Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring
A nationwide cohort study
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Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring – a nationwide cohort study

Short running title: paternal thiopurine or methotrexate exposure and long-term outcomes in offspring

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**Highlights**

- Concerns have been raised regarding the reproductive safety of azathioprine/6-mercaptopurine and methotrexate as these drugs may cause chromosomal abnormalities in the sperm of male mice and may be potential mutagens.

- Recent Danish national cohort studies have shown no significantly increased risk of adverse birth outcomes in the children of men who used these immunomodulators within 3 months before conception.

- There is no negative impact on selected long-term outcomes of the children of fathers exposed to azathioprine/6-mercaptopurine or methotrexate within 3 months before conception.

**Abstract**
Purpose
We examined the effect of preconception paternal use of azathioprine (AZA)/6-mercaptopurine (6-MP) or methotrexate (MTX) and the risk of adverse long-term outcomes in the offspring.

Methods
This study included all children born in Denmark from 1 January 1997 through 2013. Exposed cohort: children fathered by men who used AZA/6-MP (N=735) or MTX (N=209) within three months before conception; unexposed cohort: children fathered by men who did not use AZA/6-MP/MTX (N=1,056,524). Outcomes: malignancies, autism spectrum disorders (ASD)/schizophrenia/psychosis, and attention deficit hyperactivity disorder (ADHD).

Results
Outcomes of children: AZA/6-MP exposure: one with leukemia (0.14%), one with ASD/schizophrenia (0.14%) and three with ADHD (0.41%); MTX exposure: three with ADHD (1.4%). Unexposed: 1,710 with malignancies (0.16%), 2,107 with ASD/schizophrenia (0.20%), 2,799 with ADHD (0.26%). Median follow up times were 6.7 [IQR:3.6-11.3] and 9.9 [IQR:5.7-14.3] years respectively.

Conclusions
There was no negative impact of paternal preconception use of AZA/6-MP/MTX on selected childhood health outcomes.

Keywords: paternal; thiopurines; methotrexate; cancer; reproduction; offspring; epidemiology

Introduction
Azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX) are immunomodulatory agents that have been used for over 50 years to treat inflammatory bowel disease (IBD) and a variety of other autoimmune conditions. MTX is a folic acid antagonist with known teratogenicity in pregnant women\textsuperscript{1} but AZA/6-MP use during pregnancy has not been associated with adverse birth outcomes\textsuperscript{2,3}. IBD has a peak incidence during the fertile years\textsuperscript{4}, and many fathers are treated with AZA/6-MP/MTX during the time of conception. Additionally, all three medications are commonly used to treat men with rheumatologic and dermatologic diseases and AZA/6-MP are used to prevent organ transplant rejection. It is therefore a matter of concern whether it is safe for future fathers using AZA/6-MP/MTX prior to conception to stay on these medications or whether there is an increased risk of passing diseases to their offspring due to a drug effect. We do have some knowledge about the risk of perinatal outcomes in children whose fathers took AZA/6-MP\textsuperscript{2,5} or MTX\textsuperscript{6,7,8} within three months before conception but we have no data on the long-term outcomes in the offspring.

Two of the main concerns are whether paternal use of AZA/6-MP or MTX in the period before conception might have an impact on the long-term risk of cancer or developmental disabilities in the offspring.

Although semen analysis in men who use AZA/6-MP is normal\textsuperscript{9}, or in the case of MTX, the oligospermia seen in humans is reversible\textsuperscript{7,10}, this does not rule out genetic abnormalities or occult sperm damage which may affect the offspring\textsuperscript{10,11}, and a potential long-term risk of cancer is always a matter of concern. Another worry with paternal AZA/6-MP/MTX use before conception is the risk of autism spectrum disorders (ASD) and attention deficit hyperactivity disorders (ADHD) in the offspring. There is preliminary evidence suggesting a possible association between ASD and a family history of autoimmune disease\textsuperscript{12,13} but there is no analysis of whether a possible association is due to the underlying diseases or the medication used to treat them. ADHD is included in the spectrum of developmental disabilities along with
ASD, and ADHD has been linked to specific prenatal drug and chemical exposures\textsuperscript{14,15}.

Since that this is the first study of long-term outcomes in the children of men who used 6-MP/AZA/MTX within three months of conception, our goal was two-fold. First, we wished to examine the long-term risk of malignancy in children whose fathers took AZA/6-MP/MTX within 3 months before conception. Second, given the preliminary data on the effect of certain parental factors on the incidence of childhood ADHD and ASD, we wished to further explore the specific effect of paternal use of 6-MP/AZA/MTX within three months before conception on the risk of these developmental disorders in the offspring. To do this, we used data abstracted from the Danish national registries. We examined all men in Denmark who conceived a child, and investigated the effect of paternal use of AZA/6-MP/MTX within 3 months before conception on the risk of malignancies, ASD, schizophrenia, psychosis, and ADHD in the offspring.

**Materials and Methods**

In this study we linked individual based data on children and their fathers from nationwide Danish registries. This linkage is possible due the unique civil registration number that is assigned to all Danish residents at birth from the Central Personal Registration system since 1968\textsuperscript{16,17}. By use of the civil registration number, data from all Danish health registries can unambiguously be linked on an individual level. In Denmark, all citizens have free and equal access to a tax supported health care system, and its uniform organization allowed us to use a population-based study design.

**STUDY POPULATION**

The study cohort included all children born alive in Denmark in the period of 1 January 1997-31 December 2013 as recorded in the Danish Medical Birth Registry (MBR). Since 1973 the MBR has recorded information on all births in Denmark, and the MBR includes data on the
mother, the father, pregnancy-related information, and information on birth outcomes\textsuperscript{18}. From
the MBR, we identified persons registered as fathers to live born children.

\textit{EXPOSED COHORTS, CHILDREN FATHERED BY MEN TREATED WITH AZA/6-MP or MTX PRIOR TO CONCEPTION}

For the children in the study population, we linked information on paternal filled prescriptions
of AZA/6-MP (anatomical therapeutic chemical (ATC) classification codes: L04A X01
(AZA), L01B B02 (6-MP) and MTX (ATC L04AX03 and L01BA01) in a period of three
months before the time of conception. In the exposed cohort we thus included children fathered
by men with at least one filled prescription for AZA/6-MP or MTX within three months before
the date of conception. This is an overlapping cohort of fathers used in our prior studies
examining birth outcomes in fathers using AZA/6-MP or MTX within 3 months before
conception\textsuperscript{5,6} but here we included all children rather than just singletons.

Information on prescriptions was obtained from the nationwide prescription database\textsuperscript{19}. 
Since 1 January 1995, data on all outpatient drug prescriptions are available from the
nationwide prescription database maintained by the Danish Medicine Agency. All pharmacies
in Denmark are equipped with a computerized accounting system which sends key data on
outpatient drug prescriptions directly to the database, and the data transferred to the
prescription database include the patient’s civil registration number, the type of drug prescribed
according to the ATC classification system, and the date of filed prescription\textsuperscript{19}. By using the
civil registration numbers, it is thus possible to obtain the prescription history of each person,
and in this study information on use of AZA/6-MP/MTX was retrieved. The prescription
database does not include data on over-the-counter sales, but in Denmark AZA/6-MP/MTX are
only available by prescription.

\textit{UNEXPOSED COHORT, CHILDREN FATHERED BY MEN NOT TREATED WITH AZA/6-}
MP or MTX PRIOR TO CONCEPTION

The unexposed cohort consisted of all children fathered by men who had no filled prescriptions for AZA/6-MP or MTX three months prior to the conception.

OUTCOMES IN THE OFFSPRING

Outcome information derived from the Danish National Patient Registry (NPR). The NPR includes records of all discharges from Danish hospitals since 1977 and all outpatient visits since 1994. Information in the NPR includes patients’ civil registration numbers, hospital, department, date of admission and discharge, procedures performed and up to 20 discharge diagnoses based on the International Classification of Diseases. From the NPR we identified whether the children from time of birth until the age of 19 years or the end of follow-up on 31 May 2015 had at least one code within the categories of 1) malignancies 2) ASD; 3) Schizophrenia, psychosis; 4) ADHD. All diagnostic codes are provided in Table S1. To calculate our results, ASD was grouped with schizophrenia and psychosis because it is difficult to make an exact diagnosis in children. These diagnoses cannot be determined in children until they are much older than the ages in our current cohort (the second and third decades of life for schizophrenia and psychosis) and the NPR does not separate out these individual diagnoses in children.

INFORMATION ON POSSIBLE CONFOUNDERS

From the MBR we obtained information on age of the father at the time of delivery, gender of the child, maternal body mass index (BMI), maternal smoking during pregnancy (yes/no), and calendar year of birth (1997-2000, 2001-2004, 2005-2008, 2009-2012, 2013). From the MBR we obtained information on preterm birth (birth before 37 completed weeks of pregnancy), and birth weight as small-for-gestational age (SGA), i.e. below the mean -2 SD according to
gestational age and sex\textsuperscript{20}.

\textit{STATISTICAL ANALYSES}

Contingency tables were constructed for the main study variables according to the exposed and unexposed cohort. In the study, the follow up started on the date for live birth and ended on the date of cancer diagnosis or diagnoses of ASD/ schizophrenia/ psychosis or ADHD, emigration, death, or 31 May 2015, whichever came first. Data from the Central Personal Registration system provided the information on the civil registration number, death, and immigration\textsuperscript{16,17}. We described the time span from date of childbirth until first time the child was given one of the diagnoses under study. If there were a sufficient number of outcomes, we planned to perform Kaplan-Meier plots of cumulative incidence proportions, and to perform Cox proportional–hazards regression to compute the crude and adjusted hazard ratios as estimates of the incidence rate ratios (adjusting for mother’s and father’s age, BMI of the mother, parity, multiple birth, maternal smoking in pregnancy, gender of the child, calendar year of birth, preterm birth, SGA and congenital abnormalities).

For fathers in the exposed cohort, we examined in a sub-analysis the proportion of men who were also treated with AZA/6-MP or MTX in the time window preceding the three-month window, i.e., 90-180 days before conception. This was to clarify whether the fathers were regular users of AZA/6-MP or MTX. In another sub-analysis, we disregarded the month before conception when there is no sperm mitotic or meiotic activity and changed the exposure window to 30-120 days before conception.

All calculations were performed using STATA Release 14.0 (StataCorp, College Station, TX, USA).
Results

A total of 735 and 209 children were fathered by men who filled at least one prescription for AZA/6-MP or MTX respectively within three months before conception, and 1,056,524 children were fathered by men who had not filled a prescription for AZA/6-MP or MTX within three months before conception. The characteristics of these exposed and unexposed cohorts are shown in Table 1. The basic characteristics were similar between the three cohorts according to mother’s and father’s age, maternal BMI, and parity. The majority of fathers on AZA/6-MP were treated for IBD (N=556, 75.6%). Other paternal diseases in the AZA/6-MP cohort included rheumatologic diseases (N=84, 11.4%), psoriasis (N=12, 1.6%), organ transplantation (N=30, 4.1%), connective tissue disease (N=45, 6.1%) or were unknown (N=106, 14.4%). Paternal diseases in the MTX cohort included IBD (N=18, 8.6%), rheumatologic diseases (N=126, 60.3%), connective tissue disease (N=11, 5.3%) and psoriasis (N=73, 34.9%).

We identified the following outcomes among AZA/6-MP exposed children: one with leukemia (0.14%), one with ASD/schizophrenia (0.14%) and three with ADHD (0.41%). There were three children with ADHD (1.44%) in the MTX exposed cohort. The median follow up time among all exposed children was 6.7 years [interquartile range (IQR) 3.6-11.3]. Among the unexposed cohort we identified 1,710 (0.16%) with malignancies, 2,107 (0.20%) with ASD/schizophrenia and 2,799 (0.26%) with ADHD. The median follow up time among non-exposed children was 9.9 years [IQR 5.7-14.3].

Regression models could not be applied due to the low number of cases among exposed. The proportions of fathers from the exposed cohort who were also treated with AZA/6-MP or MTX in the time window of 90-180 days before conception were 540/735= 73.47% and 81/209 = 38.76%, respectively. In the sub-analysis where we changed the exposure window to 30-120 days before conception our results did not change, and we found
the same number of cases among the exposed.

Conclusions

This is the only study to date to examine the long-term outcomes of the children of fathers who used AZA/6-MP or MTX within 3 months before conception. Our results are reassuring since we found no significant differences in malignancies, ASD/schizophrenia and ADHD between the exposed and unexposed. Of course, the follow up period would ideally be even longer in our cohorts, but since these are first data on long-term outcomes in the offspring, our length of follow up is reasonable with 25% of exposed children having a follow up period longer than 11.3 years. The reason for the shorter follow up period among our exposed children versus unexposed was that paternal AZA/6-MP/MTX exposure was less frequent at the beginning of the study period compared to later in the study period.

The rationale for examining the outcome of malignancy stems from studies on the possible mutagenic effects of AZA/6-MP/MTX on developing sperm or direct toxicity via seminal fluid and the studies linking environmental and chemical exposures in fathers to childhood cancers. Although there is no evidence of an increased risk of adverse birth outcomes of the children of fathers who took AZA/6-MP/MTX within three months before conception, mutagenic or teratogenic effects might take longer to develop. Animal studies have shown adverse effects of paternal preconception medications and environmental exposures on offspring. Diet, stress and chemical exposures in rodents have been associated with offspring health and these effects are mediated by epigenetic modifications transmitted through sperm DNA, histones, and RNA. Several human case control studies have reported several types of cancers among children of fathers with preconception exposures to benzene, aniline, creosote, diesel fuel, turpentine, lacquer thinner, insecticides, fungicides, and herbicides. Pooled and meta-analyses show that the risk of childhood leukemia may be elevated among
children born to fathers with preconception benzene and pesticide exposures\textsuperscript{21-23}. Paternal smoking during the conception period may be associated with childhood leukemia, Burkitt’s and non-Hodgkin’s lymphoma\textsuperscript{24,25}, and epidemiologic studies have suggested that paternal employment in the medical/dental/veterinary and pharmaceutical industries may be associated with multiple types of childhood tumors\textsuperscript{26,27}.

Although several epidemiological studies have linked ASD in children to a family history of autoimmune disease\textsuperscript{12,13} one Danish study found no increased risk of ASD among children born to parents with IBD\textsuperscript{28}. The authors of this Danish study, however, did not examine medication use. One such example of a drug possibly linked to ASD in the offspring of women is the anti-epileptic drug valproate. A population-based Danish study found a significantly increased risk of ASD in children exposed to valproate during gestation\textsuperscript{29}. ADHD has been linked to specific prenatal drug and chemical exposures such as anti-depressants, polybrominated diphenyl ether, manganese and selenium\textsuperscript{14,15}.

The potential impact of drugs taken by fathers during conception on reproductive outcomes has not been clarified since drugs are not tested in this fashion before they are released on the market. Knowledge of specific drug effects on the fetus is usually limited to experiences from animal studies whose results often cannot be extrapolated to humans. Consequently, clinical decisions on pharmacotherapy during conception are most often based on evidence from observational studies that might be vulnerable to different kinds of bias and problems with statistical precision due to low prevalence of adverse outcomes. Despite these methodological challenges, we have an ethical obligation to study and monitor drug related safety profiles and epidemiologic studies are the most informative way to find answers in this area of research.

Although we were unable to perform further statistical analyses, this is the first and
only study to date examining the long-term outcomes of the children of fathers exposed to AZA/6-MP/MTX prior to conception. AZA/6-MP/MTX are widely used and the question of adverse drug effects is frequently raised in men wishing to conceive. Given the increasing research on the mutagenic effects of medications on sperm and the possible link of autoimmunity, drug and environmental exposures to ASD and ADHD, we believe it is important to report all available data so far, and not wait many years for a longer follow up time. The strengths of this study were that i) it was based on nationwide data that included information on all children in the country during the study period, ii) we have no loss to follow up on the children, which prevents selection bias iii) the information on fathers’ drug exposure was based on prescriptions and not on patient recall, as drug exposure based on self-reported use may lead to recall bias, iv) we collected information on the outcomes independently of the exposure, which prevents information bias and vi) we used nationwide Danish health registries with high validity. Our algorithms for our outcomes on malignancies, ASD, schizophrenia, psychosis and ADHD have high validity in the NPR\textsuperscript{30-32}. Finally, in our study we had access to a complete nationwide prescription database, ensuring that all fathers could be classified according to the possible prescriptions for AZA/6-MP/MTX prior to conception, and the data in the prescription database are of high quality as a result of direct computerized transfer of information when a prescribed drug is dispensed at a pharmacy\textsuperscript{19}.

Our study has limitations. We had no information on drug compliance. However, patient non-compliance is not likely to have a major impact, because AZA/6-MP/MTX are drugs typically used for long-term treatment in these usually very cooperative patients with severe chronic diseases. In addition, we were unable to evaluate a possible AZA/6-MP/MTX dose effect. Additionally, we cannot rule out that the shorter follow-up period among the exposed cohort has hidden a higher rate of adverse outcomes usually developing later in childhood. Finally, we were unable to evaluate an impact of maternal drug exposure and
maternal underlying diseases, but we do not believe these factors have confounded our results since the distribution of such factors in our exposed and unexposed cohorts should be equal. In register-based dataset it is impossible to collect detailed drug information covering all aspects of drug therapy during pregnancy; and as in other register-based research we were left with the challenge to use the available data with conscientiousness and in respect to their limitations.

In conclusion, this is the first study to examine the long-term effects in the children of fathers who used AZ/6-MP/MTX within 3 months before conception. It is a large nationwide study with follow-up of exposed and unexposed cohorts of children. Since AZA/6-MP/MTX are widely used medications for a variety of conditions including IBD, other autoimmune diseases and transplant rejection, it is reassuring that there was no excess of adverse outcomes in the offspring. In the future, our data should be confirmed in other settings, but so far men using AZA/6-MP/MTX and planning to conceive should be advised not to stop their medications.

Contributors
SF: funding, conception, interpretation of results, manuscript writing and editing, approved the final version.
MDL: design, data analyses, interpretation of results, manuscript editing, approved the final version.
BM: Data analysis, interpretation of results, manuscript editing, approved the final version.
LRJ: interpretation of results, manuscript editing, approved the final version.
PDS: interpretation of results, manuscript editing, approved the final version.
BMN: funding, conception, design, data collection, assistance with data analysis, interpretation of results, manuscript writing, editing, approved the final version.

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**Competing interests**

None

**Permissions**

The study was approved by the Danish Data Protection Agency (j.nr. 2014-41-3466).

According to Danish law, there are no ethical approvals of register-based studies necessary.
References


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<th>Children fathered by men treated with AZA/6-MPa</th>
<th>Children fathered by men treated with MTXa</th>
<th>Children fathered by men not treated with AZA/6-MP/MTXa</th>
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<td>N=735</td>
<td>N=209</td>
<td>N=1,056,524</td>
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<td><strong>Mother’s age at time of childbirth (year)</strong></td>
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<tr>
<td>Median [25-75 percentiles]</td>
<td>30.5 [27.6-33.3]</td>
<td>32.2 [29.1-35.2]</td>
<td>30.4 [27.3-33.7]</td>
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<tr>
<td>IBD (UC or CD)</td>
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<td>30</td>
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<td>(14.4)</td>
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<td>373</td>
<td>(50.7)</td>
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<td>2013, N (%)</td>
<td>76</td>
<td>(10.3)</td>
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</table>

a) Represents 602 different fathers exposed to AZA/6-MP, 188 different fathers exposed to MTX and 611,586 different unexposed fathers.

b) Missing BMI: AZA/6-MP: 205 (27.9%); MTX: 54 (25.8%); unexposed 481,664 (46.5%)

Missing smoking: AZA/6-MP: 14 (1.9%); MTX: 6 (2.9%); unexposed 30,301 (2.9%)