

ORIGINAL ARTICLE

Prenatal fever and autism risk

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Some studies suggest that prenatal infection increases risk of autism spectrum disorders (ASDs). This study was undertaken in a prospective cohort in Norway to examine whether we could find evidence to support an association of the prenatal occurrence of fever, a common manifestation of infection, with ASD risk. Prospective questionnaires provided maternal exposure data; case status was established from clinical assessments and registry linkages. In a large, prospectively ascertained cohort of pregnant mothers and their offspring, we examined infants born ≥ 32 weeks for associations between fever exposure in each trimester and ASD risk using logistic regression. Maternal exposure to second-trimester fever was associated with increased ASD risk, adjusting for presence of fever in other trimesters and confounders (adjusted odds ratio (aOR), 1.40; 95% confidence interval, 1.09–1.79), with a similar, but nonsignificant, point estimate in the first trimester. Risk increased markedly with exposure to three or more fever episodes after 12 weeks' gestation (aOR, 3.12; 1.28–7.63). ASD risk appears to increase with maternal fever, particularly in the second trimester. Risk magnified dose dependently with exposure to multiple fevers after 12 weeks' gestation. Our findings support a role for gestational maternal infection and innate immune responses to infection in the pathogenesis of at least some cases of ASD.

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INTRODUCTION

Autism spectrum disorders (ASD) are associated with prenatal exposure to a wide range of infectious agents.^{1–4} The diversity of potential infectious triggers suggests that host factors, such as activation of maternal immunity, may have a role in the genesis of neurodevelopmental consequences.⁵ Consistent with this concept, some studies have demonstrated higher levels of inflammatory cytokines in amniotic fluid⁶ or maternal mid-gestational serum.⁷ Maternal responses to infection, therefore, including the timing of fever episodes relative to fetal brain development and measures to mitigate fever, may influence risk of ASD.^{8,9}

Maternal fever is common in pregnancy. Twenty percent of pregnant US women report one or more fever episodes.¹⁰ Primarily (though not exclusively) first-trimester fever episodes have been linked to severe brain damage and structural anomalies.^{9,11} Although first-trimester exposure may also influence subsequent more subtle disruptions of brain development, some investigators have hypothesized that exposure to fever later in pregnancy should be more strongly related to more subtle disruptions—including effects on neuronal migration,¹² proliferation^{12,13} and myelination¹⁴—such as those reported in some studies of ASD.^{15–19} Few studies have examined the association of prenatal fever, *per se*, with autism outcomes, as opposed to effects of specific types of maternal infection (for example, influenza). Fever was associated with a 1.4-fold increased risk of infantile autism in a prospective Danish cohort study wherein fever reporting was restricted to the first 32 weeks of gestation.²⁰ Fever persisting for 7 days or more was associated with a 1.6-fold increased risk for ASD and greater than threefold

increase in risk for infantile autism. A retrospective case-control study in the US found a twofold increased risk of ASD or another developmental disorder with prenatal fever; risk was lower in mothers treated with antipyretics.²¹ However, no prospective studies have examined risk after fever across all of pregnancy or in conjunction with antipyretic use. In addition, prior work has not examined the possibility that different classes of antipyretics may differentially influence fever risk through their distinct biological effects. These include acetaminophen, an antipyretic with minimal anti-inflammatory effects that is used by over 50% of women in both Scandinavia²² and the US²³ at least once during pregnancy that also affects oxidative stress,²⁴ endocrine²⁵ and cannabinoid receptor pathways,²⁶ and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID). Understanding the influence on ASD risk of exposure to multiple fever events, and of the timing of these episodes across pregnancy, is also incomplete. Here we report results from a study in a Norwegian birth cohort where questionnaires and capture of cases through a national registry allowed us to investigate associations between prenatal fever and ASD risk. We also examined the potential for antipyretics to modify risk.

MATERIALS AND METHODS

Study design and participants

The Norwegian Mother and Child Cohort Study (MoBa)²⁷ includes 114 500 children born in 1999–2009. ASD cases are identified through the Autism Birth Cohort (ABC) Study,²⁸ a case-cohort study nested within MoBa. Analyses reflect data collected through December 2014. Children from

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multiple births or with birth weight < 2500 grams or gestational age < 32 weeks (6.6%, Supplementary Figure S1) were excluded. Given questionnaire design, we focused on subjects with gestational ages ≥ 32 weeks to ensure that all women could report fever for at least the first 4 weeks of the third trimester. Low birth weight is associated with a multitude of pre- and postnatal risk factors; thus, we also excluded subjects with low birth weight.²⁹ This exclusion was also motivated by the nearly complete overlap in our study population of preterm and low birth weight status (887 subjects out of 892 with gestational age < 32 weeks had low birth weight, or 99.44%).

Studies were approved by the Regional Committee for Medical and Health Research Ethics for Southeastern Norway and the Columbia University Medical Center Institutional Review Board.

Case diagnoses

ASD cases were identified through MoBa screening (3, 5 and 7 years), referrals and annual linkages to the Norwegian Patient Register (NPR).³⁰ Through 2012, potential cases were invited for assessment by research clinicians using standardized diagnostic instruments.^{31,32} Best-estimate ASD diagnoses were assigned using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR)³³ criteria. ASD cases among NPR-identified children not evaluated at the ABC Study Clinic were those assigned *International Classification of Diseases, Tenth Revision* (ICD-10) F84 diagnoses (Supplementary Methods).³⁴ NPR ASD diagnoses have high validity: 58 out of 60 children with NPR ASD diagnoses met DSM-IV-TR ASD criteria at later ABC clinic assessment (positive predictive value: 96.7%, 95% confidence interval (CI), 87.5–99.4%; false positive rate: 3.3%, 95% CI, 0.6–12.5%).³⁰

To explore the possibility that prenatal fever effects may be specific for certain ASD phenotypes, cases were classified as ASD with or ASD without mental retardation/intellectual disability (ID). Comorbidity with ID was based on intelligence quotient (IQ) data from ABC clinic assessments, as available (IQ < 70)¹¹ or NPR ICD-10 data consistent with a diagnosis of an ID. ASD cases without an ABC clinic IQ score < 70 and who also had not received an NPR ID ICD-10 code were assigned to the ASD without ID group (Supplementary Methods).

Exposure data

Exposure timing. Data on prenatal fever and antipyretic use were obtained from questionnaires completed around gestational weeks 17 and 30, and 6 months postpartum. Mothers reported fever and medication use in 4-week intervals through 13+ and 29+ weeks' gestation, respectively, on the 17- and 30-week questionnaires and from gestational week 30 through parturition on the 6-month postnatal questionnaire (Supplementary Table S1). An interval was considered positive for fever or antipyretic exposure if one or more exposures occurred during that interval. Trimesters were designated by gestational weeks as: first, 0–12 weeks; second, 13–28 weeks; and third, 29 weeks through birth. Overlap in timing across questionnaires was resolved as described in Supplementary Methods. Main analyses included women with at least one completed questionnaire containing prenatal data.

Fever and antipyretic exposures. Questionnaire items solicited data from mothers regarding the presence of specific conditions, including fever, along with their timing, as well as the names of medications used for fever, and the timing of that medication use. Response options for presence and timing of fever episodes and medication use varied across the three questionnaires (Supplementary Table S1). To enhance cross-questionnaire comparability, we collapsed data for 17-week questionnaire items—fever with rash and fever > 38.5 °C—into one category. Questionnaire-specific procedures for counting fever episodes and assigning their timing to specific trimesters are detailed further in Supplementary Methods.

We assessed use of any acetaminophen- or ibuprofen-containing medications for the reported indication of fever. Methods for addressing report of multiple medications and timing of medication use are described in Supplementary Methods, along with secondary analysis procedures for examining risk modification by antipyretic use (acetaminophen or the NSAID, ibuprofen).

Supplementary Table S2 summarizes methods for resolving discrepancies in reported fever timing and in the timing of antipyretic use in relationship to fever episodes, along with the number of affected subjects. Inconsistency in reported fever timing took on three major forms. First, some mothers indicated timing of the medication taken for fever and the

name of the antipyretic, but failed to report the specific timing of fever episodes for which they reported taking an antipyretic. In these instances, maternally provided medication timing defined the fever timing. Second, when timing of fever episodes was provided but timing of the selected fever-associated antipyretics (acetaminophen, ibuprofen) was not, maternally provided fever timing defined the timing of medication use. Third, missing fever timings were imputed for the high-exposure subset of mothers who endorsed the 'fever more than three times' item on the 30-week questionnaire but failed to provide complete timing for all reported fever episodes (Supplementary Methods). Supplementary Table S2 shows that the number of affected women, and thus the scope of the problem, was small.

Potential confounders

We evaluated variables that might influence associations between primary maternal exposures (fever in all three trimesters) and ASD risk: maternal age; smoking and parity; parental education; birth month; and birth year (Supplementary Methods and Supplementary Tables S3A and S3B). Potential confounders demonstrating a significant association ($P < 0.05$) with both the primary exposure (fever in any of the three trimesters) and the outcome (ASD) were retained in our analyses.

Statistical analysis

Main analyses. Crude and adjusted odds ratios (ORs and aORs, respectively) of ASD risk in association with maternal fever in each trimester, and for any time during pregnancy, and their associated 95% CIs were estimated by logistic regression. We first examined associations between fever and risk by fitting separate models for each time period, using all subjects responding to at least one questionnaire containing prenatal data. Analyses examining ASD risk in association with fever at any time during pregnancy included subjects responding to all questionnaires.

Subsequent analyses restricted the study sample to mothers who responded to all questionnaires addressing prenatal fever. We used three adjusted models: (1) Adjusted Model 1 (aOR1), adjusting for fever exposure in either/both of the other trimesters; (2) Adjusted Model 2 (aOR2), adjusting for all other selected confounders; and (3) Adjusted Model 3 (aOR3), adjusting for both fever in other trimesters and all confounders. This same population of respondents was used for stratified analyses comparing ASD risk in association with prenatal fever within the subgroup of ASD cases with comorbid ID and within the ASD subset without such comorbidity.

Dose–response analyses. The cumulative effect of maternal fever was estimated by counting numbers of individual time intervals wherein mothers reported fever episodes. We categorized fever exposure into three levels (0 (referent), 1–2, ≥ 3 episodes), with exposure periods of any time during pregnancy or > 12 weeks of gestation. Using logistic regression, we estimated ORs and aORs for both exposure periods.

Fever-associated risk stratified on use of antipyretics. In exploratory analyses, we examined whether the risk effect of fever exposure was modified by acetaminophen use. Mothers reporting fever in each trimester were divided into two subgroups based on reported use or nonuse of acetaminophen specifically for fever. Crude and adjusted ORs (aOR1, aOR2 and aOR3, as above) of ASD for each subgroup (compared with the no-fever referent) were estimated by logistic regression. We performed similar secondary analyses substituting ibuprofen for acetaminophen to further examine antipyretic modification of fever-associated ASD risk. Although both agents reduce fever, as an NSAID, ibuprofen has anti-inflammatory potential that acetaminophen does not; if, as prior studies have suggested, fever-related activation of maternal immunity mediates neurodevelopmental consequences among offspring, use of ibuprofen as an antipyretic might be anticipated to be associated with greater reduction in fever-associated ASD risk than acetaminophen (Supplementary Methods).

Supplementary and sensitivity analyses. Influences of confounders on ORs of ASD were examined individually and sequentially (Supplementary Methods and Supplementary Tables S4A and S4B).

To address possible influences relating to trends across birth years in ASD prevalence (incomplete ascertainment of cases in later birth years, given follow-up in some subjects only through age 5) and maternal fever report, we performed an analysis of fever effects stratified by early (1999–2004) and late (2005–2009) birth year periods.

We also examined fetal sex effects. Trophoblasts from male placentae are reported to respond to infection-related signals with proinflammatory cytokine production,^{35,36} consistent with studies suggesting increased risk of preterm birth in males, particularly in the context of infection.^{36–38} Because

of low numbers of girls with ASD, we pursued potential influences of sex through sensitivity analyses restricted to boys (Supplementary Methods).

Other sensitivity analyses addressed potential biases relating to gestational age at birth and fever timing imputation. Preterm births

Table 1. Characteristics of mothers and children in study population, by fever exposure status and diagnosis

Subject characteristics	All subjects (N = 95 754)	Any fever (N = 15 701)	No fever (N = 80 053)	ASD (N = 583)	Non-case (N = 95 171)	P-value ^a
<i>Parental characteristics</i>						
Maternal age (years), N (%)						< 0.0001
< 20	971 (1.0)	180 (1.1)	791 (1.0)	10 (1.7)	961 (1.0)	
20–24	9691 (10.1)	1605 (10.2)	8086 (10.1)	94 (16.1)	9597 (10.1)	
25–29	31 597 (33.0)	5174 (33.0)	26 423 (33.0)	191 (32.8)	31 406 (33.0)	
30–34	36 893 (38.5)	6090 (38.8)	30 803 (38.5)	188 (32.2)	36 705 (38.6)	
35–39	14 701 (15.4)	2356 (15.0)	12345 (15.4)	91 (15.6)	14 610 (15.4)	
≥ 40	1901 (2.0)	296 (1.9)	1605 (2.0)	9 (1.5)	1892 (2.0)	
Parental education, N (%)						< 0.0001
< 12 years	3261 (3.4)	444 (2.8)	2817 (3.5)	41 (7.0)	3220 (3.4)	
12 years	21 862 (22.8)	3325 (21.2)	18 537 (23.2)	171 (29.3)	21 691 (22.8)	
13–16 years	36 168 (37.8)	5964 (38.0)	30 204 (37.7)	203 (34.8)	35 965 (37.8)	
≥ 17 years	33 033 (34.5)	5737 (36.5)	27 266 (34.1)	160 (27.4)	32 843 (34.5)	
Missing ^b	1460 (1.5)	231 (1.5)	1229 (1.5)	8 (1.4)	1452 (1.5)	
Maternal smoking, N (%)						< 0.0001
Yes	8965 (9.4)	1490 (9.5)	7 475 (9.3)	89 (15.3)	8876 (9.3)	
No	68 929 (72.0)	11 843 (75.4)	57 086 (71.3)	385 (66.0)	68 544 (72.0)	
Missing ^b	17 860 (18.7)	2368 (15.1)	15 492 (19.4)	109 (18.7)	17 751 (18.7)	
Parity, N (%)						< 0.0001
0	42 412 (44.3)	6377 (40.6)	36 035 (45.0)	319 (54.7)	42 093 (44.2)	
≥ 1	53 342 (55.7)	9324 (59.4)	44 018 (55.0)	264 (45.3)	53 078 (55.8)	
Mode of delivery, N (%)						0.065
Spontaneous	77 472 (80.9)	12 604 (80.3)	64 868 (81.0)	450 (77.2)	77 022 (80.9)	
Induced	12 339 (12.9)	2085 (13.3)	10 254 (12.8)	92 (15.8)	12 247 (12.9)	
Cesarean section	5943 (6.2)	1012 (6.4)	4931 (6.2)	41 (7.0)	5902 (6.2)	
<i>Child characteristics</i>						
Sex, N (%)						< 0.0001
Male	49 197 (51.4)	8030 (51.1)	41 167 (51.4)	487 (83.5)	48 710 (51.2)	
Female	46 557 (48.6)	7671 (48.9)	38 886 (48.6)	96 (16.5)	46 461 (48.8)	
Gestational age, N (%)						0.002
32–36 weeks	2552 (2.7)	431 (2.7)	2121 (2.6)	23 (3.9)	2529 (2.7)	
37–38 weeks	15 301 (16.0)	2602 (16.6)	12 699 (15.9)	98 (16.8)	15 203 (16.0)	
39–41 weeks	70 202 (73.3)	11 420 (72.7)	58 782 (73.4)	395 (67.8)	69 807 (73.3)	
≥ 42 weeks	7 699 (8.0)	1248 (7.9)	6451 (8.1)	67 (11.5)	7632 (8.0)	
Birth weight (g), mean (s.d.)						0.009
2500–2999	8 378 (8.7)	1323 (8.4)	7055 (8.8)	68 (11.7)	8310 (8.7)	
3000–3499	28 519 (29.8)	4703 (30.0)	23 816 (29.8)	155 (26.6)	28 364 (29.8)	
3500–3999	36 779 (38.4)	6025 (38.4)	30 754 (38.4)	205 (35.2)	36 574 (38.4)	
4000–4499	17 648 (18.4)	2935 (18.7)	14 713 (18.4)	119 (20.4)	17 529 (18.4)	
≥ 4500	4430 (4.6)	715 (4.6)	3715 (4.6)	36 (6.2)	4394 (4.6)	
Birth year, N (%)						< 0.0001
1999	35 (0.0)	0 (0.0)	35 (0.0)	1 (0.2)	34 (0.0)	
2000	1859 (1.9)	261 (1.7)	1598 (2.0)	17 (2.9)	1842 (1.9)	
2001	3670 (3.8)	597 (3.8)	3073 (3.8)	38 (6.5)	3632 (3.8)	
2002	7713 (8.1)	1159 (7.4)	6554 (8.2)	87 (14.9)	7626 (8.0)	
2003	11 220 (11.7)	1640 (10.4)	9580 (12.0)	110 (18.9)	11 110 (11.7)	
2004	12 091 (12.6)	1992 (12.7)	10 099 (12.6)	83 (14.2)	12 008 (12.6)	
2005	14 024 (14.6)	2373 (15.1)	11 651 (14.6)	86 (14.8)	13 938 (14.6)	
2006	15 707 (16.4)	2509 (16.0)	13 198 (16.5)	60 (10.3)	15 647 (16.4)	
2007	14 387 (15.0)	2654 (16.9)	11 733 (14.7)	53 (9.1)	14 334 (15.1)	
2008	12 001 (12.5)	1958 (12.5)	10 043 (12.5)	41 (7.0)	11 960 (12.6)	
2009	3047 (3.2)	558 (3.6)	2489 (3.1)	7 (1.2)	3040 (3.2)	
Birth month, N (%)						0.156
January	7979 (8.3)	1000 (6.4)	6979 (8.7)	48 (8.2)	7931 (8.3)	
February	7661 (8.0)	1105 (7.0)	6556 (8.2)	51 (8.7)	7610 (8.0)	
March	8610 (9.0)	1446 (9.2)	7164 (8.9)	52 (10.7)	8558 (9.0)	
April	8642 (9.0)	1611 (10.3)	7031 (8.8)	62 (10.6)	8580 (9.0)	
May	8567 (8.9)	1820 (11.6)	6747 (8.4)	47 (8.1)	8520 (9.0)	
June	8024 (8.4)	1750 (11.1)	6274 (7.8)	43 (7.4)	7981 (8.4)	
July	8800 (9.2)	1666 (10.6)	7134 (8.9)	39 (6.7)	8761 (9.2)	
August	8386 (8.8)	1488 (9.5)	6898 (8.6)	37 (6.3)	8349 (8.8)	
September	8037 (8.4)	1211 (7.7)	6826 (8.5)	53 (9.1)	7984 (8.4)	
October	7700 (8.0)	980 (6.2)	6720 (8.4)	55 (9.4)	7645 (8.0)	
November	6763 (7.1)	829 (5.3)	5934 (7.4)	40 (6.9)	6723 (7.1)	
December	6585 (6.9)	795 (5.1)	5790 (7.2)	47 (8.1)	6538 (6.9)	
ASD, N (%)	583 (0.6)	113 (0.7)	470 (0.6)			
Non-case, N (%)	95 171 (99.4)	15 588 (99.3)	79 583 (99.4)			

Abbreviation: ASD, autism spectrum disorder. Key: g, grams. ^aP-values are those associated with χ^2 -tests comparing prevalence of each characteristic in the ASD and non-case groups. ^bMissing data imputed for subsequent analyses (Supplementary Methods).

(32–36 weeks) might have obscured the ability to assess the impact of fever and antipyretic events in later pregnancy; thus, we restricted to term births (that is, gestational age >36 weeks) in sensitivity analyses. In an additional sensitivity analysis, we excluded mothers who reported high levels of fever exposure on the 30-week questionnaire (>3 fever episodes) without specifying the timing of those episodes (Supplementary Methods).

RESULTS

Study cohort

The study sample included 95 754 children (51.4% boys) after exclusions (Supplementary Figure S1). Mean age was 9.4 years (s.d., 2.2 years; range, 5.6–15.2 years) by end of follow-up (31 December, 2014).

Table 1 shows characteristics of mothers and their pregnancies vis-à-vis prenatal fever and offspring diagnosis (ASD, non-case). The mothers of 15 701 children (16.4%) reported fever in one or more 4-week intervals throughout pregnancy. Women reporting fever were more likely to have offspring at earlier gestational ages (<39 weeks), in later cohort birth years (≥2005) and in March through August. Fever exposures were more prevalent, and ASD less prevalent, in more recent birth years (Table 1; Spearman's rank correlation coefficient: both $P < 0.0001$).

Autism spectrum disorder

We identified 583 cases of ASD (0.6%) through 2014. Males were overrepresented fivefold (Table 1). Mothers of ASD children were younger and less educated than non-case mothers and more likely to smoke and be first-time mothers. ASD offspring identified through end of follow-up were also more often born in earlier cohort years (<2006; higher prevalence of children not yet old enough to be diagnosed).

Main models

Table 2 shows associations between prenatal fever exposure and ASD risk for any time in pregnancy and by trimester. Women reporting fever at any time during pregnancy had increased odds of ASD in both unadjusted and adjusted models. Examining by trimester, offspring of mothers with second-trimester fever had a 1.4-fold increased risk in adjusted models (aOR, 1.40; 1.11–1.77). The first trimester showed similar, but nonsignificant, point estimates (aOR, 1.34; 0.89–2.02).

The presence of fever in the first trimester was associated with fever episodes in other trimesters. Second-trimester fever was also associated with fever in the third trimester (Pearson's χ^2 -test: all associations, $P < 0.0001$). To permit analyses that could adjust the fever-associated risk found in one trimester by accounting for fever episodes in other trimesters, we restricted to mothers

completing all questionnaires containing prenatal data. As with results using all questionnaire respondents, offspring of mothers with second-trimester fever had increased risk in the crude model (OR, 1.33; 1.04–1.70; Table 3). Adjustment for fever in other trimesters had little effect. Fever-associated risk in second trimester was similar when adjusting for confounders either alone or in combination with presence of fever in other trimesters (Table 3). The first trimester showed similar but nonsignificant point estimates.

Fever-associated risk in ASD subsets with and without ID. As compared with non-cases, ASD cases with comorbid ID showed a tendency toward increased fever-associated risk in fully adjusted models both with exposure in the first (aOR3, 2.28; 0.91–5.75) and the second trimesters (aOR3, 1.64; 0.89–3.03). For ASD cases without ID, fever-associated risk was modestly but significantly increased (1.36-fold) and restricted to second-trimester exposures (Supplementary Table S5).

Dose-response models. With exposure at any time during pregnancy, risk increased 1.3-fold with one to two fever episodes (aOR, 1.31; 1.04–1.64) and more than twofold (albeit not significant) with three or more episodes (aOR, 2.15; 0.95–4.84). After gestational week 12, risk increased with higher frequency of exposure (one to two episodes: aOR, 1.30; 1.02–1.66; three or more episodes: aOR, 3.12; 1.28–7.63; Table 4).

Fever-associated risk stratified on use of antipyretics. In secondary stratified analyses, we examined whether use of acetaminophen for fever modified fever-associated ASD risk. Risk tended to be lower within each trimester in febrile women who took acetaminophen for fever than in febrile women who did not (compared to the referent group of afebrile women; Supplementary Table S6A). The risk was similar both for women febrile in the second trimester who did and who did not specifically report taking acetaminophen for fever.

Additional secondary stratified analyses examined the potential for modification of fever-associated risk through the use of the NSAID, ibuprofen, given that, unlike acetaminophen, it has anti-inflammatory properties in addition to its antipyretic effects. These analyses were compromised by overall small numbers and cells with zero values. Among febrile women whose offspring were later diagnosed with ASD, none had taken ibuprofen for fever in any trimester (Supplementary Table S6B).

Supplementary and sensitivity analyses. Accounting for confounders slightly increased ORs in main models. Birth year, introduced either individually or sequentially into the models, had the most

Table 2. Association between maternal fever and risk of ASD in offspring, at any time during pregnancy and by trimester

Exposure period	ASD fever-exposed N (%)	Non-case fever-exposed N (%)	Crude model				Adjusted model			
			OR	95% CI	P-value		aOR ^a	95% CI	P-value	
Any time during pregnancy ^b (N = 79 109)	98 (20.68)	13 509 (17.18)	1.26	1.01	1.57	0.045	1.34	1.07	1.67	0.011
First trimester ^c (N = 95 115)	24 (4.14)	3069 (3.25)	1.29	0.85	1.94	0.229	1.34	0.89	2.02	0.162
Second trimester ^d (N = 87 648)	85 (16.04)	11 067 (12.70)	1.31	1.04	1.66	0.022	1.40	1.11	1.77	0.005
Third trimester ^e (N = 79 748)	17 (3.56)	2627 (3.31)	1.08	0.66	1.75	0.761	1.15	0.70	1.87	0.583

Abbreviations: aOR, adjusted odds ratio; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio. Key: bold text represents significant findings, $P < 0.05$. ^aAdjusted for: maternal age, smoking and parity; parental education and birth year. ^bRespondents to all three questionnaires containing prenatal fever data: ASD, N = 474; non-case, N = 78 635. ^cAll respondents to 17-week prenatal questionnaire: ASD, N = 580; non-case, N = 94 535. ^dAll respondents to both the 17- and 30-week prenatal questionnaires: ASD, N = 530; non-case, N = 87 118. ^eAll respondents to both the 30-week prenatal and the 6-month postnatal questionnaires: ASD, N = 477; non-case, N = 79 271.

Exposure period	ASD fever-exposed N (%)	Non-case fever-exposed N (%)
0-10 days	10 (100)	10 (100)
11-20 days	10 (100)	10 (100)
21-30 days	10 (100)	10 (100)
31-40 days	10 (100)	10 (100)
41-50 days	10 (100)	10 (100)
51-60 days	10 (100)	10 (100)
61-70 days	10 (100)	10 (100)
71-80 days	10 (100)	10 (100)
81-90 days	10 (100)	10 (100)
91-100 days	10 (100)	10 (100)
101-110 days	10 (100)	10 (100)
111-120 days	10 (100)	10 (100)
121-130 days	10 (100)	10 (100)
131-140 days	10 (100)	10 (100)
141-150 days	10 (100)	10 (100)
151-160 days	10 (100)	10 (100)
161-170 days	10 (100)	10 (100)
171-180 days	10 (100)	10 (100)
181-190 days	10 (100)	10 (100)
191-200 days	10 (100)	10 (100)
201-210 days	10 (100)	10 (100)
211-220 days	10 (100)	10 (100)
221-230 days	10 (100)	10 (100)
231-240 days	10 (100)	10 (100)
241-250 days	10 (100)	10 (100)
251-260 days	10 (100)	10 (100)
261-270 days	10 (100)	10 (100)
271-280 days	10 (100)	10 (100)
281-290 days	10 (100)	10 (100)
291-300 days	10 (100)	10 (100)
301-310 days	10 (100)	10 (100)
311-320 days	10 (100)	10 (100)
321-330 days	10 (100)	10 (100)
331-340 days	10 (100)	10 (100)
341-350 days	10 (100)	10 (100)
351-360 days	10 (100)	10 (100)
361-370 days	10 (100)	10 (100)
371-380 days	10 (100)	10 (100)
381-390 days	10 (100)	10 (100)
391-400 days	10 (100)	10 (100)
401-410 days	10 (100)	10 (100)
411-420 days	10 (100)	10 (100)
421-430 days	10 (100)	10 (100)
431-440 days	10 (100)	10 (100)
441-450 days	10 (100)	10 (100)
451-460 days	10 (100)	10 (100)
461-470 days	10 (100)	10 (100)
471-480 days	10 (100)	10 (100)
481-490 days	10 (100)	10 (100)
491-500 days	10 (100)	10 (100)
501-510 days	10 (100)	10 (100)
511-520 days	10 (100)	10 (100)
521-530 days	10 (100)	10 (100)
531-540 days	10 (100)	10 (100)
541-550 days	10 (100)	10 (100)
551-560 days	10 (100)	10 (100)
561-570 days	10 (100)	10 (100)
571-580 days	10 (100)	10 (100)
581-590 days	10 (100)	10 (100)
591-600 days	10 (100)	10 (100)
601-610 days	10 (100)	10 (100)
611-620 days	10 (100)	10 (100)
621-630 days	10 (100)	10 (100)
631-640 days	10 (100)	10 (100)
641-650 days	10 (100)	10 (100)
651-660 days	10 (100)	10 (100)
661-670 days	10 (100)	10 (100)
671-680 days	10 (100)	10 (100)
681-690 days	10 (100)	10 (100)
691-700 days	10 (100)	10 (100)
701-710 days	10 (100)	10 (100)
711-720 days	10 (100)	10 (100)
721-730 days	10 (100)	10 (100)
731-740 days	10 (100)	10 (100)
741-750 days	10 (100)	10 (100)
751-760 days	10 (100)	10 (100)
761-770 days	10 (100)	10 (100)
771-780 days	10 (100)	10 (100)
781-790 days	10 (100)	10 (100)
791-800 days	10 (100)	10 (100)
801-810 days	10 (100)	10 (100)
811-820 days	10 (100)	10 (100)
821-830 days	10 (100)	10 (100)
831-840 days	10 (100)	10 (100)
841-850 days	10 (100)	10 (100)
851-860 days	10 (100)	10 (100)
861-870 days	10 (100)	10 (100)
871-880 days	10 (100)	10 (100)
881-890 days	10 (100)	10 (100)
891-900 days	10 (100)	10 (100)
901		

Abbreviations: aOR, adjusted odds ratio; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio. Key: bold text represents significant findings, $p < 0.05$. ^aASD, $N = 474$; non-case, $N = 78\ 635$. ^baOR1: adjusted for presence of fever in the other trimesters (Adjusted Model 1). ^caOR2: adjusted for maternal age, smoking and parity; parental education; and birth year (Adjusted Model 2). ^daOR3: adjusted for presence of fever in the other trimesters and confounder variables (maternal age, smoking and parity; parental education; and birth year) (Adjusted Model 3).

For the remaining sensitivity analyses, we found minimal differences in ORs (Supplementary Materials and Supplementary results).

The strengths of our study are its basis in a large, prospective, population-based birth cohort with exposure data collected in 4-week intervals and linkage to a patient registry for case ascertainment. Maternal self-reporting and differences across the three questionnaires may contribute to some exposure misclassification; however, differential reporting is minimized by our study design, as fever reporting precedes the diagnosis of autism. Maternal self-report may also detect fevers that healthcare records might miss. In addition, the overall rate of maternally reported fever in our cohort across pregnancy (16.4%) was similar to that reported in a retrospective study in the US (20.5%) for any fever with infection during pregnancy.¹⁰

Our findings complement prior literature on prenatal fever and ASD risk.^{20,21} Prospective examination of fever exposures through birth revealed that fever-associated risk, most prominent in second trimester, was not influenced by the presence of fever in the other two trimesters. Similar patterns pertained for the first trimester but not the third. The only prior prospective study found an association with prolonged fever in the first and second trimesters but could not exclude a possible third-trimester effect, as no data were collected after 32 weeks' gestation.²⁰

ASD is associated with increased prevalence of autoimmune disorders in mothers and first-degree relatives.³⁹ Microglial

Table 4. Dose–response analysis of the association of maternal fever episodes and risk of ASD in offspring, any time during pregnancy and after 12 weeks of gestation to birth (*N* = 79 109)^a

Exposure period	Number of fever episodes	ASD N (%)	Non-case N (%)	Crude analysis				Adjusted analysis ^b			
				OR	95% CI		P-value	aOR	95% CI		P-value
Any time during pregnancy	1–2	92 (19.41)	12 976 (16.50)	1.23	0.98	1.54	0.078	1.31	1.04	1.64	0.023
	≥ 3	6 (1.27)	533 (0.68)	1.95	0.87	4.39	0.107	2.15	0.95	4.84	0.066
After 12 weeks	1–2	81 (17.09)	11 477 (14.60)	1.22	0.96	1.55	0.111	1.30	1.02	1.66	0.033
	≥ 3	5 (1.05)	303 (0.39)	2.84	1.17	6.92	0.021	3.12	1.28	7.63	0.013

Abbreviations: aOR, adjusted odds ratio; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio. Key: bold text represents significant findings, *P* < 0.05. ^aStudy population restricted to mothers responding to all three questionnaires (17-week prenatal, 30-week prenatal and 6-month postnatal); ASD, *N* = 474; non-case, *N* = 78 635. ^bAdjusted for: maternal age, smoking and parity; parental education; birth year.

activation^{40–43} and elevated brain chemokine levels⁴² are also reported. Animal models of maternal gestational infection or exposure to noninfectious mimics of bacterial (lipopolysaccharide)^{44,45} or viral (polyinosinic:polycytidylic acid)^{46,47} infection result in neurodevelopmental damage reminiscent of ASD. Evidence from these models suggests that maternal fever-associated immune responses mediate consequences in offspring^{47–52} and are abrogated by NSAIDs.⁴⁷ As in ASD, effects are most prominent in males.⁵³ Our results are consistent with these models in that fever is associated with increased risk, risk is accentuated in males and antipyretics tend to decrease fever-associated risk.

Questionnaire analysis did not indicate an association between risk and maternally reported symptoms of infection in individual organ systems that might implicate specific infectious agents. Nonetheless, we are testing the possibility that risk is associated with specific infectious agents through sequence-based and serological assays of samples collected mid-pregnancy and at birth from cases and controls. Linkage to patient register data, including hospitalization records, may also be used in future work to confirm timing and severity of illness episodes. Other evidence relating to severity of illness, such as degree of fever, may also prove informative; however, study questionnaires did not ask mothers to report this information for all time periods in pregnancy.

We acknowledge that our findings are limited by small numbers, particularly for first- and third-trimester exposures to fever and antipyretics; replication in other populations will also be critical before determining the implications of this work for management of fever in pregnancy. However, factors besides small numbers may have contributed to the wider CI we obtained for the first-trimester effect across all birth years, including shorter length of follow-up for ASD outcomes among younger cohort children, heterogeneity in the composition of the ASD group, or both. Our analyses stratified on earlier vs later birth year periods—despite even smaller numbers than in analyses including all birth years—provide evidence within the later birth year group of a more robust first-trimester effect (1.89-fold, with CIs excluding 1). Although the difference between aORs by birth year are not statistically significant in either trimester comparison, precision is lacking for testing such an interaction, and birth-year-dependent differences in the composition of the ASD group (DSM-IV-TR subsets) may have influenced our trimester-based results.

It is also important to bear in mind that causality cannot be definitively established through observational research. Nonetheless, we found consistently increased risk with higher levels of fever exposure. Opposing patterns of prevalence of ASD and fever exposure in our study sample—decreased prevalence of ASD but increased prevalence of fever exposure in later cohort years—may have biased results. However, our age-specific ASD prevalence

patterns are similar to those reported in other work in Norway⁵⁴ as well as other Nordic countries, where diagnoses are often registered at ages far exceeding those at which symptoms typically begin.⁵⁵ Follow-up studies may resolve whether ASD underascertainment in younger cohort children diminished effect sizes. Birth in later cohort years had a greater influence on ascertainment of higher-functioning cases, as these subsets are typically diagnosed at older ages, as well as more generally for younger members of the cohort, based on reduced length of follow-up. The case sample is thus perhaps weighted toward more severe cases. However, the rate of ID comorbidity did not vary substantially between early and late birth year periods (15.30 vs 13.99%, respectively). Although ID is not a simple proxy for ASD severity, our key finding—an increase in risk for ASD in association with maternal second-trimester fever—was restricted to ASD without ID, suggesting a degree of specificity. Prenatal fever increased risk in the ASD group with ID in the first but not the second trimester, consistent with previous work indicating a relationship of first-trimester fever exposure with severe structural defects of the central nervous and other organ systems.⁹ More conclusive analysis awaits detection of additional cases with extended follow-up.

Our findings support the hypothesis that fever and associated immune disturbances are implicated in a subset of ASD cases. Although acetaminophen was associated with a small decrease in risk in the context of fever, prior studies reporting ablation of fever-associated risk with use of a diverse range of medications with antipyretic properties, including NSAIDs as well as acetaminophen—along with our own limited data on ibuprofen—suggest that the choice of antipyretic warrants scrutiny. We have not addressed microbial causes of maternal fever and immune activation. Accordingly, future work should focus on identifying and preventing prenatal infections and inflammatory responses that may contribute to ASD pathogenesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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