RESEARCH LETTER

WOMEN'S HEALTH

Acetaminophen Exposure During Pregnancy and the Risk of Autism in Offspring

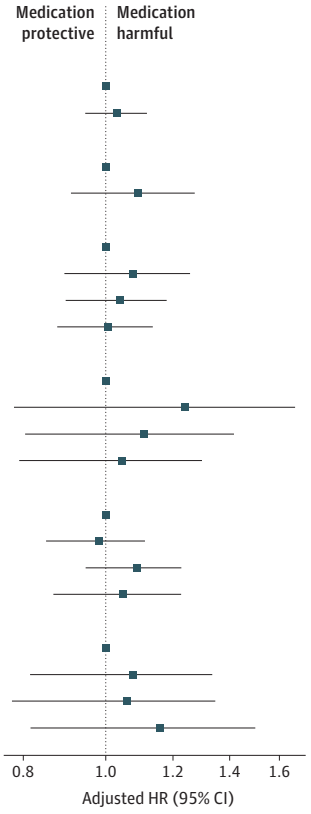
Evidence regarding the association between prenatal acetaminophen exposure and risk of autism in offspring remains inconsistent.[1] One large Swedish cohort study reported a small but statistically significant increase in autism risk among children in a population-level analysis; however, the association was not observed in a sibling matched analysis, raising questions about residual confounding.[2] Due to renewed public attention, we evaluated the potential association between prenatal acetaminophen exposure and risk of autism using Danish nationwide registers.

Supplemental content

Methods | We conducted a nationwide cohort study, linking individual-level information prospectively collected in the Danish national demographic and health care registers, described elsewhere.[3] We constructed a source population of all children born from singleton pregnancies in Denmark between January 1, 1997, and July 31, 2022, who were alive at age 1 year. Children were excluded due to missing gestational age,

Figure. Forest Plot of the Association Between Acetaminophen Use During Pregnancy and the Risk of Autism in Offspring

Variable	Events, No. (%)	Risk-time, y	Crude IR[a]	Adjusted HR (95% CI)[b,c,d]
Overall population cohort				
No use	44 667 (3.0)	19 323 146	23.1	1 [Reference]
Acetaminophen exposure	554 (1.8)	190 842	29.0	1.03 (0.95-1.12)
Overall sibling cohort				
No use	471 (3.0)	185 755	25.4	1 [Reference]
Acetaminophen exposure	148 (1.8)	56 662	26.1	1.09 (0.91-1.27)
Dosage in population cohort				
No use	44 667 (3.0)	19 323 146	23.1	1 [Reference]
Low dose <300 mg/d	118 (1.9)	42 346	27.9	1.08 (0.89-1.26)
Medium dose 300-699 mg/d	197 (1.6)	71 959	27.4	1.04 (0.90-1.18)
High dose ≥700 mg/d	239 (1.9)	76 537	31.2	1.01 (0.88-1.14)
Dosage in sibling cohort				
No use	471 (3.0)	185 755	25.4	1 [Reference]
Low dose <300 mg/d	20 (3.5)	7314	27.3	1.24 (0.78-1.70)
Medium dose 300-699 mg/d	45 (1.7)	18 304	24.6	1.11 (0.80-1.42)
High dose ≥700 mg/d	83 (1.7)	31 044	26.7	1.04 (0.79-1.30)
Time of exposure in population cohort				
No use	44 667 (3.0)	19 323 146	23.1	1 [Reference]
First trimester	233 (2.0)	77 673	30.0	0.98 (0.85-1.11)
Second trimester	200 (1.8)	67 958	29.4	1.09 (0.95-1.23)
Third trimester	121 (1.4)	45 210	26.8	1.05 (0.87-1.23)
Time of exposure in sibling cohort				
No use	471 (3.0)	185 755	25.4	1 [Reference]
First trimester	63 (2.1)	22 424	28.1	1.08 (0.82-1.34)
Second trimester	50 (1.7)	20 685	24.2	1.06 (0.78-1.35)
Third trimester	35 (1.6)	13 553	25.8	1.16 (0.82-1.50



In 2013, over-the-counter sales of acetaminophen were restricted in Denmark to a maximum of 10 tablets per purchase. An interaction analysis comparing the pre- and post-2013 periods was therefore performed for the sibling analysis and yielded a *P* value of .49. HR indicates hazard ratio; IR, incidence rate.

[a]Per 10 000 person years.

[b]Adjusted for maternal age (categorical), calendar year (categorical), prepregnancy body mass index (categorical), smoking status, birth in Denmark, highest attained educational level, income quartile (categorical), urban residency, cohabitation, parity, asthma, chronic pain, diabetes, diagnosed headache, fever, fibromyalgia, gastric bypass, infection, migraine, neuropathic pain, rheumatoid arthritis, psychiatric disease, aspirin use, antidepressive use, migraine medication use, antiseizure medication use, nonsteroidal anti-inflammatory drug use, psycholeptic use, opioid use, hospital visits during the year before pregnancy, antenatal hospital visits, prescriptions purchased during the year before pregnancy, registered father's age (categorical), registered father's history of psychiatric disorder, maternal sibling history of psychiatric disease, child sex, and season of delivery.

[c]Missing value imputed in 2 datasets.

[d]Sibling analyses not adjusted for fibromyalgia due to nonconvergence of the statistical model.

[e]Total dose of acetaminophen fulfilled during pregnancy divided by pregnancy duration in days.

missing maternal age, diseases inherently linked to autism, and death or emigration before age 1 year.

Exposure to acetaminophen during pregnancy was identified by maternal fulfilment of a prescription for Anatomic Therapeutic Chemical code N02BE in the National Prescription Register. The main outcome of interest was an incident diagnosis of autism based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*: F84.0, F84.5, F84.8, or F84.9; for details, see the eTable in Supplement 1. Children were followed up from age 1 year until emigration, end of follow-up (July 31, 2023), or an autism diagnosis, whichever came first. The study was reported using the STROBE reporting guideline.

Hazard ratios and 95% CIs were calculated using a Cox proportional hazards model. Models were adjusted for other analgesics, and all covariates are listed in the **Figure**. The proportional hazards assumption was fulfilled based on evaluation of Schoenfeld residuals. Missing values were imputed in 2 datasets, using the mice package for R (eMethods in Supplement 1).[4] A sibling analysis compared sibling groups with discordant acetaminophen exposure during pregnancy, identified by common mother, using a clustering term on the maternal ID. The study was approved by the Danish Data Protection Agency. Ethics approval is not required for register studies in Denmark. All analyses were conducted in R, version 4.5.1 (R core team). A 2-sided $P < .05$ was considered significant.

Results | Of 1 506 155 included children, 31 098 (2.1%) were exposed to acetaminophen during pregnancy, of whom 554 (1.8%) were later diagnosed with autism, as compared with 44 667 of 1 475 057 (3.0%) in the unexposed group. Women prescribed acetaminophen during pregnancy were generally older (median [IQR] age, 31.2 [28.1-34.7] years vs 30.5 [27.4-33.9] years); had higher parity, higher body mass index, and more comorbidities; and used more prescription medicine than unexposed women (**Table**). After adjusting for confounders and other analgesics, the adjusted hazard ratio of autism after exposure to acetaminophen in utero was 1.03 (95% CI, 0.95-1.12) in the population analysis and 1.09 (95% CI, 0.91-1.27) in the sibling analysis (Figure).

Similarly, there was no evidence of a significant association between acetaminophen exposure during pregnancy and development of autism in stratified analyses of dose response patterns, exposure during different trimesters, and analyses restricted to pregnancies after 2013.

Discussion | In this nationwide cohort study, acetaminophen exposure during pregnancy was not significantly associated with an excess risk of autism. Given the upper limits of the CI, a relatively higher risk of more than 12% for autism is unlikely to be associated with acetaminophen exposure. These results are consistent and corroborate results from a 2024 Swedish study.[2]

Limitations include possible misclassification of the outcome, although the positive predictive value of an autism diagnosis has been found to be 94%.[5] Individual-level information about over-the-counter medication was

Table. Baseline Characteristics of Children and Mothers

Characteristic	Acetaminophen exposure during pregnancy, No. (%)	
	Yes (n = 32 966)	No (n = 1 497 441)
Maternal characteristics at pregnancy onset		
Age, median (IQR), y	31.2 (28.1-34.7)	30.5 (27.4-33.9)
Age group, y		
<25	2653 (8.0)	177 945 (11.9)
25-29	10 459 (31.7)	497 313 (33.2)
30-34	11 993 (36.4)	538 464 (36.0)
35-39	6244 (18.9)	237 819 (15.9)
>40	1617 (4.9)	45 900 (3.1)
Year		
1997-1999	1144 (3.5)	235 685 (15.7)
2000-2002	843 (2.6)	189 867 (12.7)
2003-2005	1077 (3.3)	189 363 (12.6)
2006-2008	1196 (3.6)	188 324 (12.6)
2009-2011	1198 (3.6)	176 468 (11.8)
2012-2014	4730 (14.3)	162 980 (10.9)
2015-2017	7375 (22.4)	129 448 (8.6)
2018-2020	10 006 (30.4)	156 033 (10.4)
2021-2022	5397 (16.4)	69 273 (4.6)
Highest attained education		
Below secondary school	6551 (19.9)	267 157 (17.8)
Upper secondary school or higher	13 336 (40.5)	631 401 (42.2)
Bachelor's degree or higher	12 641 (38.3)	573 478 (38.3)
Unknown	438 (1.3)	25 405 (1.7)
Personal income		
First quartile	9680 (29.4)	369 913 (24.7)
Second quartile	9030 (27.4)	370 618 (24.8)
Third quartile	7350 (22.3)	372 288 (24.9)
Fourth quartile	6670 (20.2)	372 970 (24.9)
Unknown	236 (0.7)	11 652 (0.8)
Born in Denmark		
Yes	26 658 (80.9)	1 256 618 (83.9)
No	6263 (19.0)	238 198 (15.9)
Unknown	45 (0.1)	2625 (0.2)
Urban residency[a]	12 574 (38.1)	670 319 (44.8)
Cohabitation		
Yes	22 536 (68.4)	992 723 (66.3)
No	10 079 (30.6)	480 583 (32.1)
Unknown	351 (1.1)	24 135 (1.6)
Parity		
Nulliparous	12 233 (37.1)	681 483 (45.5)
1	12 617 (38.3)	551 797 (36.8)
2	5412 (16.4)	197 003 (13.2)
≥3	2704 (8.2)	67 158 (4.5)
Pregnancy BMI		
<18.5	806 (2.4)	44 827 (3.0)
18.5-29.9	22 655 (68.7)	921 816 (61.6)

(continued)

Table. Baseline Characteristics of Children and Mothers (continued)

Characteristic	Acetaminophen exposure during pregnancy, No. (%)	
	Yes (n = 32 966)	No (n = 1 497 441)
30-34.9	4385 (13.3)	93 463 (6.2)
≥35	2948 (8.9)	49 100 (3.3)
Unknown	2172 (6.6)	388 235 (25.9)
Smoking status		
Yes	4259 (12.9)	197 597 (13.2)
No	27 588 (83.7)	1 190 664 (79.5)
Unknown	1119 (3.4)	109 180 (7.3)
Comorbidity[b]		
Asthma	599 (1.8)	13 939 (0.9)
Chronic pain	1857 (5.6)	20 215 (1.3)
Diabetes	1992 (6.0)	44 628 (3.0)
Diagnosed headache	803 (2.4)	10 847 (0.7)
Fever	279 (0.8)	5259 (0.4)
Fibromyalgia	106 (0.3)	336 (0.0)
Gastric bypass	417 (1.3)	2934 (0.2)
Infection	3831 (11.6)	132 956 (8.9)
Migraine	669 (2.0)	9001 (0.6)
Neuropathic pain	61 (0.2)	583 (<0.1)
Obesity	3555 (2.4)	58 102 (3.9)
Rheumatoid arthritis	166 (0.5)	1493 (0.1)
Any psychiatric diagnosis[b]	2150 (6.5)	59 154 (4.0)
Pharmacotherapy[c]		
Aspirin	1381 (4.2)	13 579 (0.9)
Antidepressant medications	3788 (11.5)	65 933 (4.4)
Antimigraine medications	2650 (8.0)	34 183 (2.3)
Antiseizure medications	644 (2.0)	10 085 (0.7)
Nonaspirin NSAIDS	14 795 (44.9)	223 779 (14.9)
Psycholeptic medications	2755 (8.4)	48 052 (3.2)
Opioid use	5171 (15.7)	49 584 (3.3)
Hospital visits in the year before pregnancy		
0	12 436 (37.7)	832 845 (55.6)
1	6025 (18.3)	286 423 (19.1)
2	4053 (12.3)	162 554 (10.9)
≥3	10 452 (31.7)	215 619 (14.4)
Antenatal visits during pregnancy		
0-2	5384 (16.3)	575 033 (38.4)
3-6	11 171 (33.9)	665 653 (44.5)
≥7	16 411 (49.8)	256 755 (17.1)
Prescriptions filled in the year before pregnancy		
0-4	7853 (23.8)	636 043 (42.5)
5-9	5864 (17.8)	323 121 (21.6)
≥10	19 249 (58.4)	538 277 (35.9)
Listed father characteristics at pregnancy onset		
Age, median (IQR), y	33.2 (29.7-37.4)	32.7 (29.3-36.5)
Any psychiatric diagnosis[b]		
No	27 097 (82.2)	1 351 210 (90.2)
Yes	4599 (14.0)	115 389 (7.7)
Unknown	1270 (3.9)	30 842 (2.1)
Maternal sibling characteristics at pregnancy onset		
Any psychiatric diagnosis[b]	1665 (5.1)	34 848 (2.3)
Child characteristics at birth		
Female sex	16 177 (49.1)	728 981 (48.7)
Season of birth		
Winter	7549 (22.9)	350 499 (23.4)
Spring	8036 (24.4)	373 126 (24.9)
Summer	8893 (27.0)	399 929 (26.7)
Fall	8488 (25.7)	373 887 (25.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAID, nonsteroidal anti-inflammatory drug.

[a] Living in urban municipality as characterized by Statistics Denmark.

[b] From 5 years before pregnancy to the calculated day of pregnancy start.

[c] From 1 year before pregnancy start to day of delivery.

unavailable; thus, the true exposure level among those with low-level exposure was likely underestimated. However, previous simulation studies of over-the-counter drugs have shown such bias to be largely negligible.[6] In conclusion, acetaminophen exposure during pregnancy was not associated with an increased risk of autism.

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