OPEN ACCESS

Check for updates

# Preconception antidepressant use in fathers and risk of metabolic disorders in offspring: Danish population based cohort study

Jinmei Chen,[1] Nhung T H Trinh,[2,3] Hedvig Marie Egeland Nordeng,[3,4] Esben Agerbo,[1] Yongfu Yu,[5] Lars Henning Pedersen,[6,7,8] Alison C Holloway,[9] Thomas Munk Laursen,[1] Tine Brink Henriksen,[10,11] Veerle Bergink,[12,13] Xiaoqin Liu[1]

For numbered affiliations see end of the article

Correspondence to: J Chen jinmei.chen@ph.au.dk; (ORCID 0009-0006-1477-9651)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;395:e101239 http://dx.doi.org/10.1136/bmj-2026-101239

Accepted: 28 October 2026

## ABSTRACT

### OBJECTIVES

To investigate the associations between paternal antidepressant use during spermatogenesis and risk of metabolic disorders in offspring.

### DESIGN

Nationwide population based cohort study.

### SETTING

Danish national registers.

### PARTICIPANTS

1 365 887 liveborn singleton infants in Denmark from 2000 to 2023, followed from birth until 31 December 2023, death, emigration, or first occurrence of outcome, whichever came first.

### MAIN OUTCOME MEASURES

Metabolic disorders in offspring, including type 2 diabetes, hypertension, hypercholesterolaemia, and overweight or obesity, were identified from hospital and prescription records. Offspring of fathers who took antidepressants during spermatogenesis (three months before pregnancy) were compared with those of fathers who did not take antidepressants during this period and fathers who used antidepressants only during pregnancy to further account for underlying paternal mental health conditions. Associations between paternal antidepressant use and metabolic disorders, collectively and individually, were estimated as propensity score weighted hazard ratios using Cox regression.

### RESULTS

23 572 (1.7%) offspring were born to fathers who used antidepressants during spermatogenesis. During a mean follow-up of 12.1 years (standard deviation 7.0 years), 18 353 (1.3%) offspring were diagnosed with a metabolic disorder, including 364 whose fathers used antidepressants during spermatogenesis and 17 989 whose fathers did not use antidepressants during this period (1.39 *v* 1.11 events per 1000 person years, respectively). Offspring whose fathers used antidepressants during spermatogenesis had a slightly higher risk of developing metabolic disorders (weighted hazard ratio 1.20, 95% confidence interval (CI) 1.04 to 1.38) compared with offspring who were unexposed. The associations varied by specific metabolic outcomes, with weighted hazard ratios ranging from 0.81 (95% CI 0.45 to 1.47) for hypercholesterolaemia to 1.64 (95% CI 1.21 to 2.22) for hypertension. However, when compared with offspring of fathers who took antidepressants during the pregnancy period only, no increased risk was found of any metabolic disorders (0.75, 95% CI 0.58 to 0.98) or of specific metabolic disorders.

### CONCLUSIONS

The slightly increased risk of metabolic disorders in offspring of fathers using antidepressants during spermatogenesis was probably attributable to underlying paternal mental health disorders. These findings offer reassurance for men treated with antidepressants before pregnancy.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of antidepressants among men of reproductive age has risen in recent years

Previous studies have examined the association of paternal antidepressant use before conception with birth outcomes and neurodevelopmental outcomes; however, studies focused on metabolic disorders in offspring are limited

## WHAT THIS STUDY ADDS

Paternal antidepressant use during spermatogenesis was associated with a slightly increased risk of metabolic disorders in offspring compared with those with no paternal antidepressant use

Increased risks were not observed in children whose fathers used antidepressants only during pregnancy, suggesting that the association may reflect underlying paternal mental health conditions rather than antidepressant use

## Introduction

Depression is highly prevalent and a leading cause of disability worldwide.[1] An estimated one in 10 men will experience depression over their lifetime.[2] Antidepressants are the first line pharmacological treatment for moderate to severe major depression.[3] Beyond major depression, these drugs are also commonly prescribed for anxiety disorders, bulimia nervosa, panic disorders, and obsessive-compulsive disorder.[4] The use of antidepressants among men of reproductive age has risen in recent years. The percentage of children conceived after paternal antidepressant treatment in Denmark has increased threefold over the past two decades from 0.8% in 1997-2001 to 2.6% in 2012-17.[5] Similarly, approximately 1.4% of fathers in Norway and the Netherlands received antidepressants during the three months before conception.[6 7]

Whether paternal antidepressant use before conception affects offspring health remains uncertain, although reported effects on male reproductive function provide some biological plausibility. Evidence, primarily from studies of selective serotonin

reuptake inhibitors (SSRIs), reported that paternal SSRI use impairs semen parameters or increases sperm DNA fragmentation,[8-12] or both, potentially altering embryonic development.[13-15] Beyond effects on DNA integrity, paternal antidepressant use might also influence sperm borne epigenetic information, including epigenetic marks at imprinted genes.[16] During embryonic reprogramming, a process where most epigenetic marks are erased,[17 18] those at imprinted genes are largely preserved and can be transmitted from fathers to offspring.[19-21] Epigenetic dysregulation, including imprinted genes, has been associated with metabolic phenotypes in animals and humans.[22 23] However, whether these potential mechanisms translate into adverse metabolic outcomes after paternal antidepressant use in humans remains unknown. Epidemiological evidence is limited, with previous studies focusing on adverse birth or neurodevelopmental outcomes in offspring.[24-27] To date, studies directly examining the potential impact of paternal antidepressant use before pregnancy on metabolic disorders in offspring are lacking.

We aimed to determine whether paternal antidepressant use during spermatogenesis (ie, within 90 days before pregnancy) was associated with metabolic disorders in offspring by using Danish nationwide registers with up to 23 years of follow-up. We hypothesised that offspring born to fathers treated with antidepressants during spermatogenesis would have an increased risk of developing metabolic disorders.

## Methods

### Study population

We conducted a population based cohort study using data from several nationwide registers in Denmark. All live births are assigned a unique personal identification number, which can be used to link individual level data across registers (see eTable 1 for details on data sources). We first identified 1 484 916 live births between 2000 and 2023 from the Danish Medical Birth Registry.[28] We excluded 48 287 offspring who could not be linked to either parent, 52 467 multiple births owing to their distinct fetal growth and perinatal characteristics,[29] and 18 275 offspring with missing or implausible gestational age (<154 or >315 days). We used information from first or second trimester ultrasound scans to determine the start of pregnancy, calculated by subtracting the ultrasound based gestational age from the date of delivery. When ultrasound data were unavailable, we used the first day of the woman's last menstrual period to estimate the start of pregnancy.[28] Altogether, 1 365 887 offspring were eligible for analysis (see fig 1).

### Paternal antidepressant prescription during spermatogenesis—exposure of interest

Information on paternal antidepressant prescriptions was retrieved from the Danish National Prescription Registry,[30] which contains data on all drugs dispensed at community pharmacies in Denmark (eg, date of dispensing, drug name, and Anatomical Therapeutic Chemical (ATC) code). Paternal antidepressant use was defined as at least one filled prescription for an antidepressant with ATC code N06A, including SSRIs (N06AB), serotonin-norepinephrine reuptake inhibitors (N06AX), tricyclic antidepressants (N06AA), and monoamine oxidase inhibitors (N06AF, N06AG; see eTable 2 for detailed ATC codes). Given that spermatogenesis is estimated to take approximately 74 days,[31] we defined the exposure window as the 90 days before the start of pregnancy to capture the susceptible period. We classified a child as exposed if the dispensing date fell within this window.

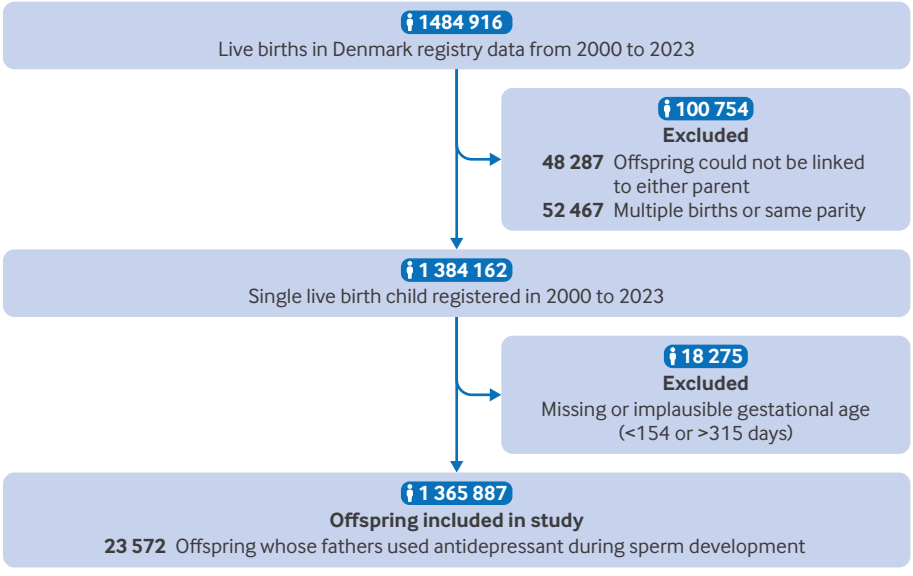


Fig 1 | Flowchart of study population


doi: 10.1136/bmj-2026-101239 | BMJ 2026;395:e101239 | the bmj

### Metabolic disorders in offspring—outcome of interest

We applied age specific definitions of metabolic disorders. For all offspring, metabolic disorders were identified through hospital diagnoses of type 2 diabetes, hypertension, hypercholesterolaemia, or overweight or obesity from the Danish National Patient Registry.[32] For those aged 18 years or older (or ≥12 years for antidiabetic drugs), metabolic disorders were additionally defined as having filled at least two prescriptions within one year for treatment of these conditions from the Danish National Prescription Registry (see eTable 3 for the international classification of diseases (ICD) and ATC codes used to define outcomes). These age specific definitions reflect differences in diagnostic and treatment pathways between children and adults because paediatric metabolic disorders are generally managed within specialist care,[33 34] with pharmacological treatment used according to disease specific clinical indications.[35] The earliest occurrence of a metabolic disorder was defined as the first hospital diagnosis or the second redeemed prescription for treating metabolic disorders, whichever occurred first. We analysed a composite outcome of all metabolic disorders and each disorder separately to assess specific associations.

### Covariates

We selected the covariates that are potentially relevant to metabolic disorders in offspring using directed acyclic graphs[36] (see eFigure 1). These covariates included calendar year of birth, paternal age at delivery, paternal education in the year of delivery, other paternal drugs prescribed during spermatogenesis (including opioid analgesics, antiseizure drugs, antipsychotics and lithium, anxiolytics, benzodiazepines or Z-hypnotics, and attention-deficit/hyperactivity disorder drugs), and paternal psychiatric history before delivery. We included an interaction term between paternal age at delivery and education level at delivery to account for the possibility that the socioeconomic implications of education may vary according to paternal age.

Additionally, we included maternal characteristics as risk factors for metabolic disorders in offspring, including maternal age at delivery, primiparity, education in the year of delivery, smoking during pregnancy, body mass index before pregnancy, psychotropic treatment during pregnancy (including antidepressants, opioid analgesics, antiseizure drugs, antipsychotics and lithium, anxiolytics, benzodiazepines or Z-hypnotics, and attention-deficit/hyperactivity drugs), and psychiatric history before delivery.

Recognising that parental metabolic disorders can increase offspring metabolic risk,[37] we further adjusted for parental history of metabolic conditions before birth, specifically type 2 diabetes, hypertension, hypercholesterolaemia, and overweight or obesity. eTable 1 provides covariate information extracted from national registries, and eFigure 2 depicts the timeline for assessing exposures, outcomes, and covariates. ATC codes for drugs and ICD codes for mental health disorders are provided in eTables 4 and 5.

### Statistical analysis

We included two comparison groups. Firstly, we compared metabolic disorders of offspring whose fathers used antidepressants during spermatogenesis (ie, antidepressant exposure) with offspring whose fathers did not use antidepressants during this period (ie, no antidepressant exposure). Secondly, to further account for the underlying indication for antidepressant use, we restricted the analysis to offspring of fathers with antidepressant use during spermatogenesis but not pregnancy (ie, spermatogenesis-only exposure) and offspring of fathers with antidepressant use during pregnancy but not spermatogenesis (ie, pregnancy-only exposure). Fathers with pregnancy-only exposure were more likely to have severe underlying mental health disorders during spermatogenesis, making them more comparable to fathers with spermatogenesis-only exposure with respect to underlying indications. For outcome categories with fewer than 10 child outcomes in the cohort, we did not conduct analyses because of insufficient statistical precision.[38]

We applied inverse probability of treatment weighting (IPTW) separately for each comparison to adjust for potential covariates, with propensity scores estimated using logistic regression models. We truncated extreme weights at the 99.5th centile, setting values above this threshold to the threshold value.[39 40] Covariate balance was assessed using standardised mean differences, where an absolute standardised mean difference of less than 0.1 was considered indicative of adequate balance between exposure groups.[41] Offspring were followed from birth until the first occurrence of any metabolic disorder (composite outcome), death, emigration, or 31 December 2023, whichever came first. For analyses of individual metabolic disorders, follow-up ended at the first occurrence of the specific metabolic disorder, death, emigration, or 31 December 2023, whichever came first. We used Cox regression with IPTW to estimate weighted hazard ratios and 95% confidence intervals (CIs), using the child's age as the underlying timescale. Robust standard errors were estimated using the Huber sandwich estimator to account for clustering of multiple children per father. Adjusted cumulative incidence curves of metabolic disorders were plotted based on paternal antidepressant use during spermatogenesis using IPTW for covariate adjustment. We interpreted the findings based on the magnitude, direction, and precision of the association estimates rather than statistical significance alone.[42] Data were missing for any covariate in 21.3% of offspring, primarily owing to missing maternal body mass index before pregnancy (20.0%) because this variable was not recorded in the Danish Medical Birth Registry until 2004 and is therefore likely missing at random. We used multiple imputations by chained equations with 20 imputations.[43] All data management and analysis were conducted in RStudio (version 4.4.1).

### Sensitivity analyses

We conducted five prespecified sensitivity analyses to test the robustness of our findings. Firstly and secondly, to address potential misclassification of antidepressant exposure, we applied two alternative definitions: at least one prescription filled within six months before pregnancy, providing a broader exposure window; and at least two prescriptions filled within three months before pregnancy, reflecting likely ongoing use. Thirdly, to address the lower specificity of drug based definitions of metabolic disorders, we retained the hospital based definition and updated the drug based criteria to require at least two prescriptions filled within 180 days among people aged ≥18 years (or ≥12 years for antidiabetic drugs). Fourthly, to account for genetic or stable familial factors, we conducted full sibling and common father sibling analyses using a stratified Cox regression model. We defined full siblings as offspring born to the same mother and father, whereas common father siblings had the same father only. Finally, to

**Table 1 | Baseline characteristics based on offspring's exposure to paternal antidepressant use during spermatogenesis**

| Characteristics | Antidepressant exposure* (n=23 572) | No antidepressant exposure* (n=1 342 315) |
|---|---|---|
| Calendar year at delivery | | |
| 2000-05 | 4160 (17.6) | 360 853 (26.9) |
| 2006-11 | 7153 (30.3) | 347 108 (25.9) |
| 2012-17 | 6382 (27.1) | 309 674 (23.1) |
| 2018-23 | 5877 (24.9) | 324 680 (24.2) |
| Paternal age at delivery, mean (SD)† | 34.2 (6.3) | 32.8 (5.8) |
| Paternal highest education in year of delivery | | |
| Mandatory school | 6701 (28.4) | 243 688 (18.2) |
| High school or vocational school | 9693 (41.1) | 597 309 (44.5) |
| College or university | 6892 (29.2) | 486 989 (36.3) |
| Missing | 286 (1.2) | 14 329 (1.1) |
| Paternal other prescriptions | | |
| Opioid analgesics | 1614 (6.8) | 14 702 (1.1) |
| Antiseizure drugs | 1480 (6.3) | 6412 (0.5) |
| Antipsychotics and lithium | 2245 (9.5) | 3733 (0.3) |
| Anxiolytics, benzodiazepine or Z-hypnotics | 1405 (6.0) | 3711 (0.3) |
| ADHD drugs | 725 (3.1) | 4232 (0.3) |
| Paternal psychiatric history before delivery | 9325 (39.6) | 69 845 (5.2) |
| Paternal metabolic disorders history before delivery | | |
| Type 2 diabetes | 669 (2.8) | 18 133 (1.4) |
| Hypertension | 1837 (7.8) | 30 129 (2.2) |
| Hypercholesterolaemia | 908 (3.9) | 13 747 (1.0) |
| Overweight or obesity | 894 (3.8) | 22 526 (1.7) |
| Maternal age at delivery, mean (SD)‡ | 30.8 (5.2) | 30.3 (4.8) |
| Primiparous | 9699 (41.1) | 606 982 (45.2) |
| Maternal highest education in the year of delivery | | |
| Mandatory school | 5729 (24.3) | 227 998 (17.0) |
| High school or vocational school | 8447 (35.8) | 497 618 (37.1) |
| College or university | 9227 (39.1) | 607 443 (45.3) |
| Missing | 169 (0.7) | 9256 (0.7) |
| Maternal smoking during pregnancy | | |
| Yes | 4830 (20.5) | 197 313 (14.7) |
| No | 18 725 (79.4) | 1 144 203 (85.2) |
| Missing | 17 (0.1) | 799 (0.1) |
| Maternal body mass index before pregnancy, mean (SD)§ | 25.4 (8.8) | 24.5 (8.8) |
| Maternal psychotropic treatment during pregnancy | | |
| Opioid analgesics | 447 (1.9) | 12 112 (0.9) |
| Antiseizure drugs | 287 (1.2) | 7399 (0.6) |
| Antipsychotics and lithium | 260 (1.1) | 4233 (0.3) |
| Anxiolytics, benzodiazepine or Z-hypnotics | 207 (0.9) | 4993 (0.4) |
| Antidepressant | 1937 (8.2) | 33 427 (2.5) |
| ADHD drugs | 104 (0.4) | 2468 (0.2) |
| Maternal psychiatric history before delivery | 4029 (17.1) | 125 796 (9.4) |
| Maternal metabolic disorders history before delivery | | |
| Type 2 diabetes | 672 (2.9) | 29 558 (2.2) |
| Hypertension | 960 (4.1) | 40 278 (3.0) |
| Hypercholesterolaemia | 157 (0.7) | 4924 (0.4) |
| Overweight or obesity | 5192 (22.0) | 227 320 (16.9) |

Data are numbers (%) unless specified otherwise.
ADHD=attention-deficit/hyperactivity disorder; SD=standard deviation.
*Antidepressant exposure: offspring whose fathers used antidepressants during spermatogenesis; no antidepressant exposure: offspring whose fathers did not use antidepressants during spermatogenesis.
†Paternal age missing for 170 (0.01%).
‡Maternal age missing for 40 (<0.01%).
§Maternal body mass index before pregnancy missing for 272 682 (20.00%).


doi: 10.1136/bmj-2026-101239 | *BMJ* 2026;395:e101239 | the bmj

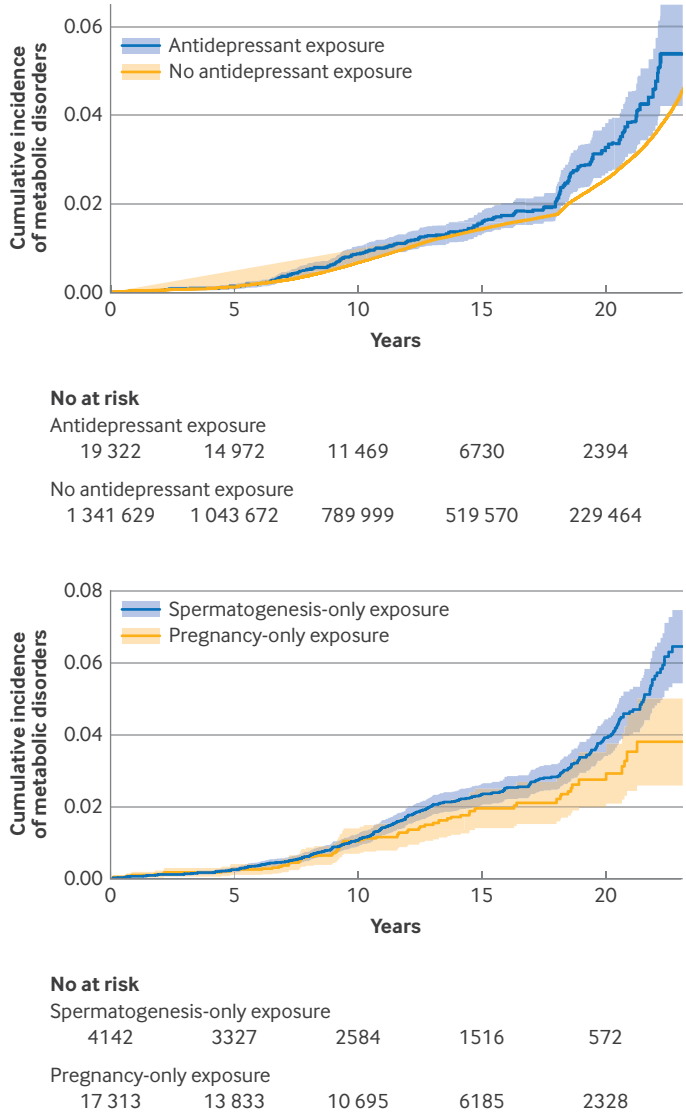


**Fig 2 | Inverse probability of treatment weighting adjusted cumulative incidence of metabolic disorders among offspring by paternal antidepressant use. Upper panel: antidepressant use during sperm development versus no use; lower panel: antidepressant use during sperm development only versus use during pregnancy period only**

ensure adequate follow-up for detecting metabolic disorders in offspring, we limited our study population to liveborn children born between 2000 and 2011, ensuring at least 12 years of follow-up.

We conducted two post hoc analyses. To assess whether potential overadjustment existed, we excluded maternal smoking and psychotropic treatment during pregnancy from the propensity score model, restricting adjustment to covariates measured before paternal antidepressant exposure. Additionally, to account for antidepressant treatment history, paternal antidepressant use during spermiogenesis was further classified into incident use (when antidepressants were taken during sperm development but not during the year before sperm development) and continuing use (when antidepressants were taken both in the year before and during sperm development).

### Patient and public involvement

The study used only routinely collected, anonymised data from Danish nationwide registers and involved no direct contact with patients. Patients and members of the public were not involved in setting the research question or outcome measures, or in the design, conduct, or interpretation of the study. Patient and public involvement was not incorporated when the study was originally designed, and no dedicated resources or framework for such involvement were established.

## Results

Of the 1 365 887 liveborn singleton infants, 23 572 (1.7%) were born to fathers who filled at least one antidepressant prescription during spermatogenesis. Among these fathers, the median duration of antidepressant use during spermatogenesis was 50 days (interquartile range 29-75 days), assuming one defined daily dose per day (eFigure 3 shows the distribution of number of days with antidepressant use). Among the 23 572 offspring with exposure, 14 298 (60.7%) were born to fathers who used SSRI monotherapy, 8141 (34.5%) to fathers who used non-SSRI antidepressant monotherapy, and 1133 (4.8%) to fathers who used both SSRI and non-SSRI antidepressants (detailed numbers for each antidepressant class are presented in eTable 2). Compared with offspring without antidepressant exposure, those with exposure had fathers who were older, more likely to have psychiatric and metabolic disorders, and more frequently used other psychotropic agents (table 1). Mothers of offspring with antidepressant exposure also had a higher prevalence of psychiatric history and were more likely to use antidepressants during pregnancy than mothers of offspring without antidepressant exposure (table 1). Baseline parental characteristics were generally comparable between offspring with spermatogenesis-only and pregnancy-only exposure (see eTable 6). After weighting, characteristics were well balanced between offspring of fathers who used antidepressants during spermatogenesis and each comparison group (eFigures 4 and 5).

### Risk of any metabolic disorders

During a mean follow-up of 11.1 years (standard deviation 6.4 years) for the antidepressant exposed group and 12.1 years (standard deviation 7.0 years) for the unexposed group, 364 (1.5%) in the exposed group were diagnosed with any metabolic disorders. After 23 years of follow-up, the IPTW adjusted cumulative incidence of metabolic disorders was 5.4% (95% CI 4.2% to 6.5%) in the antidepressant exposed group versus 4.4% (4.3% to 4.5%) in the unexposed group (fig 2, upper panel). The risk of any metabolic disorder was higher among the antidepressant exposed group compared with the unexposed group (weighted hazard ratio 1.20, 95% CI 1.04 to 1.38; table 2).

**Table 2 | Hazard ratios for associations between paternal antidepressant use during spermatogenesis and any metabolic disorders and specific metabolic disorders in offspring**

| | Antidepressant exposure *v* no antidepressant exposure* | | | | Spermatogenesis-only exposure *v* pregnancy-only exposure† | | | |
|---|---|---|---|---|---|---|---|---|
| Outcome | Exposure (n=23 572)‡ | No exposure (n=1 342 315)‡ | Crude hazard ratio (95% CI) | Weighted hazard ratio (95% CI) | Exposure (n=4156)‡ | No exposure (n=17 318)‡ | Crude hazard ratio (95% CI) | Weighted hazard ratio (95% CI) |
| **Composite outcome** | | | | | | | | |
| Metabolic disorders | 364 (1.39) | 17 989 (1.11) | 1.42 (1.28 to 1.58) | 1.20 (1.04 to 1.38) | 66 (1.30) | 340 (1.65) | 0.79 (0.61 to 1.03) | 0.75 (0.58 to 0.98) |
| **Specific outcome§** | | | | | | | | |
| Type 2 diabetes | 29 (0.11) | 2855 (0.17) | 1.06 (0.74 to 1.53) | 1.00 (0.63 to 1.57) | 6 (0.12) | 49 (0.24) | NA | NA |
| Hypertension | 63 (0.24) | 3513 (0.22) | 1.61 (1.25 to 2.06) | 1.64 (1.21 to 2.22) | 12 (0.23) | 38 (0.18) | 1.35 (0.71 to 2.59) | 1.19 (0.61 to 2.31) |
| Hypercholesterolaemia | 22 (0.08) | 1317 (0.08) | 1.31 (0.84 to 2.03) | 0.81 (0.45 to 1.47) | <5¶ | 19 (0.09) | NA | NA |
| Overweight or obesity | 266 (1.01) | 11 427 (0.70) | 1.44 (1.27 to 1.63) | 1.14 (0.96 to 1.35) | 51 (1.00) | 255 (1.23) | 0.81 (0.60 to 1.09) | 0.78 (0.58 to 1.06) |

CI=confidence interval; NA=not applicable.
*Antidepressant exposure: offspring whose fathers used antidepressants during spermatogenesis; no antidepressant exposure: offspring whose fathers did not use antidepressants during spermatogenesis.
†Spermatogenesis-only exposure: offspring whose fathers used antidepressants during spermatogenesis but not pregnancy period; pregnancy-only exposure: offspring whose fathers used antidepressants during pregnancy period but not spermatogenesis.
‡No of offspring (incidence rate per 1000 person years).
§For outcome categories with <10 child outcomes in the cohort, analysis was not conducted owing to lack of statistical precision.
¶To comply with Danish regulations aimed at safeguarding anonymity of people included in register based research studies, numbers <5 cannot be shown.

Furthermore, we compared 4156 offspring born to fathers who used antidepressants during spermatogenesis but not during pregnancy (spermatogenesis-only exposure) with 17 318 offspring born to fathers who used antidepressants during pregnancy but not during spermatogenesis (pregnancy-only exposure). After 23 years of follow-up, the IPTW adjusted cumulative incidence of metabolic disorders at 23 years was 3.1% (95% CI 2.6% to 5.0%) in the spermatogenesis-only exposure group and 6.5% (95% CI 5.4% to 7.5%) in the pregnancy-only exposure group (fig 2, lower panel). In adjusted analyses, the association reversed, with spermatogenesis-only exposure linked to a lower risk of metabolic disorders (weighted hazard ratio 0.75, 95% CI 0.58 to 0.98; table 2).

### Risk of specific metabolic disorders

Among the antidepressant exposed group, 29 (0.1%) developed type 2 diabetes, 63 (0.3%) developed hypertension, 22 (0.1%) developed hypercholesterolaemia, and 266 (1.1%) had overweight or obesity. Compared with the antidepressant unexposed group, paternal antidepressant use during spermatogenesis was associated with an increased risk of offspring hypertension (weighted hazard ratio 1.64, 95% CI 1.21 to 2.22). No associations were observed for type 2 diabetes (1.00, 0.63 to 1.57), hypercholesterolaemia (0.81, 0.45 to 1.47), and overweight or obesity (1.14, 0.96 to 1.35; table 2).

When comparing offspring whose fathers used antidepressants only during spermatogenesis with those whose fathers used them only during pregnancy, no association was found between paternal antidepressant use and hypertension in offspring (weighted hazard ratio 1.19, 95% CI 0.61 to 2.31). Similarly, no increased risks were observed for obesity or overweight (0.78, 0.58 to 1.06). Results for type 2 diabetes and hypercholesterolaemia were not reported owing to small numbers (table 2).

### Sensitivity analysis

Sensitivity analyses included applying broader and stricter definitions of antidepressant exposure (see eTables 7 and 8), restricting analyses to full and common father siblings (eTables 9 and 10), and limiting analyses to offspring born during 2000-11 (eTable 11). Across all sensitivity analyses, paternal antidepressant use was not associated with any metabolic disorder or specific metabolic disorders, consistent with the main findings. Redefining metabolic disorders as a hospital diagnosis or at least two filled prescriptions within 180 days (rather than 365 days in the primary analysis) resulted in a difference of fewer than five offspring identified with metabolic disorders in the antidepressant exposure group compared with the primary analysis and did not change the main results. The IPTW adjusted cumulative incidence of metabolic disorders among offspring born between 2000 and 2011 was also comparable to the primary analysis (eFigure 6).

### Post hoc analyses

We excluded maternal characteristics during the pregnancy period, including maternal smoking and drug treatment during pregnancy, from the propensity score weighting model to assess the robustness of the findings to their inclusion. The results were consistent with the primary analysis, with no association observed between paternal antidepressant use and metabolic disorders in offspring (eFigure 7). When paternal antidepressant use during spermiogenesis was further classified into incident and continuing use, no association was observed among offspring with paternal incident use, whereas associations with metabolic disorders and hypertension were observed among those with paternal continuing use (eFigure 8).

## Discussion

### Principal findings

In this population based cohort of 1 365 887 offspring with up to 23 years of follow-up, paternal use of antidepressants during spermatogenesis was


doi: 10.1136/bmj-2026-101239 | *BMJ* 2026;395:e101239 | the bmj

linked to an increased risk of metabolic disorders overall, particularly hypertension, compared with no antidepressant use. The associations disappeared or reversed compared with offspring of fathers who used antidepressants only during pregnancy.

### Comparison with previous studies and interpretation of results

This large scale, population based study investigated the association between paternal antidepressant use during spermatogenesis and metabolic disorders in offspring, for which previous evidence is limited. Our null findings are in line with previous research, indicating that preconception antidepressant exposure does not increase the risk of adverse birth outcomes in offspring (eg, preterm birth, low Apgar score, and congenital malformations)[24-26 44] or neurodevelopmental outcomes (eg, attention-deficit/hyperactivity disorder, autism).[27 45] Any associations observed in comparison with offspring of fathers with no antidepressant use during spermatogenesis are probably explained by underlying paternal mental health conditions rather than a direct drug effect. This interpretation is further supported by the post hoc analysis, which found associations among offspring with paternal continuing use but not among those with paternal incident use. Furthermore, a pharmacovigilance analysis of the United States Food and Drug Administration Adverse Event Reporting System found no increased risk of adverse events associated with paternal use of citalopram, fluoxetine, or olanzapine.[46]

Our findings indicate that the associations observed between paternal antidepressant use and metabolic disorders in offspring are more likely attributable to underlying paternal mental illness than to the drugs themselves. This observation is supported by comparisons between fathers treated only during spermatogenesis and those treated only during pregnancy, where treatment initiation during pregnancy likely signals worsening of mental illness that was already present during the spermatogenesis period. Animal studies have shown that paternal stress before mating is associated with altered glucose metabolism in offspring,[47] and that long term paternal psychological stress can lead to intergenerational and transgenerational transmission of adverse metabolic and developmental outcomes.[48] A human study reported an increased risk of cardiometabolic disorders of approximately 60% among offspring of parents with severe mental illnesses.[49] Cardiometabolic disorders and severe mental illness may share familial risk factors, including genetic architecture, environmental influences, and epigenetic interactions.[50] Paternal genetic and epigenetic contributions may be especially relevant because specific genes are expressed only from the paternal allele.[51 52] Additionally, type 2 diabetes, obesity, hypercholesterolaemia, and hypertension are multifactorial diseases influenced by genetics, shared family lifestyle, and intrauterine conditions,[53-55] which may overshadow any effects of paternal antidepressant exposure.

### Strengths and limitations of this study

Denmark is uniquely suited for this study because few countries maintain comprehensive data on fathers, particularly preconception drug use in large databases. In Denmark, individual level linkage of the mother-father-child triad is possible, with high data completeness. Our study provides a long follow-up (up to 23 years) on paternal antidepressant use before pregnancy and health outcomes in offspring. By using a register based design that linked several rich data sources, we were able to cover all stages of life, from preconception, through gestation, infancy, and childhood, to early adulthood, therefore minimising recall and selection biases.

Our study also has limitations. Fathers who filled antidepressant prescriptions may not actually have taken them, and offspring may have been misclassified in the exposed group. To address this limitation, we restricted our study population to fathers who filled at least two prescriptions, which provided consistent results with the primary analysis. Conception by donor sperm could also potentially introduce exposure misclassification, but the proportion affected is small and unlikely to have a major impact on the findings.[56 57] Additionally, register data may not fully capture metabolic disorders because offspring who did not receive pharmacological or hospital based treatment would not be identified, particularly children, for whom non-pharmacological management is more common. Furthermore, the absence of laboratory data limits the identification of conditions such as dyslipidaemia, metabolic syndrome, and hyperuricaemia. Consequently, our outcome definitions may have captured offspring with more severe metabolic disorders while missing those with milder conditions or those who were undiagnosed, resulting in outcome misclassification that would likely bias associations towards the null.

Despite the large sample size, the limited number of metabolic disorder events constrained precision; therefore, we focus on the direction and magnitude of associations rather than statistical significance alone. Additionally, the heterogeneity of antidepressant classes could not be explored because the sample size was insufficient for subtype specific analyses, especially in comparisons considering mental health conditions in fathers. Furthermore, the limited follow-up period up to early adulthood limits tracking of metabolic conditions that typically manifest in middle or late adulthood. Finally, as with any observational study using registry data, despite extensive adjustment for potential confounders and risk factors, residual confounding from unmeasured factors cannot be ruled out.

### Clinical implications

Antidepressants are the first line pharmacological treatment for depression in adults and are also used to treat anxiety disorders, bulimia nervosa, panic disorder, and obsessive-compulsive disorder. In Denmark, the proportion of children conceived after

paternal antidepressant treatment has increased threefold over the past two decades. This trend has raised concerns about potential long term effects in offspring caused by epigenetic alterations during spermatogenesis related to paternal antidepressant use, with implications for clinical decision making in men of reproductive age considering fatherhood. The findings of this cohort study provide reassurance for men treated with antidepressants who are planning a family. Importantly, the findings suggest that underlying paternal mental health disorders, rather than the drugs themselves, may contribute to metabolic disorders in offspring.

## Conclusion

In this large population based cohort study, we found an increased risk of any metabolic disorder among offspring exposed to paternal antidepressant use during spermatogenesis compared with those without exposure. The observed associations were attenuated to the null compared with offspring of fathers who used antidepressants during pregnancy, suggesting confounding by underlying paternal mental health conditions.


## AUTHOR AFFILIATIONS

[1]NCRR—The National Centre for Register-based Research, Department of Public Health, Aarhus University, Aarhus, Denmark

[2]Clinical Pharmacy and Pharmacoepidemiology Research Group (IPSUM), Department of Pharmacy, The Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[3]Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, University of Oslo, Oslo, Norway

[4]Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

[5]Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China

[6]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

[7]Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark

[8]Institute of Biomedicine, Aarhus University, Aarhus, Denmark

[9]Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada

[10]Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark

[11]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[12]Department of Psychiatry, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands

[13]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA



**Contributors:** JC and XL conceived and designed the study and were involved in data acquisition and preparation of analytical datasets. JC performed the data analysis and drafted the manuscript. JC, NTHT, EA, YY, TML, and XL provided critical methodological and statistical input. HMEN, LHP, ACH, TBH, and VB contributed to the clinical interpretation of the findings. All authors contributed to the analytical plan, critically revised the manuscript for important intellectual content, and approved the final version for submission. XL is responsible for the overall content as guarantor. JC and XL have full access to all data and take responsibility for the integrity and accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Funding:** This study is supported by the Independent Research Fund Denmark (DFF, 4309-00039B). XL received funding from the DFF (5336-00008B). VB is funded by the National Institute of Mental Health (R01MH122869). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Independent Research Fund Denmark for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** Under Danish law, no ethical approval or patient consent is required for studies using registry data.

**Data sharing:** Owing to the sensitive nature of individual level data, access to these data is restricted to secure servers, where downloading individual level information is prohibited. Each scientific project must be approved before initiation, and approval is granted to a specific research institution in Denmark. International researchers may gain access to data through collaboration with a Danish research institution. To support research transparency and reproducibility, the analytical codes used in this study are openly available on GitHub (https://github.com/jmc246/Manuscript_Paternal_AD_MD_analysis_code.git).

**Transparency:** The lead author affirms 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 authors will share findings with academic audiences through scientific publications and presentations at relevant conferences and seminars. To engage a wider audience, they will communicate key findings through institutional press releases and social media, focusing on clear and accessible explanations of the implications for families and healthcare professionals.

**Provenance and peer review:** Not commissioned; externally peer reviewed.



This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.



1 World Health Organization. Depression and other common mental disorders: global health estimates 2017. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

2 Beck C, Pedersen CB, Plana-Ripoll O, et al. A comprehensive analysis of age of onset and cumulative incidence of mental disorders: a Danish register study. *Acta Psychiatr Scand* 2024;149:467-78. doi:10.1111/acps.13682

3 Rommel AS, Momen NC, Molenaar NM, et al. Antidepressant use during pregnancy and risk of adverse neonatal outcomes: a comprehensive investigation of previously identified associations. *Acta Psychiatr Scand* 2022;145:544-56. doi:10.1111/acps.13409

4 Bachmann CJ, Aagaard L, Burcu M, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. *Eur Neuropsychopharmacol* 2016;26:411-9. doi:10.1016/j.euroneuro.2016.02.001

5 Wensink MJ, Rizzi S, Jensen TK, et al. Paternal prescription medication before conception: a retrospective cohort study of all births in Denmark 1997-2017. *Scand J Public Health* 2021;49:884-90. doi:10.1177/1403494820987468

6 Engeland A, Bramness JG, Daltveit AK, et al. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004-2006. *Br J Clin Pharmacol* 2008;65:653-60. doi:10.1111/j.1365-2125.2008.03102.x

7 Crijns I, Bos J, Knol M, et al. Paternal drug use: before and during pregnancy. *Expert Opin Drug Saf* 2012;11:513-8. doi:10.1517/14740338.2012.674109

8 Beeder LA, Samplaski MK. Effect of antidepressant medications on semen parameters and male fertility. *Int J Urol* 2020;27:39-46. doi:10.1111/iju.14111

9 Koyuncu H, Serefoglu EC, Yencilek E, et al. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. *Int J Impot Res* 2011;23:257-61. doi:10.1038/ijir.2011.35

10 Tanrikut C, Feldman AS, Altemus M, et al. Adverse effect of paroxetine on sperm. *Fertil Steril* 2010;94:1021-6. doi:10.1016/j.fertnstert.2009.04.039

11 Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. *Urology* 2007;69:185.e5. doi:10.1016/j.urology.2006.10.034
12 Elnazer HY, Baldwin DS. Treatment with citalopram, but not with agomelatine, adversely affects sperm parameters: a case report and translational review. *Acta Neuropsychiatr* 2014;26:125-9. doi:10.1017/neu.2013.60
13 Bhadsavle SS, Golding MC. Paternal epigenetic influences on placental health and their impacts on offspring development and disease. *Front Genet* 2022;13:1068408. doi:10.3389/fgene.2022.1068408
14 Lismer A, Kimmins S. Emerging evidence that the mammalian sperm epigenome serves as a template for embryo development. *Nat Commun* 2023;14:2142. doi:10.1038/s41467-023-37820-2
15 Robertson SA. Seminal plasma and male factor signalling in the female reproductive tract. *Cell Tissue Res* 2005;322:43-52. doi:10.1007/s00441-005-1127-3
16 Pecorelli S, Lucchini R, Lambertini L, et al. Fathers matter too: sperm-borne epigenetic messages link paternal exposures to next-generation health. *Nat Rev Urol* 2026;23:556-7. doi:10.1038/s41585-026-01128-9
17 Caldwell BA, Bartolomei MS. DNA methylation reprogramming of genomic imprints in the mammalian germline: a TET-centric view. *Andrology* 2023;11:884-90. doi:10.1111/andr.13303
18 Ben Maamar M, Wang Y, Nilsson EE, et al. Transgenerational sperm DMRs escape DNA methylation erasure during embryonic development and epigenetic inheritance. *Environ Epigenet* 2023;9:dvad003. doi:10.1093/eep/dvad003
19 Braz CU, Passamonti MM, Khatib H. Characterization of genomic regions escaping epigenetic reprogramming in sheep. *Environ Epigenet* 2024;10:dvad010. doi:10.1093/eep/dvad010
20 Li Y, Sasaki H. Genomic imprinting in mammals: its life cycle, molecular mechanisms and reprogramming. *Cell Res* 2011;21:466-73. doi:10.1038/cr.2011.15
21 Fowden AL, Sibley C, Reik W, et al. Imprinted genes, placental development and fetal growth. *Horm Res* 2006;65Suppl 3:50-8. doi:10.1159/000091506
22 Capobianco E, Pirrone I. Paternal programming of fetoplacental and offspring metabolic disorders. *Placenta* 2023;141:71-7. doi:10.1016/j.placenta.2023.06.009
23 Hur SSJ, Cropley JE, Suter CM. Paternal epigenetic programming: evolving metabolic disease risk. *J Mol Endocrinol* 2017;58:R159-68. doi:10.1530/JME-16-0236
24 Garvik OS, Jølving LR, Lund K, et al. Paternal use of selective serotonin reuptake inhibitors and adverse health outcomes: a nationwide cohort study on 13,547 exposed children. *Andrology* 2025;13:259-67. doi:10.1111/andr.13646
25 Viktorin A, Levine SZ, Altemus M, et al. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. *BMJ* 2018;361:k2233. doi:10.1136/bmj.k2233
26 Wensink M, Lu Y, Tian L, et al. Nervous system drugs taken by future fathers and birth defects in offspring: a prospective registry-based cohort study. *BMJ Open* 2022;12:e053946. doi:10.1136/bmjopen-2021-053946
27 Yang F, Chen J, Miao MH, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. *BMJ Open* 2017;7:e016368. doi:10.1136/bmjopen-2017-016368
28 Bliddal M, Broe A, Pottegård A, et al. The Danish Medical Birth Register. *Eur J Epidemiol* 2018;33:27-36. doi:10.1007/s10654-018-0356-1
29 McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 2005;85:571-633. doi:10.1152/physrev.00053.2003
30 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39:38-41. doi:10.1177/1403494810394717
31 Cordier S. Evidence for a role of paternal exposures in developmental toxicity. *Basic Clin Pharmacol Toxicol* 2008;102:176-81. doi:10.1111/j.1742-7843.2007.00162.x
32 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30-3. doi:10.1177/1403494811401482
33 Svensson J, Cerqueira C, Kjærsgaard P, et al. Danish Registry of Childhood and Adolescent Diabetes. *Clin Epidemiol* 2016;8:679-83. doi:10.2147/CLEP.S99469
34 Andersen J. Diabetes mellitus hos børn. Lægehåndbogen, sundhed.dk. Updated 13 February 2025. https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/paediatri/tilstande-og-sygdomme/endokrinologi/diabetes-mellitus-hos-boern/
35 Johansen A, Holm JC, Pearson S, et al. Danish clinical guidelines for examination and treatment of overweight and obese children and adolescents in a pediatric setting. *Dan Med J* 2015;62:C5024. .
36 Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. *Am J Epidemiol* 2006;163:1149-56. doi:10.1093/aje/kwj149
37 Park JH, Cho MH, Shim YS, et al. Differential impact of maternal and paternal metabolic syndrome on offspring's cardiometabolic risk factors. *Sci Rep* 2025;15:17651. doi:10.1038/s41598-025-02854-7
38 Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;165:710-8. doi:10.1093/aje/kwk052
39 Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656-64. doi:10.1093/aje/kwn164
40 Xiao Y, Moodie EEM, Abrahamowicz M. Comparison of approaches to weight truncation for marginal structural Cox models. *Epidemiol Methods* 2013;2:1-20. doi:10.1515/em-2012-0006
41 Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228-34. doi:10.1080/03610910902859574
42 Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. *Am Stat* 2016;70:129-33. doi:10.1080/00031305.2016.1154108
43 Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. doi:10.1136/bmj.b2393
44 Engeland A, Bjørge T, Daltveit AK, et al. Effects of preconceptional paternal drug exposure on birth outcomes: cohort study of 340 000 pregnancies using Norwegian population-based databases. *Br J Clin Pharmacol* 2013;75:1134-41. doi:10.1111/j.1365-2125.2012.04426.x
45 Yang F, Liang H, Chen J, et al. Prenatal paternal selective serotonin reuptake inhibitors use and risk of ADHD in offspring. *Pediatrics* 2018;141:e20171081. doi:10.1542/peds.2017-1081
46 Zeng Y, Lin W, Zhuang W. Safety concerns of paternal drug exposure on fertility, pregnancy and offspring: an analysis based on the FDA adverse event reporting system. *Andrology* 2025;13:1420-31. doi:10.1111/andr.13790
47 Wu L, Lu Y, Jiao Y, et al. Paternal psychological stress reprograms hepatic gluconeogenesis in offspring. *Cell Metab* 2016;23:735-43. doi:10.1016/j.cmet.2016.01.014
48 Zheng X, Li Z, Wang G, et al. Sperm epigenetic alterations contribute to inter- and transgenerational effects of paternal exposure to long-term psychological stress via evading offspring embryonic reprogramming. *Cell Discov* 2021;7:101. doi:10.1038/s41421-021-00343-5
49 Protsenko M, Kerkelä M, Miettunen J, et al. Cardiometabolic disorders in the offspring of parents with severe mental illness. *Psychosom Med* 2022;84:2-9. doi:10.1097/PSY.0000000000001022
50 Mothi SS, Tandon N, Padmanabhan J, et al. Increased cardiometabolic dysfunction in first-degree relatives of patients with psychotic disorders. *Schizophr Res* 2015;165:103-7. doi:10.1016/j.schres.2015.03.034
51 Nordin M, Bergman D, Halje M, et al. Epigenetic regulation of the Igf2/H19 gene cluster. *Cell Prolif* 2014;47:189-99. doi:10.1111/cpr.12106
52 Huang JY, Low FM, Kee MZL, et al. More equitable preconception health: paternal life course opportunities for better pregnancy, child, and family outcomes. *Lancet* 2026;407:1459-70. doi:10.1016/S0140-6736(26)00148-0
53 Singh S, Kriti M, K S A, et al. Deciphering the complex interplay of risk factors in type 2 diabetes mellitus: a comprehensive review. *Metabol Open* 2024;22:100287. doi:10.1016/j.metop.2024.100287
54 Fernandez-Twinn DS, Hjort L, Novakovic B, et al. Intrauterine programming of obesity and type 2 diabetes. *Diabetologia* 2019;62:1789-801. doi:10.1007/s00125-019-4951-9
55 Guarner-Lans V, Ramírez-Higuera A, Rubio-Ruiz ME, et al. Early programming of adult systemic essential hypertension. *Int J Mol Sci* 2020;21:1203. doi:10.3390/ijms21041203
56 Catalini L, Fedder J, Nørgård BM, et al. Assisted reproductive technology results using donor or partner sperm: a Danish nationwide register-based cohort study. *J Clin Med* 2023;12:2571. doi:10.3390/jcm12072571
57 Sundhedsdatastyrelsen. *Assisteret reproduktion 2019* . Copenhagen: Sundhedsdatastyrelsen, 2021.


**Supplementary file:** Supplementary online content