OBJECTIVES: To estimate the association between maternal use of acetaminophen during pregnancy and of paternal use before pregnancy with attention-deficit/hyperactivity disorder (ADHD) in offspring while adjusting for familial risk for ADHD and indications of acetaminophen use.

METHODS: Diagnoses were obtained from the Norwegian Patient Registry for 112,973 offspring from the Norwegian Mother and Child Cohort Study, including 2,246 with ADHD. We estimated hazard ratios (HRs) for an ADHD diagnosis by using Cox proportional hazard models.

RESULTS: After adjusting for maternal use of acetaminophen before pregnancy, familial risk for ADHD, and indications of acetaminophen use, we observed a modest association between any prenatal maternal use of acetaminophen in 1 (HR = 1.07; 95% confidence interval [CI] 0.96–1.19), 2 (HR = 1.22; 95% CI 1.07–1.38), and 3 trimesters (HR = 1.27; 95% CI 0.99–1.63). The HR for more than 29 days of maternal acetaminophen use was 2.20 (95% CI 1.50–3.24). Use for <8 days was negatively associated with ADHD (HR = 0.90; 95% CI 0.81–1.00). Acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR = 6.15; 95% CI 1.71–22.05). Paternal and maternal use of acetaminophen were similarly associated with ADHD.

CONCLUSIONS: Short-term maternal use of acetaminophen during pregnancy was negatively associated with ADHD in offspring. Long-term maternal use of acetaminophen during pregnancy was substantially associated with ADHD even after adjusting for indications of use, familial risk of ADHD, and other potential confounders.

WHAT'S KNOWN ON THIS SUBJECT: In previous studies, researchers have identified an association between acetaminophen use during pregnancy and attention-deficit/hyperactivity disorder (ADHD) in offspring. Maternal use of acetaminophen is associated with impulsivity; hence, it is unknown if the association is due to indications of use or familial risk for ADHD.

WHAT THIS STUDY ADDS: After adjusting for familial risk for ADHD, indications of use, and acetaminophen use before pregnancy, long-term acetaminophen use during pregnancy is related to more than a twofold increase in risk for offspring ADHD.
Acetaminophen is the recommended medication for pregnant women with fever or pain and is widely used during pregnancy. Reports have suggested that acetaminophen is used by ~65% to 70% of pregnant women in the United States and by ~50% to 60% of pregnant women in western and northern Europe.\(^1,2\) Acetaminophen crosses the placenta and can be traced in the infant’s urine after prenatal exposure.\(^3\) In 2013, researchers conducting a sibling comparison in a large, population-based Norwegian birth cohort study suggested that prenatal acetaminophen use for 28 or more days was associated with poorer motor and communicational development and externalizing problems (ie, inattentiveness and aggression) in offspring.\(^4\) The following year, researchers conducting a large Danish birth cohort study found an association between prenatal acetaminophen use and both a clinical attention-deficit/hyperactivity disorder (ADHD) diagnosis and ADHD symptoms in offspring;\(^5\) later, researchers in other studies related prenatal acetaminophen use to rating scales of disinhibited behavior.\(^6,7\)

The Danish study\(^5\) had several strengths, including prospective assessment, a large sample size, and a number of relevant covariates. It also had some important limitations, especially possible residual confounding.\(^8\) Acetaminophen is recommended for pregnant women with fever and pain; it is also used for a wide array of other inflammatory conditions during pregnancy. Furthermore, it has been suggested that the presence of some of these conditions during pregnancy (eg, fever, inflammation, and autoimmunity) are associated with increased risk of neurodevelopmental disorders in offspring.\(^9^-^12\) To investigate potential adverse effects of acetaminophen on fetal development, it is therefore essential to allow for the potential influence of such underlying conditions. We have previously found that an impulsive personality is associated with acetaminophen use during pregnancy.\(^13\) It is therefore possible that acetaminophen use during pregnancy could be influenced by familial factors (including genetic influences) that may also influence the risk of offspring ADHD. It is therefore important to adjust for parental symptoms of ADHD.

If the association between acetaminophen use during pregnancy and offspring ADHD is due to unobserved maternal factors (eg, impulsive personality traits\(^13\)), we would expect use before pregnancy to be no less associated with offspring ADHD than use during pregnancy. Prepregnancy use therefore serves as a negative control for the specificity of the gestational effect.\(^14\)

If the association is due to unobserved familial factors (eg, genetic factors), paternal use of acetaminophen may also be associated with ADHD in a way similar to maternal use of acetaminophen. However, acetaminophen and endocrine disruptors have been shown to have potential for transgenerational disease transmission effects in mouse models via male germ-line epigenetic effects, and endocrine disruption effects of acetaminophen have been shown in the human testis.\(^15,16\) It is therefore important to estimate the effect of paternal prepregnancy use.

In the current study, we used data from a large, prospective, population-based birth cohort from Norway to examine whether acetaminophen use during pregnancy was associated with ADHD in the offspring after adjusting for potential confounders. In contrast to researchers in previous studies, we were able to adjust for indications of acetaminophen use and parental symptoms of ADHD. We were furthermore able to analyze maternal use of acetaminophen before pregnancy as a negative control\(^17\) and to estimate the effect of paternal use before pregnancy on offspring ADHD.

**METHODS**

**Sample**

Data were drawn from the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health.\(^18\) Invitations were sent by mail to pregnant women in Norway in connection with the routine ultrasound examination offered at the local hospitals around pregnancy week 18, and 40.6% of the invited women consented to participate. The cohort includes 114,744 children born between 1999 and 2009, 95,242 mothers, and 75,217 fathers from all over Norway. The establishment and data collection in MoBa has obtained a license from the Norwegian Data Inspectorate and approval from the Regional Committee for Medical Research Ethics. The current study was approved by the Regional Committee for Medical Research Ethics. Self-report questionnaires were sent to the mothers and fathers at approximately 18 weeks of gestation and to mothers later in pregnancy and after delivery. We used information from maternal questionnaires when children were 6 months old, 1.5 years old, and 3 years old in version 9 of the quality-assured MoBa data files. We excluded 1,283 study subjects who died or emigrated during childhood and 488 subjects without a recorded date of birth in the Medical Birth Registry of Norway. Our final sample comprised the eligible 112,973 children and their parents.

**Measure of ADHD**

We obtained information about children’s ADHD diagnosis from the Norwegian Patient Registry (NPR).\(^19\) Since 2008, all government-owned
and government-financed hospitals and outpatient clinics mandatorily report individual-level International Classification of Diseases, 10th Revision diagnoses to NPR to receive financial reimbursement. By using individual personal identification numbers, diagnostic information from NPR was linked to MoBa. Thus, all MoBa children registered with an International Classification of Diseases, 10th Revision diagnosis of hyperkinetic disorder (F90.0, F90.1, F90.8, or F90.9) between 2008 and 2014 were identified and regarded as having ADHD. Hyperkinetic disorder requires the combination of inattentive and hyperactive symptoms, and as a result, hyperkinetic disorder is a subtype nested within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition classification of ADHD. In comparison with ADHD, hyperkinetic disorder is characterized by a higher proportion of patients with impaired language and motor development. Two cases were excluded from the analyses because of an F90 diagnosis before the age of 3.

Prenatal Use of Acetaminophen

Information on acetaminophen use was obtained through MoBa questionnaires. Acetaminophen use was available from 2 prenatal and 1 postnatal questionnaires. At week 18, week 30, and 6 months postpartum, the mothers were asked to report on 77, 32, and 19 different medical conditions, respectively. The mothers reported details on medication use specifically for each medical condition. In addition, at each time point, the mothers listed names of any additional medications used. For each indication, the mother could name the medication taken in an open textbox and specify the following exposure windows: 6 months before gestation; gestational weeks 0 to 4, 5 to 8, 9 to 12, and ≥13 (until completion of the first questionnaire); 13 to 16, 17 to 20, 21 to 24, 25 to 28, and ≥29 (until completion of the second questionnaire); and ≥30 (until birth), 0 to 3 months postpartum, and 4 to 6 months postpartum. Use 6 months before gestation was reported on 53 of the 77 indications reported at week 18. In addition, mothers were asked to report all other medication use for all exposure windows in all questionnaires. Questionnaires can be found at www.fhi.no.

Number of days was reported as a total across all exposure windows in each questionnaire. The percentage of indications relating to acetaminophen use having 0, 1, or ≥2 comedications were 88.9%, 10.0%, and 1.1%, respectively. Fathers filled out a separate questionnaire at gestational week 18. Therein, they reported their medication use for the last 6 months before pregnancy. We classified and grouped medication exposure according to the Anatomic Therapeutic Chemical Classification System developed by the World Health Organization. Acetaminophen exposure was defined as using a drug with the Anatomic Therapeutic Chemical code N02BE01.

Covariates

On the basis of previous literature, the following covariates were considered potential confounders: parental symptoms of ADHD (in MoBa, these are measured by the 6-item World Health Organization adult ADHD self-report scale screener measuring risk for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition classification of ADHD), maternal self-reported alcohol use during pregnancy, maternal self-reported daily smoking during pregnancy, symptoms of anxiety and depression at the 18th and 30th week of gestation (in MoBa, this is measured by the 5- and 8-item short version of the Hopkins Symptom Checklist 25), maternal education, marital status, BMI at the 18th week of gestation, maternal age, parity, birth year squared to adjust for nonlinear cohort effects. Maternal age and parity were obtained from the Medical Birth Registry of Norway. In addition, we assessed 128 medical conditions at the 17th week and 30th week of gestation and at 6 months postpartum. Acetaminophen was used for 96 of these indications.

Statistical Analyses

The associations between acetaminophen use and offspring ADHD were examined in Cox proportional hazard models with the offspring’s age in months as the time metric. Offspring were defined as being at risk from 3 years of age and were followed to the time of ADHD diagnosis or censored at December 31, 2014. To replace missing values on self-reported comedications, we used multiple imputation with 50 imputations.

For the analysis in which we investigated duration of acetaminophen use, we used the indication nested within each mother as our observational unit. For example, a mother having used acetaminophen for 5 out of the 128 possible indications at any time point during pregnancy contributed 5 units in the analyses (ie, 1 for each indication of use). Because the number of days was reported as a total across all exposure windows in each questionnaire, we adjusted the analyses of number of days used for number of comedications, use before pregnancy, and use after pregnancy within each indication. We grouped the effects of use across types of indications (ie, fever and infections, pain conditions, and indication not specified). We used a stratified Cox model to account for duration of acetaminophen use, with indications as strata. To account for clustering...
of indications within mothers, we used robust standard errors. We used Stata version 14.1 (StataCorp, College Station, TX) for all analyses.\textsuperscript{29}

**RESULTS**

The study population included 112,973 children, of whom 2246 had been diagnosed with ADHD. In Fig 1, we present the estimated cumulative number of expected ADHD events across age. We estimated that \(\sim\)4\% of children in MoBa will have an ADHD diagnosis at the age of 13 (Fig 1).

Fifty-two thousand seven-hundred and seven (46.7\%) women used acetaminophen during pregnancy (Table 1). Twenty-seven percent used acetaminophen in 1 trimester, 16\% in 2 trimesters, and 3.3\% in all 3 trimesters. Maternal preconceptional use and use in the first trimester was approximately equally associated (\(r = 0.49\)) with use in the first and second trimester (\(r = 0.56\)) and in the second and third trimester (\(r = 0.49\)) (Supplemental Table 4). Paternal use was associated with maternal preconceptional use and use during pregnancy (\(r = 0.18–0.10\)) (Supplemental Table 4).

Offspring prenatally exposed to acetaminophen had an increased unadjusted hazard rate of ADHD of 17\%, 39\%, and 46\% after 1, 2, and 3 trimesters of exposure, respectively (Table 1). These associations were not attenuated when we adjusted for maternal and paternal use before pregnancy (model 1), but they were slightly lower after we adjusted for parental symptoms of ADHD (model 2). In model 3, we adjusted for a range of potential confounders (Supplemental Table 5), and the hazard ratios (HRs) for the associations between 1, 2, and 3 trimesters of prenatal acetaminophen exposure were 1.07 (95\% confidence interval [CI] 0.96–1.19), 1.22 (95\% CI 1.07–1.38), and 1.27 (95\% CI 0.99–1.63), respectively. The negative control, maternal preconceptional use of acetaminophen, had no effect on offspring ADHD. Paternal preconceptional use had no weaker effect than maternal use during pregnancy (Table 1).

In Table 2, we present the HRs for offspring ADHD by number of days of prenatal acetaminophen exposure, adjusted for each indication of use by stratification. We found that use of acetaminophen <7 days was negatively associated with offspring ADHD. For use >7 days, the HR for offspring ADHD increased with the number of days exposed. Prenatal use of acetaminophen for 29 or more days was associated with a substantially increased hazard rate of ADHD (HR = 2.20; 95\% CI 1.50–3.24), even after adjusting for indications of use by stratification (Supplemental Table 6). The associations with use of 29 days or more did not differ across groups of indications (HR = 2.13–2.56). Acetaminophen use for fever and infections for 22 to 28 days was strongly associated with ADHD (HR = 6.15; 95\% CI 1.71–22.05). Associations between paternal preconceptional use of acetaminophen and ADHD are presented in Table 3. Short-term paternal use was not negatively associated with ADHD (HR = 1.10; 95\% CI 0.92–1.30); paternal use for 29 days or more was as strongly associated with ADHD (HR = 2.06; 95\% CI 1.36–3.13) as the corresponding maternal prenatal use.

**DISCUSSION**

We found maternal prenatal acetaminophen use to be associated with a higher hazard rate for offspring ADHD, supporting the findings of Liew et al\textsuperscript{13} based on Danish registry data. Liew et al\textsuperscript{13} did not, however, control for the indications for use or ADHD-related familial factors. In our study, the association persisted after adjusting for acetaminophen use before pregnancy and for parental symptoms of ADHD. We had the advantage of having medication data separately for each indication, allowing us to account for confounding by each indication in a stratified model. Offspring prenatally exposed to acetaminophen for 29 days or more had a twofold HR for receiving a clinical diagnosis of ADHD from specialist health services. This estimate was the same regardless of indication (ie, fever and infections...
TABLE 1 HRs for ADHD Diagnosis According to Maternal Acetaminophen Use During Pregnancy in 112973 Offspring

<table>
<thead>
<tr>
<th></th>
<th>Complete Cases</th>
<th>Estimated Data by Multiple Imputation</th>
<th>HRs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Total n</td>
<td>%</td>
</tr>
<tr>
<td>Acetaminophen use 6 mo before pregnancy</td>
<td>27584</td>
<td>104084</td>
<td>26.5</td>
</tr>
<tr>
<td>Paternal acetaminophen use</td>
<td>11119</td>
<td>61543</td>
<td>18.1</td>
</tr>
<tr>
<td>Acetaminophen use during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used during pregnancy</td>
<td>45615</td>
<td>93216</td>
<td>48.9</td>
</tr>
<tr>
<td>Ever used during pregnancy</td>
<td>47601</td>
<td>93216</td>
<td>51.1</td>
</tr>
<tr>
<td>Any 1 trimester</td>
<td>23444</td>
<td>85854</td>
<td>27.1</td>
</tr>
<tr>
<td>First trimester only</td>
<td>7448</td>
<td>85854</td>
<td>8.7</td>
</tr>
<tr>
<td>Second trimester only</td>
<td>14688</td>
<td>85854</td>
<td>1.1</td>
</tr>
<tr>
<td>Third trimester only</td>
<td>1108</td>
<td>85854</td>
<td>1.3</td>
</tr>
<tr>
<td>Any 2 trimesters</td>
<td>13988</td>
<td>85854</td>
<td>16.0</td>
</tr>
<tr>
<td>Both first and second trimesters</td>
<td>11538</td>
<td>85854</td>
<td>13.4</td>
</tr>
<tr>
<td>Both second and third trimesters</td>
<td>1653</td>
<td>85854</td>
<td>1.9</td>
</tr>
<tr>
<td>Both first and third trimesters</td>
<td>508</td>
<td>85854</td>
<td>0.6</td>
</tr>
<tr>
<td>All 3 trimesters</td>
<td>2908</td>
<td>85854</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Two thousand two hundred and forty-six children were diagnosed with ADHD by December 31, 2014. All estimates are adjusted for birth year, model 2 is furthermore adjusted for parental ADHD symptoms, and model 3 is furthermore adjusted for alcohol use during pregnancy, smoking during pregnancy, symptoms of anxiety and depression during pregnancy, maternal education, marital status, BMI at 17th week of gestation, maternal age, and parity.
ADHD are not related to the recorded indications but are related to unmeasured factors. Maternal preconceptional use was not associated with ADHD. This is in line with a recent study in which researchers found no effect of maternal postnatal acetaminophen use on maternal reports of behavior problems.

Furthermore, we found that maternal preconceptional use was as associated with use during the first trimester as use across 2 trimesters. This supports the employment of maternal preconceptional use as a negative (or specificity) control and is consistent with a causal link.

The mechanics of the ADHD effect of paternal acetaminophen use before pregnancy are unclear. It may be due to male germ-line epigenetic effects as described in endocrine disruption effects of acetaminophen on the human testis.

At least 3 plausible hypotheses are proposed to explain the association between maternal acetaminophen use and ADHD. First, neonatal exposure to acetaminophen changes the levels of brain-derived neurotropic factor in mice and results in altered behavior, lowered fear responses, and reduced learning abilities in adulthood. Second, brain-derived neurotropic factor promotes neuronal survival and regulates cell migration, axonal and dendritic outgrowth, and formation of synapses. Third, maternal preconceptional use may be associated with use during pregnancy, which is consistent with the employment of maternal preconceptional use as a negative control. This supports the employment of maternal preconceptional use as a negative control.
Our finding that acetaminophen use for <8 days is negatively associated with offspring ADHD indicates that the antipyretic effect could be beneficial with regard to fetal development.11,12

We address 3 limitations that could have biased the results. First, although we were able to stratify on each indication of use, long-term use within each indication is likely to represent a more severe form of the disorder. We were not able to adjust for the severity of each condition indicative of acetaminophen use. Second, the ADHD diagnosis was not validated in a research clinic but was based on a diagnosis registered by a specialist in the Norwegian health care system. Finally, young parents and parents who were smokers are underrepresented in MoBa,43 which may limit generalization of results to all children. It has, however, previously been shown that although estimates of frequencies and means were biased because of selective participation, selected exposure-outcome associations did not differ between MoBa participants and the general Norwegian population.44-45

**CONCLUSIONS**

Long-term maternal use of acetaminophen during pregnancy is associated with ADHD in offspring. This holds true even after adjusting for potential confounders, including parental symptoms of ADHD and indicators of acetaminophen use. Although maternal preconceptional use was substantially correlated with use during pregnancy, only use during pregnancy was associated with ADHD. However, given that paternal use of acetaminophen is also associated with ADHD, the causal role of acetaminophen in the etiology of ADHD can be questioned. We do not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD.

**ACKNOWLEDGMENTS**

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**ABBREVIATIONS**

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
HR: hazard ratio
MoBa: Norwegian Mother and Child Cohort Study
NPR: Norwegian Patient Registry

**TABLE 3** HRs for Offspring ADHD by Number of Days of Paternal Acetaminophen Use 6 Months Before Pregnancy

<table>
<thead>
<tr>
<th>No. of Fathers Reporting Each Category</th>
<th>HRa</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use</td>
<td>64348</td>
<td>1.00</td>
</tr>
<tr>
<td>1–7 d</td>
<td>8887</td>
<td>1.10</td>
</tr>
<tr>
<td>8–28 d</td>
<td>1079</td>
<td>1.81</td>
</tr>
<tr>
<td>29 or more d</td>
<td>657</td>
<td>2.06</td>
</tr>
</tbody>
</table>

*a Adjusted for year of birth, paternal age, and parity.

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