

## ORIGINAL ARTICLE

WILEY

# Prenatal exposure to non-steroidal anti-inflammatory drugs and risk of attention-deficit/hyperactivity disorder: A follow-up study in the Norwegian mother, father and child cohort

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## Funding information

European Research Council, Grant/Award Number: 639377; PharmaTox Strategic Research Initiative

## Abstract

**Purpose:** To estimate the association between Attention-Deficit/Hyperactivity Disorder (ADHD) in children in preschool and primary school, and prenatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) by timing and duration.

**Methods:** This study was based on the Norwegian Mother, Father and Child Cohort Study linked to the Medical Birth Registry of Norway, the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NSAID exposure was identified by maternal self-report in pregnancy. Child diagnosis of ADHD was obtained from NPR and NorPD. Symptoms of ADHD at age 5 years were measured using Conners' Parent Rating Scale-Revised, where higher scores correspond to more symptoms. To account for time-varying exposure and confounders, marginal structural models were fitted to estimate hazard ratios and mean difference in z-scores.

**Results:** The analyses on ADHD diagnosis and ADHD symptoms included 56 340 and 34 961 children respectively. Children exposed to NSAIDs prenatally had no increased risk of ADHD diagnosis (first trimester: HR 1.12, 95% CI 0.86;1.45, second trimester: HR 0.98, 95% CI 0.69;1.38, third trimester: HR 0.68, 95% CI 0.31; 1.46) or ADHD symptoms (first trimester: standardized mean difference 0.03, 95% CI -0.03;0.09, second trimester: standardized mean difference 0.03, 95% CI -0.04;0.11, third trimester: standardized mean difference 0.11, 95% CI -0.03; 0.25). There was no duration-response relationship for either outcome.

**Conclusion:** Though non-differential misclassification of the exposure may have attenuated results, these findings are reassuring and suggest no substantially increased risk of ADHD diagnosis or symptoms in children prenatally exposed to NSAIDs, regardless of timing or duration.

## KEYWORDS

anti-inflammatory agents, attention deficit disorder with hyperactivity, Medical Birth Registry of Norway, Norwegian mother, prenatal exposure delayed effects, father and child cohort study, non-steroidal

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## 1 | INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in 5–15% of pregnancies,<sup>1,2</sup> can cross the placenta,<sup>3</sup> and the blood–brain-barrier.<sup>4</sup> NSAIDs inhibit cyclooxygenase-1 and -2,<sup>4</sup> and first and third trimester use is associated with an increased risk of negative birth outcomes.<sup>3,5</sup> Both cyclooxygenase-1 and -2 are expressed in the brain.<sup>6</sup> Prenatal exposure to NSAIDs might therefore influence child neurodevelopment.

Findings from previous studies on child neurodevelopment after prenatal NSAID exposure are in general reassuring with no associations.<sup>7–12</sup> However, only two studies had follow-up beyond 3 years of age,<sup>11,13</sup> and one found slightly poorer executive function in exposed children.<sup>13</sup> Brain development continues into early adulthood,<sup>14</sup> and some functions cannot be assessed until children have reached an age where more complex tasks are demanded.<sup>15</sup> Among these tasks are behavioral inhibition and sustained attention; tasks that are problematic for children with Attention-Deficit/Hyperactivity Disorder (ADHD).<sup>16</sup>

ADHD is among the most common behavioral disorders in childhood.<sup>17</sup> The worldwide prevalence is approximately 7% using DSM-IV criteria, and approximately 3% using ICD-10 criteria.<sup>17</sup> The etiology of ADHD is unclear, but thought to be highly genetic.<sup>18,19</sup> Many environmental factors have also been proposed as influencing ADHD risk,<sup>18</sup> among them maternal inflammation in pregnancy,<sup>20,21</sup> one of the indications for NSAID use.

Several studies have investigated prenatal exposure to acetaminophen and risk of ADHD,<sup>22–24</sup> but to our knowledge, only one previous study on prenatal NSAID exposure had information on symptoms of ADHD,<sup>11</sup> and none had information on ADHD diagnosis. Further, NSAIDs are often used intermittently, so any time-varying effect of prenatal exposure would be important to guide clinical decisions.

In this study, the primary objective was to investigate associations between timing and duration of prenatal exposure to NSAIDs and risk of ADHD diagnosis and symptoms. A secondary objective was to investigate whether associations differed by maternal indication for NSAID use.

## 2 | MATERIALS AND METHODS

### 2.1 | Data sources and study population

This study was based on data from the Norwegian Mother, Father and Child Cohort (MoBa). MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers.<sup>25</sup> The present study is based on version 9 of the quality-assured data files, which was released for research in 2016. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical Research Ethics. All

### Key Points

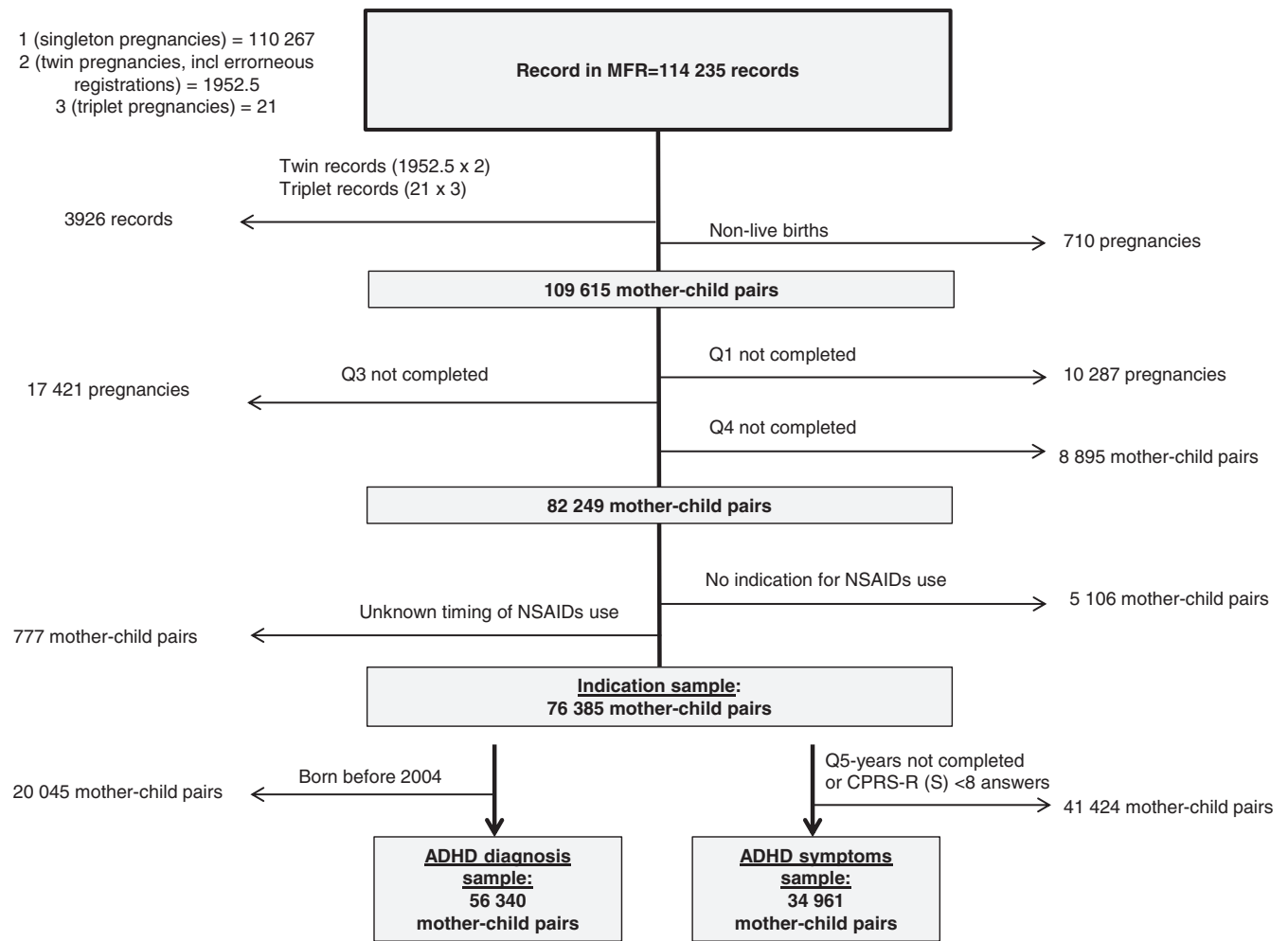
- In a large Norwegian cohort, there was no substantially increased risk of ADHD diagnosis or ADHD symptoms in children prenatally exposed to NSAIDs, when accounting for time-varying exposure and confounding.
- There was no duration-response relationship for either outcome, and the results were stable in sensitivity analyses.
- If these findings are corroborated in other populations, prenatal exposure to NSAIDs may be used as a negative exposure control in studies on prenatal exposure to acetaminophen and risk of ADHD in children.

mothers and fathers in the cohort provided written, informed consent to participation and to the use of their data from the Norwegian Health Registries. MoBa is currently regulated by the Norwegian Health Registry Act. The present study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway; approval number: 2015/2137/REK Sør-Øst. Data were handled in accordance with the General Data Protection Regulation.

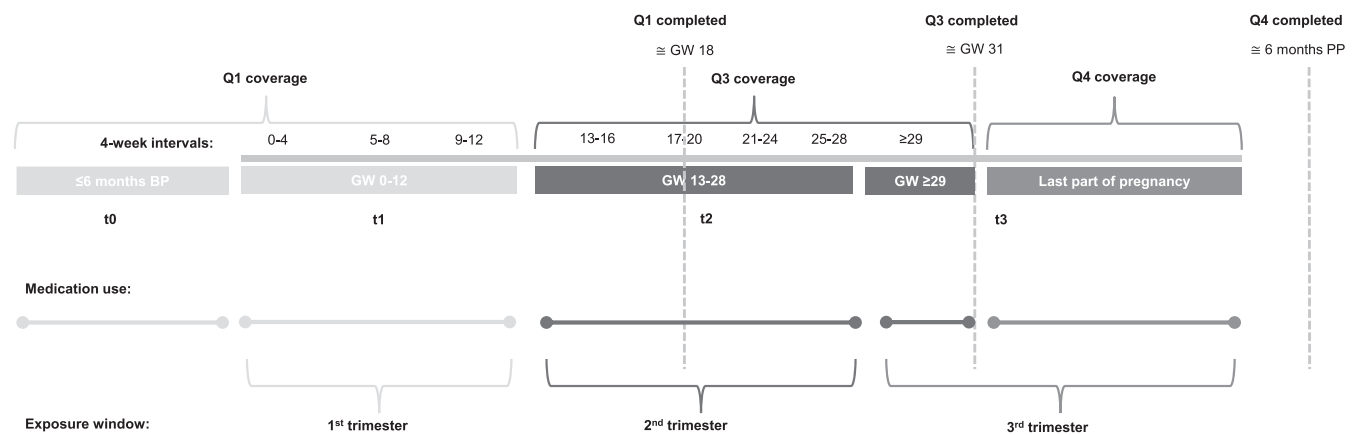
In addition to MoBa data, we used data from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), and the Norwegian Patient Registry (NPR). MBRN is a national health registry containing information about all births in Norway since 1967.<sup>26</sup> NorPD has stored data on prescriptions redeemed at pharmacies by patients in ambulatory care since 2004.<sup>27</sup> NPR has stored individual level data on diagnoses in secondary and tertiary health care settings since 2008.<sup>28</sup> Data was linked using the unique personal identification number given to all residents in Norway. Only live born singletons were included. In an attempt to meet the assumption of positivity<sup>29</sup> and account for confounding by indication, the study sample was restricted to women reporting indications for NSAID use during pregnancy (fever, infection, pain, or headache/migraine). The indications are specified in the Supporting Information. Further inclusion and exclusion criteria are presented in Figure 1.

### 2.2 | Exposure

Exposure was defined as prenatal exposure to NSAIDs (M01A in the World Health Organization's Anatomical Therapeutic Chemical [ATC] Classification System,<sup>30</sup> except glucosamine, M01AX05), as reported by the mother in any of two prenatal and one post-partum self-administered questionnaires (Figure 2). The mothers were presented with a list of symptoms and asked to check the ones that they had experienced. For each checked item on the list, the mothers were also asked to note any medications taken and specify the timing of use by checking one or more boxes that each represented a four-week interval (e.g., week 5–8 of pregnancy). To investigate the first objective of



**FIGURE 1** Flowchart of the study samples. Conditions of exclusion can overlap. ADHD, attention-deficit/hyperactivity disorder; CPRS-R (S), Conners' Parent Rating Scale-Revised, Short Form; NSAID, non-steroidal anti-inflammatory drug; Q, questionnaire



**FIGURE 2** Timing and coverage of the questionnaires in the Norwegian mother, father and child cohort. BP, before pregnancy; GW, gestational week; PP, post partum; Q, questionnaire; t, time point in the marginal structural model

this study, we evaluated (a) timing of NSAID use (first trimester [0–12 weeks of gestation], second trimester [13–28 weeks, or to delivery if born before week 28], or third trimester [29 weeks to delivery]), (b) duration of use, defined as number of 4-week intervals during

pregnancy with exposure (grouped as “0,” “1,” “2–3,” or “4 or more”), and (c) substance-level analysis on ibuprofen (ATC code M01AE01), the most commonly used NSAID in Norway. To investigate the second objective of the study, we stratified the analyses by five

indications for NSAID use: musculoskeletal pain, head-ache/migraine, fever, infection, and other.

No studies have investigated the validity of self-reported NSAID use in pregnancy in Norway. In a US cohort, data from maternal medication diaries in early pregnancy and recall of NSAID use during a first trimester interview showed moderate agreement (Cohen's kappa 0.41, sensitivity 0.79 and specificity 0.62).<sup>31</sup> We did not use data from NorPD on filled prescriptions for NSAIDs, as (a) some NSAIDs (ibuprofen, diclofenac, and naproxen) are available over-the-counter, and (b) the filled prescriptions may be used in a later trimester than it was filled, or not at all. The first point is supported by a Danish study comparing self-reported use of acetaminophen or NSAIDs (investigated as one group) to prescription fills.<sup>32</sup> In 95% of 348 self-reports of use, the medication was purchased over-the-counter.<sup>32</sup> The number of identified prescription fills was correspondingly low (20 fills in total).<sup>32</sup>

### 2.3 | Outcome

The primary outcome was child ADHD, defined as a diagnosis of ADHD (ICD-10 code F90)<sup>16</sup> recorded in NPR by a specialist in the Norwegian health care system, and/or a filled prescription for ADHD medication (ATC codes N06BA01, N06BA02, N06BA04, N06BA09, and N06BA12)<sup>30</sup> recorded in NorPD. In Norway, these were the only ADHD medications available during the study period. Children who had filled prescriptions for the indication of narcolepsy (ICD-10 code G47.4),<sup>16</sup> and who had no diagnosis of ADHD in NPR, were considered as not having ADHD. Children were followed from birth to incident ADHD or ultimo 2016, whichever came first. We had information about whether children died or migrated during follow-up, but not about dates of deaths or migrations. We restricted the sample to children born in 2004 or later to ensure that outcome data was available from birth in at least one registry. This was done as there is no lower age limit for receiving a F90-diagnosis, though it is rare in children under the age of 5 years.

The validity of ADHD diagnoses has not been investigated for Norwegian registries, but the documentation of diagnostic procedures in medical charts was found to be poor.<sup>33</sup> In Denmark, where the health care system is similar to the Norwegian, a registered diagnosis of ADHD has a positive predictive value of 0.87.<sup>34</sup>

To identify children who had difficulties, but did not necessarily meet the diagnostic criteria for ADHD, the secondary outcome was child hyperkinetic/inattentive symptoms at age 5 years, as reported by parents on the 12-item ADHD index from the Conners' Parent Rating Scale-Revised, Short Form (CPRS-R [S]). Children were excluded if less than eight items had been completed.

The CPRS-R (S) items show high internal consistency (Cronbach's alpha 0.88), and ability to predict later ADHD diagnosis in the MoBa population.<sup>35</sup> As to content validity, the items are based on DSM-IV ADHD criteria.<sup>36</sup>

### 2.4 | Covariates

Potential confounders were identified a priori using subject knowledge and directed acyclic graphs (Figures S1 and S2).<sup>37,38</sup> The sufficient adjustment set contained socioeconomic position, maternal ADHD, unplanned pregnancy, and disease severity. Data on covariates were obtained from MoBa questionnaires, MBRN, and NorPD. We did not have information on disease severity, but used proxies for disease severity (co-medication with other analgesics and psychotropics,<sup>39,40</sup> exercise in pregnancy, and severity of depressive symptoms, which may affect pain perception).

### 2.5 | Statistical analysis

For ADHD diagnosis, crude hazard ratios with 95% confidence intervals (HRs with 95% CIs) were obtained using Cox proportional hazards models. For ADHD symptoms, an average standardized score (z-score) was calculated. The z-score has a mean of zero and a standard deviation (SD) of one. For the CPRS-R (S), higher z-scores indicate more ADHD symptoms, with a score two SD above the mean usually considered indicative of clinically important problems with attention and/or hyperactivity.<sup>36</sup> Crude mean differences in z-score with 95% CIs were identified using generalized linear models.

To account for time-varying confounding, propensity scores were estimated and used as inverse probability of treatment weights (IPTWs).<sup>41</sup> In the analyses on timing, IPTWs were estimated at three points in addition to baseline to account for time-varying exposure to NSAIDs, time-varying confounding (by co-medication and exercise in pregnancy), and confounding by baseline covariates (socioeconomic position, maternal health and life-style). The resulting four IPTWs were multiplied to obtain a total weight that was used in marginal structural models. In the analysis on duration, a single IPTW was estimated for any pregnancy exposure, using baseline covariates and baseline values of the time-varying covariates. For ADHD diagnosis, the weight was used in Cox proportional hazards models with robust standard errors to obtain weighted HRs with 95% CIs. For ADHD symptoms, we additionally accounted for loss to follow-up by estimating inverse probability of censoring weights (IPCWs) in eligible pregnancies.<sup>41</sup> The IPCWs were multiplied by the IPTWs in the sample that had answered CPRS-R (S). The IPTW\*IPCW was used in generalized linear models with robust standard errors to obtain weighted standardized mean differences with 95% CIs. Details on the variables included in the weights are presented in the Supporting Information.

To answer the second objective of the study, the analyses were repeated in the five strata of maternal indications for medication use.

### 2.6 | Missing data

Up to 27% of included pregnancies had missing values on at least one variable used to generate IPTWs. The variables with the highest proportions of missing values were alcohol intake in pregnancy (up to 12.7%), maternal education (up to 5.2%), and maternal depressive symptoms (up to 4.8%).

**TABLE 1** Characteristics of pregnancies exposed and unexposed to NSAIDs in the Norwegian mother, father and child cohort

Characteristics <sup>a</sup>	ADHD diagnosis sample N = 56 340		ADHD symptoms sample N = 34 961	
	Exposed N = 3542	Unexposed N = 52 798	Exposed N = 2175	Unexposed N = 32 786
<i>Maternal sociodemographics and lifestyle</i>				
Age, n (%)				
<25 years	401 (11.3)	5084 (9.6)	200 (9.2)	2573 (7.9)
25–29 years	1154 (32.6)	17 390 (32.9)	711 (32.7)	10 591 (32.3)
30–34 years	1325 (37.4)	20 862 (39.5)	855 (39.3)	13 376 (40.8)
35–39 years	589 (16.6)	8379 (15.9)	366 (16.8)	5507 (16.8)
≥40 years <sup>b</sup>	73 (2.1)	1083 (2.1)	43 (2.0)	739 (2.3)
Married/cohabiting, n (%)	3377 (95.3)	50 881 (96.4)	2090 (96.1)	31 721 (96.8)
College/university education <sup>c</sup> , n (%)	2134 (60.3)	35 002 (66.3)	1435 (66.0)	23 104 (70.5)
Gross yearly income <sup>d</sup> , n (%)				
Average	2088 (59.0)	31 632 (59.9)	1320 (60.7)	20 234 (61.7)
Low	944 (26.7)	12 694 (24.0)	532 (24.5)	7157 (21.8)
High	417 (11.8)	6944 (13.2)	274 (12.6)	4572 (13.9)
Primiparous, n (%)	1750 (49.4)	24 898 (47.2)	1098 (50.5)	15 583 (47.5)
Planned pregnancy, n (%)	2653 (74.9)	43 450 (82.3)	1663 (76.5)	27 395 (83.6)
Pre-pregnancy BMI, kg/m <sup>2</sup> ; mean (SD)	24.6 (4.7)	24.0 (4.2)	24.5 (4.6)	23.9 (4.1)
Leisure time physical activity, n (%)				
Less than weekly	1325 (37.4)	20 454 (38.7)	807 (37.1)	12 480 (38.1)
Once or twice a week	1472 (41.6)	21 421 (40.6)	916 (42.1)	13 541 (41.3)
More than twice a week	647 (18.3)	9322 (17.7)	400 (18.4)	5951 (18.2)
Folic acid supplementation, any, n (%)	2989 (84.4)	46 381 (87.9)	1863 (85.7)	29 250 (89.2)
Smoking in pregnancy, n (%)	362 (10.2)	3055 (5.8)	187 (8.6)	1540 (4.7)
Alcohol intake in pregnancy, n (%)	451 (12.7)	4891 (9.3)	286 (13.2)	3161 (9.6)
Illicit drug use in pregnancy, n (%)	13 (0.4)	94 (0.2)	8 (0.4)	54 (0.2)
<i>Maternal health</i>				
Chronic disease registered in MBRN <sup>e</sup> , n (%)	319 (9.0)	4639 (8.8)	206 (9.5)	2797 (8.5)
Obstetric comorbidity <sup>f</sup> , mean (SD)	0.6 (1.1)	0.5 (1.0)	0.6 (1.1)	0.5 (1.0)
Comedication in pregnancy, n (%)				
Opioid analgesics (ATC code N02A)	248 (7.0)	925 (1.8)	139 (6.4)	563 (1.7)
Acetaminophen (ATC code N02BE01)	2694 (76.1)	25 041 (47.4)	1655 (76.1)	15 479 (47.2)
Migraine medications (ATC code N02C)	129 (3.6)	495 (0.9)	86 (4.0)	311 (0.9)
Antipsychotics/anxiolytics /hypnotics (ATC code N05)	122 (3.4)	809 (1.5)	73 (3.4)	467 (1.4)
Antidepressants (ATC code N06)	79 (2.2)	580 (1.1)	44 (2.0)	334 (1.0)
Depressive symptoms in pregnancy, mean (SD)				
Average SCL-5 at GW 17 & 29	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)
ADHD symptom level (ASRS), mean (SD)	13.0 (3.6)	12.5 (3.4)	12.8 (3.5)	12.4 (3.4)
Use of ADHD medications <sup>g</sup> , n (%)	48 (1.4)	478 (0.9)	23 (1.1)	225 (0.7)
<i>Paternal characteristics</i>				
Age, n (%)				
<25 years	170 (4.8)	2174 (4.1)	82 (3.8)	1084 (3.3)
25–29 years	825 (23.3)	11 683 (22.1)	500 (23.0)	7029 (21.4)
30–34 years	1326 (37.4)	20 768 (39.3)	828 (38.1)	13 082 (39.9)
35–39 years	850 (24.0)	12 759 (24.2)	540 (24.8)	8133 (24.8)
40–44 years	260 (7.3)	3912 (7.4)	161 (7.4)	2475 (7.6)
>45 years	104 (2.9)	1371 (2.6)	60 (2.8)	904 (2.8)
College/university education <sup>c</sup> , n (%)	1538 (43.4)	27 059 (51.3)	1021 (46.9)	17 690 (54.0)
Depressive symptoms (SCL-8), mean (SD)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)

TABLE 1 (Continued)

Characteristics <sup>a</sup>	ADHD diagnosis sample N = 56 340		ADHD symptoms sample N = 34 961	
	Exposed N = 3542	Unexposed N = 52 798	Exposed N = 2175	Unexposed N = 32 786
ADHD symptom level (ASRS), mean (SD)	14.4 (3.1)	14.2 (3.2)	14.3 (3.1)	14.1 (3.1)
Use of ADHD medications <sup>e</sup> , n (%)	33 (0.9)	381 (0.7)	16 (0.7)	218 (0.7)
<i>Child characteristics</i>				
Boy, n (%)	1786 (50.4)	26 989 (51.1)	1113 (51.2)	16 703 (50.9)
Preterm (<37 weeks), n (%)	192 (5.4)	2245 (4.3)	123 (5.7)	1441 (4.4)
Low birth weight (<2500 g), n (%)	121 (3.4)	1226 (2.3)	81 (3.7)	785 (2.4)
Congenital malformation, n (%)	169 (4.8)	2536 (4.8)	102 (4.7)	1596 (4.9)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASRS, adult ADHD self-report scale; ATC, anatomical therapeutic chemical; GW, gestational week; MBRN, Medical Birth Registry of Norway; NSAID, non-steroidal anti-inflammatory drug; SCL, Hopkins Symptoms Checklist.

<sup>a</sup>Numbers may not add up to totals due to missing values, ranging from 0.01 to 1.9% (maternal smoking, paternal age, planned pregnancy, pre-pregnant BMI, preterm birth) to 2.3 to 5.2% (gross yearly income, leisure time physical activity, maternal depressive symptoms, maternal/paternal education) and 10.5–12.7% (alcohol use and obstetric comorbidity index). Paternal depressive symptoms were assessed in the paternal questionnaire and were missing for 17.0–18.4%. Maternal and paternal ADHD symptoms were only assessed in later versions of the Norwegian Mother, Father and Child Cohort Study questionnaires. Therefore, parental ADHD symptoms were missing for 17.1–57.4%.

<sup>b</sup>Age groups “40–44 years” and “45 years or older” are combined as there are less than 5 women above 45 years among exposed.

<sup>c</sup>Corresponding to at least 16 years of education.

<sup>d</sup>Low is less than 21 500 USD, high is more than 50 000 USD.

<sup>e</sup>Astma, chronic hypertension, diabetes mellitus, epilepsy, heart disease, kidney disease, rheumatoid arthritis, or thyroid disease.

<sup>f</sup>Adapted from Bateman et al,<sup>49</sup> using the variables available in MBRN or MoBa (age, alcohol abuse, asthma, congenital heart disease, chronic hypertension, diabetes mellitus, drug abuse, gestational hypertension, kidney disease, mild preeclampsia, multiple gestation, other heart disease, placenta praevia, previous cesarean section, severe preeclampsia) and weighting the variables as done by Bateman et al.

<sup>g</sup>Any filled prescriptions for psychostimulants (ATC code N06B).

Under the assumption that data were missing at random, we imputed incomplete data via multiple imputation (Supporting Information).<sup>42–44</sup>

## 2.7 | Sensitivity analyses

To assess the robustness of our findings, we conducted a number of pre-specified sensitivity analyses as described in the Supporting Information. We conducted a complete case analysis to compare with results from the imputed dataset. The robustness of the IPTWs was assessed in four additional model specifications. Among these were models including paternal characteristics (age, education, depressive symptoms, and use of ADHD medications) and parental symptoms of ADHD. In an attempt to address potential residual confounding, we used negative exposure controls by comparing unexposed children to children unexposed to NSAIDs in utero, but whose mothers used NSAIDs in the 6 months prior to pregnancy. The latter group was also used as a disease comparator by comparing them to children exposed to NSAIDs in utero. To handle potential exposure misclassification, we used probabilistic bias analysis.<sup>45,46</sup> To assess the validity of the outcome measures, we investigated the correspondence between CPRS-R (S) score and ADHD diagnosis, and the association between in utero exposure to NSAIDs and risk of ADHD, based only on diagnostic data from NPR. For ADHD diagnosis, we excluded children who died or emigrated during follow-up to investigate the impact of misclassified time at risk. All statistical analyses were performed using Stata (version15; StataCorpLP).

## 3 | RESULTS

For ADHD diagnosis, 56 340 children of 50 572 mothers were included. For ADHD symptoms, 34 961 children of 31 696 mothers

were included. A child could be included in one or both samples. NSAID use was reported in 6.2% of pregnancies with medications available over-the-counter, mainly ibuprofen, accounting for more than 95% of users. A majority of mothers had a college or university education, but mothers of exposed children were less likely to have high education, and more likely to report unplanned pregnancy, smoking, and alcohol use in pregnancy (Table 1).

### 3.1 | ADHD diagnosis

The children were followed for 9.8 years on average (SD 1.5, range 8–12 years). The prevalence of child ADHD diagnosis was 2.2%, and the average age at first diagnosis was 8.2 years (SD 1.7). In the crude analysis, first trimester exposure to NSAIDs was associated with a higher risk of ADHD (HR 1.32, 95% CI 1.03; 1.68; Table 2). After weighting, the association was no longer seen (HR 1.12, 95% CI 0.86; 1.45), and prenatal exposure to NSAIDs was not associated with higher risk of ADHD in any trimester or duration category.

Results did not differ substantially in the substance-level analysis on ibuprofen (Table S1), nor by maternal indication for NSAID use (Figure 3).

### 3.2 | ADHD symptoms

The mean average CPRS-R (S) score at age 5 years was 1.37 (SD 0.38). The proportion of children who had a z-score of two or more SD from the mean was 4.5%. In the analysis on timing of exposure, we observed no association with CPRS-R (S) score.

In the analysis on duration, we found slightly higher CPRS-R (S) scores in children exposed in 1 four-week interval (weighted



**TABLE 2** ADHD diagnosis and symptoms by timing and duration of prenatal NSAID exposure in the Norwegian mother, father and child cohort

ADHD diagnosis sample, N = 56 340							
	n	Incidence (%)		Crude HR (95% CI)		Weighted HR (95% CI) <sup>a</sup>	
<i>Timing</i>							
Exposed before pregnancy only, negative control	4067	100	(2.5)	1.16	(0.94;1.42)	1.14	(0.92;1.40)
Unexposed before pregnancy	48 731	1053	(2.2)	-	-	-	-
Exposed in 1st trimester	2354	69	(2.9)	1.32	(1.03;1.68)	1.12	(0.86;1.45)
Unexposed in 1st trimester	53 986	1177	(2.2)	-	-	-	-
Exposed in 2nd trimester	1524	39	(2.6)	1.14	(0.83;1.57)	0.98	(0.69;1.38)
Unexposed in 2nd trimester	54 816	1207	(2.2)	-	-	-	-
Exposed in 3rd trimester	612	12	(2.0)	0.90	(0.51;1.58)	0.68	(0.31;1.46)
Unexposed in 3rd trimester	55 728	1234	(2.2)	-	-	-	-
<i>Duration</i>							
0 periods (unexposed)	52 798	1153	(2.2)	-	-	-	-
1 period	2297	58	(2.5)	1.14	(0.87;1.48)	1.00	(0.76;1.32)
2–3 periods	899	27	(3.0)	1.37	(0.93;2.00)	1.32	(0.89;1.96)
4 or more periods	346	8	(2.3)	1.03	(0.51;2.07)	0.83	(0.40;1.71)
ADHD symptoms (CPRS-R(S)) sample, N = 34 961							
	n	Mean z-score (SD)		Crude mean difference (95% CI)		Weighted mean difference (95% CI) <sup>b</sup>	
<i>Timing</i>							
Exposed before pregnancy only, negative control	2627	0.15	(1.0)	0.17	(0.13;0.20)	0.14	(0.10;0.19)
Unexposed before pregnancy	30 159	-0.02	(1.0)	-	-	-	-
Exposed in 1st trimester	1441	0.10	(1.1)	0.10	(0.05;0.15)	0.03	(-0.03;0.09)
Unexposed in 1st trimester	33 520	-0.00	(1.0)	-	-	-	-
Exposed in 2nd trimester	922	0.08	(1.0)	0.08	(0.01;0.14)	0.03	(-0.04;0.11)
Unexposed in 2nd trimester	34 039	0.00	(1.0)	-	-	-	-
Exposed in 3rd trimester	369	0.18	(1.2)	0.18	(0.08;0.28)	0.11	(-0.03;0.25)
Unexposed in 3rd trimester	34 592	0.00	(1.0)	-	-	-	-
<i>Duration</i>							
0 periods (unexposed)	32 798	-0.01	(1.0)	-	-	-	-
1 period	1416	0.13	(1.1)	0.14	(0.09;0.19)	0.11	(0.05;0.17)
2–3 periods	549	0.11	(1.1)	0.11	(0.03;0.20)	0.10	(-0.00;0.20)
4 or more periods	210	-0.00	(0.9)	0.00	(-0.13;0.14)	-0.02	(-0.16;0.12)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; CPRS-R (S), Conners' parent rating scale-revised, short form; HR, hazard ratio; NSAID, non-steroidal anti-inflammatory drug.

<sup>a</sup>Inverse probability of treatment weights, model additionally adjusted for co-medication with acetaminophen as the weights failed to balance that covariate.

<sup>b</sup>Inverse probability of treatment weights, model additionally adjusted for co-medication with acetaminophen, as the weights failed to balance that covariate. For third trimester exposure, the weights also failed to balance illicit drug use, which was added to the regression model.

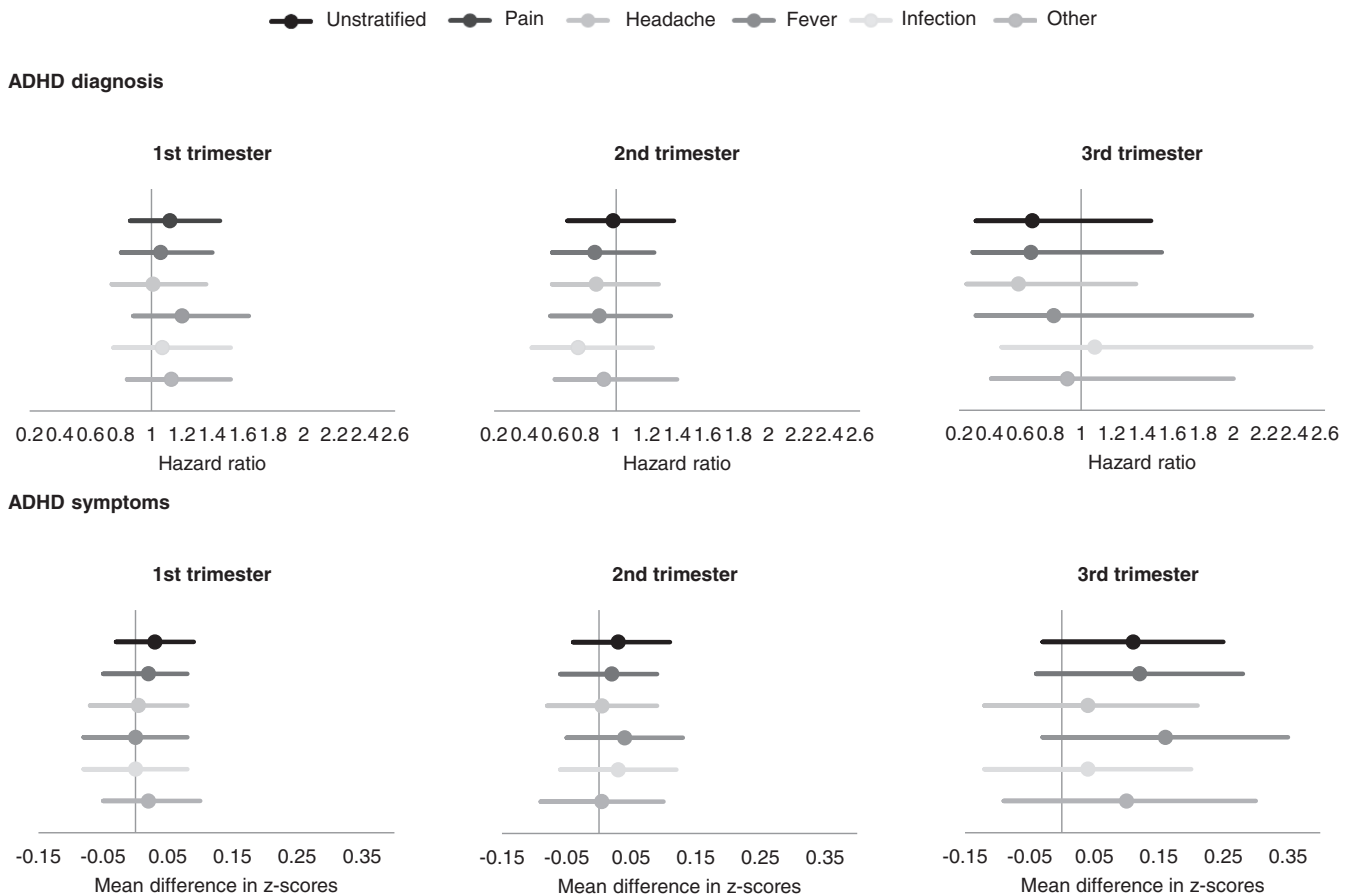
standardized mean difference 0.11, 95% CI 0.05;0.17) compared to unexposed. In children exposed for 2–3 intervals and 4 or more intervals, the weighted standardized mean differences were 0.10 (95% CI -0.00; 0.20) and -0.02 (95% CI -0.16; 0.12), respectively.

Results did not differ substantially in the substance-level analysis on ibuprofen (Table S1), nor by maternal indication for NSAID use (Figure 3).

### 3.3 | Sensitivity analyses

The inclusion of paternal characteristics and parental ADHD symptoms in alternative model specifications did not alter the estimates of association substantially (Figure S4).

In the negative exposure controls, we identified similar estimates of association between pre-pregnancy use of NSAIDs and child



**FIGURE 3** ADHD diagnosis (upper panel) and symptoms (lower panel) by timing of prenatal NSAID exposure in the Norwegian mother, father and child cohort, stratified by maternal indication for NSAID use. Points indicate weighted estimates of association, lines represent 95% confidence intervals. ADHD, attention-deficit/hyperactivity disorder; NSAID, non-steroidal anti-inflammatory drug

ADHD diagnosis, as between first trimester exposure and ADHD diagnosis (weighted HR 1.14, 95% CI 0.92; 1.40). We also identified an association between pre-pregnancy use of NSAIDs and child ADHD symptoms (weighted mean difference 0.14, 95% CI 0.10; 0.19; Table 2).

In the probabilistic bias analysis, we found that failure to account for non-differential exposure misclassification could have biased the findings toward the null by about 26–37% according to trimester.

Children with an ADHD diagnosis had a mean CPRS-R (S) z-score of 1.85 (SD 1.9) which was almost two standard deviations from the mean in children without a diagnosis (−0.03, SD 0.9).

Results from the remaining sensitivity analyses showed that the estimates of association were generally robust (Supporting Information).

## 4 | DISCUSSION

In this Norwegian birth cohort with 9.8 years of follow-up on average, we found no substantially increased risk of ADHD diagnosis among children prenatally exposed to NSAIDs. For ADHD symptoms in 5-year-olds, we observed no associations by timing of NSAID

exposure, but we found higher symptom scores in children exposed for one 4-week interval of pregnancy. Children exposed for four or more intervals did not have higher symptom scores, suggesting that associations are not causal, albeit number of cases exposed for four or more intervals was low.

To our knowledge, this is the first study to investigate prenatal NSAID exposure and risk of ADHD diagnosis. Our results on ADHD symptoms are in line with findings from Markovic et al, who used the Child Behavior Checklist to identify attention problems in children aged 5 years, and found no difference in adjusted mean score.<sup>11</sup> In spite of the current debate on acetaminophen and risk of ADHD,<sup>22–24</sup> NSAIDs are not an alternative to acetaminophen as first line analgesic in pregnancy. First trimester NSAID use is associated with increased risk of early miscarriage, and third trimester use with increased risks of oligohydramnios, premature closure of ductus arteriosus, prolonged pregnancy, and has the biological plausibility to increase blood loss at delivery.<sup>3,5</sup> The identification of safe and effective medications for the treatment of pain during pregnancy should be a priority in future research, especially given the questions surrounding the safety of long-term use of acetaminophen during pregnancy.<sup>22–24</sup> In the meantime, our findings, if corroborated in other populations, are reassuring regarding child ADHD for



the women who need to use NSAIDs during pregnancy to manage pain conditions.

An implication for research is that if our findings are corroborated, exposure to NSAIDs could be used as a negative exposure control in studies on prenatal exposure to acetaminophen and child ADHD, as the structure of bias is probably similar for NSAIDs and acetaminophen, albeit the contraindications are different.

Based on previous findings on maternal inflammation and child ADHD,<sup>20,21</sup> we expected to find a lower risk of ADHD in children exposed to anti-inflammatory treatment than in children exposed to untreated inflammation. We did not find such an association, when comparing exposed children to unexposed children whose mothers reported similar symptoms. This could be because our pre-specified categories of indications grouped heterogeneous diseases together. It is also possible that women with inflammatory conditions, who did not use NSAIDs were treated with other anti-inflammatory drugs.

Strengths of the present study include a large sample size with long follow-up and access to both diagnostic outcomes, and well-validated parent-reported outcomes. The study also has several limitations. Findings from the negative exposure controls suggest that some residual confounding, such as confounding by genetics or severity of indication, is present.

Exposure misclassification cannot be ruled out. First and second trimester exposure was reported during pregnancy, third trimester exposure 6 months after birth, where child symptoms of ADHD are unlikely, so any exposure misclassification is likely non-differential. This could have biased results toward the null. In the probabilistic bias analysis, we estimated the magnitude of such bias around 26–37%. In first trimester NSAID exposed, we might have found a higher risk of ADHD (HR around 1.5) in the absence of misclassification. However, the HR in the negative exposure controls would have been similarly higher, cautioning against a causal interpretation.

The prevalence of ADHD diagnoses was 2.2% in our sample after an average 9.8 years of follow-up, whereas the prevalence among Norwegian 12-year-olds is 3.4%.<sup>33</sup> This could reflect systematic differences between the study sample and the general population, and/or a shorter period to observe the outcomes in the present study. If exposure is in any way associated with earlier or later detection of ADHD, this could have affected our results. The validity of the ADHD diagnoses is supported by a correspondence between ADHD diagnosis and a higher score on the well-validated CPRS-R (S).

Participation rate in MoBa was 41%. Compared to the general birthing population of Norway, participants were less likely to be young parents, more likely to be married or cohabiting, and had a healthier lifestyle during pregnancy.<sup>47</sup> A study found that selection into the cohort and loss to follow-up appeared to affect estimates of association for longer-term outcomes such as child ADHD, but that IPCW was a robust method to handle such bias.<sup>48</sup> Still, the selected sample may affect the prevalence of ADHD diagnoses, and the generalizability of our findings.

## 5 | CONCLUSION

In this large cohort study with follow-up of 9.8 years on average, we found no substantially increased risk of ADHD diagnosis in children exposed to NSAIDs in utero, regardless of timing or duration of exposure. We identified a slightly higher ADHD symptom score at age 5 years in children exposed to NSAIDs for one 4-week interval in pregnancy. Exposure for more intervals was not associated with higher symptom scores, suggesting that the finding is an artifact. Our findings are reassuring for women who need to use NSAIDs in pregnancy.

## ACKNOWLEDGMENTS

This work was supported by the European Research Council Starting Grant “DrugsInPregnancy” [grant number 639377 to SH] and The PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway. The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. Data was stored at the TSD (Tjeneste for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT-Department (USIT).

## CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Hjorth S, Lupattelli A, Handal M, Spigset O, Ystrom E, Nordeng H. Prenatal exposure to non-steroidal anti-inflammatory drugs and risk of attention-deficit/hyperactivity disorder: A follow-up study in the Norwegian mother, father and child cohort. *Pharmacoepidemiol Drug Saf*. 2021;30:1380-1390. <https://doi.org/10.1002/pds.5250>