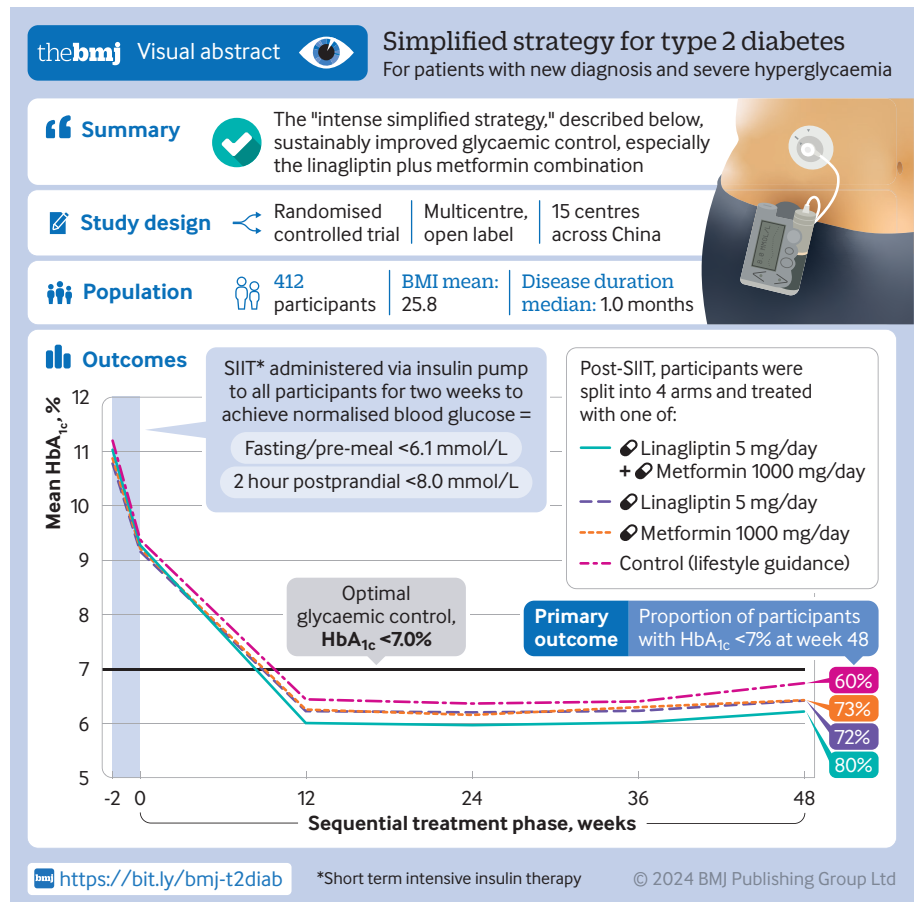
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**Study question** Can the intense simplified strategy, which comprises short term intensive insulin therapy (SIIT) followed by oral antihyperglycaemic regimens, improve long term glycaemic outcomes in patients with newly diagnosed type 2 diabetes mellitus and severe hyperglycaemia?

**Methods** This multicentre, open label, randomised trial was conducted in 15 hospitals in China and enrolled 412 patients with newly diagnosed type 2 diabetes and glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) ≥8.5%. After initial SIIT for two to three weeks, participants were allocated to four subsequent treatment groups for 48 weeks: linagliptin 5 mg/day, metformin 1000 mg/day, a combination of linagliptin plus metformin, or lifestyle modification alone (control). The primary outcome was the percentage of participants achieving HbA<sub>1c</sub> <7.0% at week 48. Secondary outcomes included glycaemic control, β cell function, and variations in insulin sensitivity.

**Study answer and limitations** The intense simplified strategy, particularly the combination of linagliptin plus metformin, significantly improved glycaemic control in patients with newly diagnosed type 2 diabetes and severe hyperglycaemia (mean HbA<sub>1c</sub> 11.0%), with 80% (78/97) achieving HbA<sub>1c</sub> <7.0% and 70% (68/97) achieving HbA<sub>1c</sub> <6.5% at week 48 in the linagliptin plus metformin



group, compared with 60% (56/93) and 48% (45/93) in the control group. Limitations include the open label design, the higher than expected attrition rate owing to covid-19, and the need for validation in more diverse populations.

**What this study adds** The study shows that the intense simplified strategy leads to excellent long term glycaemic control in patients with severe hyperglycaemia, which supports the

establishment of a de-escalation therapeutic strategy for patients with newly diagnosed type 2 diabetes.

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Study registration ClinicalTrials.gov NCT03194945.

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