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Prenatal Exposure to Acetaminophen and Risk of ADHD

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Abbreviations: the Norwegian Mother and Child Cohort Study (MoBa), the Norwegian Patient Registry (NPR), Anatomical Therapeutic Chemical (ATC), Body-mass index (BMI), Hazard ratio (HR).

Table of Contents Summary: We identify a strong association between long-term acetaminophen use and offspring ADHD that is not be explained by indications of use or familial ADHD.

What's Known on This Subject: Previous studies have identified an association between acetaminophen use during pregnancy and 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 two-fold increase in risk for offspring ADHD.

Contributors' Statement

Dr Ystrom designed the study, carried out analyses, drafted the initial manuscript, and approved the final manuscript as submitted. Drs Gustavson, Brandlistuen, Susser, Davey Smith, Stoltenberg, Surén, Håberg, Hornig, Lipkin, and Nordeng contributed substantially to conception and design of the study, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as to be published. Dr Knudsen contributed substantially in acquisition of data by coordinating the registry linkage, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as to be published. Dr Magnus contributed substantially in acquisition of data by leading the data collection of the Norwegian Mother and Child Cohort study, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as to be published. Dr Reichborn-Kjennerud contributed substantially to the conceptualization and design of the study, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract (229 words)

Objectives: To estimate the association between maternal use of acetaminophen during pregnancy and of paternal use before pregnancy with 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 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 one (hazard ratio (HR)=1.07 (95%CI, 0.96-1.19)), two (1.22 (95%CI, 1.07-1.38)), and three trimesters (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 less than 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 use of acetaminophen was similarly associated with ADHD as maternal use.

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.

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 about 65% to 70% of pregnant women in the United States, and by about 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, a sibling comparison conducted 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 in offspring [4]. The following year, a report from a large Danish birth cohort study found an association between prenatal acetaminophen use and both a clinical ADHD diagnosis and ADHD symptoms in offspring [5], and later other studies related prenatal acetaminophen use to rating scales of disinhibited behavior [5,6].

The Danish study [7] 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 [7,8]. 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 (e.g. fever, inflammation, and autoimmunity) is 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 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 (e.g. disinhibited personality traits [13]), we would expect use prior to 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 (e.g. genetic factors), paternal use of acetaminophen may also be associated with ADHD in a similar way as maternal use of acetaminophen. However, acetaminophen and other 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 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 these potential confounders. In contrast to 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 prior to pregnancy as a specificity control and to estimate the effect of paternal use prior to pregnancy.

Patients and Methods

Sample

Data were drawn from the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health [17]. 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 around 18 weeks of gestation, and to mothers later in pregnancy and after delivery. We used information from maternal questionnaires when children were 6 months, 1.5, and 3 years old in the version nine 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) [18]. From 2008, all government-owned and government-financed hospitals and outpatient clinics mandatorily report individual level ICD-10 diagnoses[19] to the NPR in order to receive financial reimbursement. Using individual personal identification numbers, diagnostic information from NPR was linked to MoBa. Thus all MoBa children registered with an ICD-10-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 DSM-5 ADHD [20]. In comparison to ADHD, hyperkinetic

disorder is characterized by a higher proportion with impaired language and motor development [21]. Two cases in the analyses were censored due to F90 diagnosis before the age of three.

Prenatal use of acetaminophen

Information on acetaminophen use was obtained through MoBa questionnaires. Acetaminophen use was available from two prenatal and one postnatal questionnaire. 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 specify the following exposure windows: Six months prior to 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, and name the medication taken in an open textbox. Use six months prior to 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.

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 co-medications 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 six months before pregnancy. We classified and grouped medication exposure according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the World

Health Organization[22]. Acetaminophen exposure was defined as using a drug with ATC code N02BE01.

Covariates

Based on previous literature, the following covariates were considered potential confounders: Acetaminophen use prior to pregnancy, parental symptoms of ADHD (in MoBa, these are measured by the six-item "World Health Organization adult ADHD self-report scale (ASRS)" screener[23] measuring risk for DSM-IV ADHD), maternal self-reported alcohol use during pregnancy, maternal self-reported daily smoking during pregnancy, symptoms of anxiety and depression at 18th and 30th week of gestation (in MoBa, this is measured by the five and eight item short version of the Hopkins Symptom Checklist 25[24,25]), maternal education, marital status, body-mass index (BMI) at 18th week of gestation, maternal age, parity, birth year centered to 1999, and birth year squared to adjust for non-linear cohort effects. Maternal age and parity was obtained from the Medical Birth Registry of Norway[26]. In addition, we assessed 128 medical conditions at 18th week and 30th week of gestation, and at six 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 followed to time of ADHD diagnosis or censored at Dec 31, 2014. To replace missing values on self-reported covariates, 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 five indications at any time point contributed with five units in the

analyses (i.e. one for each indication of use). Since 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 co-medications, use before pregnancy, and use after pregnancy within each indication. We grouped the effects of use across types of indications (i.e. 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 was for all analyses [27].

Results

The study population included 112,973 children, of whom 2,246 had been diagnosed with ADHD. In figure 1, we present the estimated cumulative number of expected ADHD events across age. We estimated that about 4% of children in MoBa will have an ADHD diagnosis at the age of 13 (figure 1). Fifty-two thousand seven-hundred and seven (46.7%) women used acetaminophen during pregnancy (table 1). Twenty-seven percent used acetaminophen in one trimester, 16% in two trimesters, and 3.3% in all three trimesters. Maternal preconceptional use and use in first trimester was about equally associated (r = .49) as use in first and second trimester (r = .56) and use in second and third trimester (r = .49) (eTable 1). Paternal use was associated with maternal preconceptional use and use during pregnancy (r = .18 to .10) (eTable 1).

Offspring prenatally exposed to acetaminophen had an increased unadjusted hazard rate of ADHD of 17%, 39%, and 46% after one, two, and three trimesters of exposure, respectively (table 1). These associations were not attenuated when we adjusted for maternal and paternal use prior to pregnancy (model 1), but were slightly lower after we adjusted for

parental symptoms of ADHD (model 2). In model 3, we adjusted for a range of potential confounders, and the associations between one, two, and three trimesters of prenatal acetaminophen exposure were hazard ratio (HR)=1.07 (95%CI 0.96-1.19), HR=1.22 (95%CI 1.07-1.38), and HR=1.27 (95%CI 0.99-1.63), respectively. The negative control, maternal preconceptual 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 hazard ratios 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 less than seven days was negatively associated with offspring ADHD. For use more than seven days, the hazard ratio 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. The associations with use of 29 days or more did not differ across groups of indications (HR from 2.13 to 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. (2013) based on Danish registry data.

Liew et al. did not, however, control for the indications for use or ADHD-related familial factors. In our study, the association persisted after adjusting for an indirect measure of risk for acetaminophen use prior to 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 29 days or more had a two-fold hazard ratio for receiving a clinical diagnosis of ADHD from specialist health services. This estimate was the same regardless of indication (i.e. fever and infections or pain conditions). Maternal use of acetaminophen for less than eight days was negatively associated with ADHD. The association between paternal preconceptional acetaminophen use with ADHD was similar to the association with maternal use of acetaminophen during pregnancy.

The considerable increased rate of ADHD associated with long-term prenatal exposure to acetaminophen (i.e. > 29 days) is in line with the findings of Brandlistuen et al. (2013), who also found small associations for short-term use and large associations for long-term use among discordant siblings in a subset of the MoBa. Liew et al. also found stronger associations by increasing number of weeks exposed.

ADHD is highly familial in both children and adults [28]. We have previously found that acetaminophen use during pregnancy was associated with impulsive personality traits in the mothers [13]. Therefore, our ability to adjust for parental symptoms of ADHD represents a considerable improvement compared with prior study designs. Our analyses showed that the association between maternal acetaminophen use and ADHD did not appear to be strongly confounded by common familial (e.g. genetic) factors for ADHD and use of acetaminophen. Previous studies have also suggested common familial risk factors for maternal depression and offspring disruptive behavior [29,30]. We examined this by adjusting for maternal symptoms of depression, but the association remained.

Even after adjusting for indications of use, there was still an association (HR = 2.20; 95%CI 1.50-3.24) between long-term prenatal acetaminophen exposure and childhood ADHD. This estimate was similar across several indications for acetaminophen use (fever, infections, and pain conditions). This indicates that putative confounding factors for long-term acetaminophen use and ADHD are not related to the recorded indications but unmeasured factors.

Maternal preconceptional use was not associated with ADHD. This is in line with a recent study finding no effect of maternal postnatal acetaminophen use on maternal reports of behavior problems [6]. Furthermore, we found that maternal preconceptional use was as associated with use during first trimester as use across two 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 human testis [15,16].

At least three 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, results in altered behavior, and in lowered fear responses, and learning abilities in adulthood [31]. Brain-derived neurotropic factor promotes neuronal survival and regulates cell migration, axonal and dendritic outgrowth, and formation of synapses [31,32,33] . Second, acetaminophen could interfere with maternal hormones, such as thyroid hormone and sex hormones, that are related to fetal brain development [7,34-38]. Third, acetaminophen could interrupt brain development by induction of

oxidative stress, leading to neuronal death [4,39-41]. All of these three putative mechanisms can be further tested in experimental animal studies.

Our finding that acetaminophen use for less than eight days is negatively associated with offspring ADHD indicates that the antipyretic effect could be beneficial with regard to fetal development [11,12].

We address three limitations that could have biased the results. First, even though 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 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, parents with low educational levels and young ages, and parents who were smokers, are under-represented in the MoBa [43], which may limit generalization of results to all children. It has, however, previously been shown that even though estimates of frequencies and means were biased due to selective participation, selected exposure-outcome-associations did not differ between MoBa participants and the general Norwegian population [43-45].

Conclusion

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 indications of acetaminophen use. Even though 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. This study does not provide definitive evidence for or against a causal relation between maternal use of acetaminophen and ADHD.

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Figure legends

Figure 1.

The figure is of the cumulative hazard estimate, and depicts the estimated proportion of children receiving an ADHD diagnosis by age after birth.

Table 1. Hazard ratios for ADHD diagnosis according to maternal acetaminophen use during pregnancy in 112,973 offspring.

	Complete cases			Estimated data by multiple imputation		Hazard ratios					
						Crude	Model 1		Model 2		Model 3	
	n	total n	%	N	%		(95% CI)		Adj.	(95% CI)	Adj.	(95% CI)
Acetaminophen use 6 months prior to pregnancy	27,584	104,084	26.5%	29 931	26.5 %	1.04	0.93	(0.83 - 1.03)	0.92	(0.82 - 1.02)	0.95	(0.85 - 1.06)
Paternal acetaminphen use	11,119	61,543	18.1%	20 151	17.8 %	1.34	1.31	(1.12 - 1.53)	1.26	(1.08 - 1.48)	1.27	(1.08 - 1.49)
Acetaminophen use during pregnancy												
Never used during pregnancy	45,615	93,216	48.9 %	60 266	53.3 %	1.00	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
Ever used during pregnancy	47,601	93,216	51.1 %	52 707	46.7 %	1.26	1.25	(1.14 - 1.37)	1.20	(1.09 - 1.32)	1.12	(1.02 - 1.24)
Any one trimester	23,244	85,854	27.1 %	30 610	27.1 %	1.17	1.17	(1.05 - 1.30)	1.13	(1.01 - 1.27)	1.07	(0.96 - 1.19)
1st trimester only	7,448	85,854	8.7 %	9 282	8.2 %	1.15	1.15	(0.97 - 1.36)	1.14	(0.97 - 1.36)	1.12	(0.94 - 1.32)
2nd trimester only	14,688	85,854	17.1 %	19 927	17.6 %	1.17	1.17	(1.03 - 1.33)	1.13	(0.99 - 1.28)	1.04	(0.92 - 1.18)
3rd trimester only	1,108	85,854	1.3 %	1 401	1.2 %	1.21	1.21	(0.80 - 1.83)	1.12	(0.74 - 1.69)	1.12	(0.75 - 1.67)
Any two trimesters	13,698	85,854	16.0 %	18 379	16.3 %	1.39	1.39	(1.23 - 1.6)	1.32	(1.16 - 1.50)	1.22	(1.07 - 1.38)
Both 1st and 2nd trimesters	11,536	85,854	13.4 %	15 254	13.5 %	1.37	1.38	(1.20 1.6)	1.32	(1.15 1.51)	1.21	(1.06 1.39)
Both 2nd and 3rd trimesters	1,653	85,854	1.9 %	2 389	2.1 %	1.46	1.46	(1.06 - 2.00)	1.30	(0.95 - 1.78)	1.20	(0.87 - 1.66)
Both 1st and 3rd trimesters	509	85,854	0.6 %	737	0.7 %	1.44	1.45	(0.83 - 2.52)	1.35	(0.77 - 2.34)	1.34	(0.77 - 2.34)
All 3 trimesters	2,908	85,854	3.4 %	3 718	3.3 %	1.46	1.46	(1.15 - 1.24)	1.34	(1.05 - 1.71)	1.27	(0.99 - 1.63)

Note. 2,246 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; 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 wk of gestation, maternal age, and parity.

Table 2. Hazard ratio for offspring ADHD by number of days of maternal acetaminophen use during pregnancy.

	All indications		Groups of indication for acetaminophen use					
			Fever and infections		Pain conditions		Indication not specified	
	Number of mothers reporting each exposure duration / Overall number of observations of use per exposure duration	Adjusted Hazard Ratio[a] / 95%CI	Number of mothers reporting each exposure duration / Overall number of observations of use per exposure duration	Adjusted Hazard Ratio[a] / 95%CI	Number of mothers reporting each exposure duration / Overall number of observations of use per exposure duration	Adjusted Hazard Ratio[a] / 95%CI	Number of mothers reporting each exposure duration / Overall number of observations of use per exposure duration	Adjusted Hazard Ratio[a] / 95%CI
no use	103,017 1,153,338	1.00 Reference	84,304 216,206	1.00 Reference	75,019 180,288	1.00 Reference	4,606 4,639	1.00 Reference
1 to 7 days	36,899 53,667	0.90 (0.81 - 1.00)	8,752 10,864	0.90 (0.75 - 1.09)	10,335 12,064	0.89 (0.76 - 1.04)	19,154 21,796	1.30 (0.98 - 1.73)
8 to 14 days	6,434 7,923	1.18 (0.98 - 1.42)	1,021 1,185	1.02 (0.55 - 1.89)	2,653 2,925	1.12 (0.83 - 1.50)	1,949 2,020	1.96 (1.36 - 2.82)
15 to 21 days	2,003 2,369	1.35 (1.00 - 1.81)	185 200	0.98 (0.24 - 3.95)	1,045 1,147	1.43 (0.96 - 2.14)	441 447	1.79 (0.95 - 3.35)
22 to 28 days	253 283	1.60 (0.70 - 3.69)	16 17	6.15 (1.71 - 22.05)	133 138	1.08 (0.34 - 3.39)	61 62	n.a.
29 or more days	1,034 1,395	2.20 (1.50 - 3.24)	72 75	2.40 (0.34 - 16.78)	609 772	2.56 (1.54 - 4.25)	200 212	2.13 (0.88 - 5.15)

[a]Adjusted for year of birth, maternal age, parity, co-medication within each indication of use, acetaminophen use first six months prior to pregnancy within each indication of use (only reports on first trimester adjusted), and acetaminophen use first six months post partum within each indication of use (only reports on last trimester adjusted). 2,246 children were diagnosed with ADHD by december 31, 2014.

Table 3. Hazard ratio for offspring ADHD by number of days of paternal acetaminophen use six months prior to pregnancy.

	Number of fathers reporting each category	Hazard Ratio[a]	95%CI
no use	64,348	1.00	Reference
1 to 7 days	8,887	1.10	(0.92 - 1.30)
8 to 28 days	1,079	1.81	(1.26 - 2.60)
29 or more days	657	2.06	(1.36 - 3.13)

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