Systematic Review and Meta-analyses: Fever in Pregnancy and Health Impacts in the Offspring

abstract

BACKGROUND AND OBJECTIVE: Fever during pregnancy has been suspected to harm the developing fetus. However, until now, no systematic analysis of the available evidence has been undertaken to assess the impact of maternal fever on health outcomes in the child. The goal of this study was to systematically review evidence from epidemiologic studies on adverse health outcomes of the offspring in relation to exposure to maternal fever during pregnancy.

METHODS: Systematic searches in PubMed, Web of Science, and the Cochrane Library were performed by using Medical Subject Headings, Boolean operators, and truncation, and references of references were reviewed. Cohort and case-control studies addressing health outcomes of prenatal fever exposure in humans were eligible for inclusion. Studies with no direct reference to fever, studies in selected populations (eg, preterm births), and studies published before 1990 were excluded.

RESULTS: The available literature supported an increased risk of adverse offspring health in association with fever during pregnancy. The strongest evidence was available for neural tube defects, congenital heart defects, and oral clefts, in which meta-analyses suggested between a 1.5- and nearly 3-fold increased risk with fever exposure in the first trimester. We did not find strong evidence of a dose–response relationship, but there was some evidence that antipyretic medications may have a protective effect when used in relation to febrile episodes.

CONCLUSIONS: We found substantial evidence to support the contention that maternal fever during pregnancy may negatively affect offspring health. The harmful effects seemed to cover both short- and longer-term health outcomes; however, for several outcomes, the evidence was insufficient to judge any association. *Pediatrics* 2014;133:e674–e688

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KEY WORDS

congenital abnormalities, developmental disabilities, fetal origins of disease, fever, hypersensitivity, meta-analysis, mortality, pregnancy, pregnant women, review, stillbirth

ABBREVIATIONS

CI—confidence interval
OR—odds ratio

Ms Dreier, Dr Andersen, and Dr Berg-Beckhoff were included in all parts of planning, analyzing, and writing the article; Ms Dreier had the idea for the research, extracted the data from the original studies, and conducted the initial analyses; Dr Andersen contributed in conceptualization and design of the review and the discussion; and Dr Berg-Beckhoff contributed in conceptualization and design of the review, supervised data extracting, analyses, and writing process. Ms Dreier drafted the initial manuscript that was jointly finalized by all authors and is the guarantor of the work.

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Fever has for many years been suspected to harm the developing fetus. Starting in the 1960s, evidence on the teratogenic effects of hyperthermia began to accumulate from animal studies.[1,2] Even short exposure to elevated maternal body temperature has been reported to lead to cell death, membrane disruptions, vascular disruptions, and placental infarction, all of which affect the risk of structural or functional defects in the offspring.[3,4] Studies in animal models provide evidence that prenatal exposure to elevated body temperature, as a marker of maternal fever, leads to increased prevalence of various adverse health outcomes in the offspring. These outcomes encompass both structural and functional defects, and they range from growth retardation, malformations, and fetal death to longer-term outcomes such as behavioral alterations and impaired cognitive functioning.[4,5] These findings have been consistent across a variety of animal species, including mice, rats, hamsters, guinea pigs, rabbits, sheep, pigs, and monkeys.[1] Despite the bulk of evidence supporting a link between exposure to maternal hyperthermia and adverse health outcomes in animal offspring, however, it remains unclear whether the experimental conditions under which these associations have been observed are applicable to conditions in which humans would naturally experience hyperthermia, and hence whether similar associations would be expected.

Maternal fever is common during pregnancy. In fact, ~1 in 5 women report having experienced fever on at least 1 occasion while being pregnant.[6–8] Observational epidemiologic studies have consequently been conducted to assess potential effects of exposure to maternal fever on fetal development and child health. Given the high proportion of pregnant women who are exposed to fever, even a small increase in the risk of these outcomes would make maternal fever a public health concern. We identified 1 previous publication that reviewed the literature on the impact of hyperthermia on neural tube defects.[9] However, up until now, no systematic analysis has been undertaken to assess the impact of maternal fever on a broader spectrum of health outcomes in human offspring. Thus, the aim of the present article was to systematically review existing evidence from epidemiologic studies on the associations between maternal fever during pregnancy and adverse health outcomes in the child.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[10] was used as a reporting guideline for this review.

Identification of Studies

To identify relevant studies for inclusion in the review, we applied a 2-stage search strategy. First, we systematically searched bibliographic databases (PubMed, Web of Science, and the Cochrane Library) by using Medical Subject Headings, Boolean operators, and truncation. We searched in titles, abstracts, topics, and key words depending on the database, and applied limits restricting the search to studies published in 1990 or later and to human studies. Search words included fever, febrile, hyperthermia, pyrexia, pregnancy, pregnant women, and gestation. Second, we used a snowballing technique, in which we pursued references of references, to detect reports of studies not found in the database search. Studies were initially identified based on title and abstract and later included through full-text evaluation. The latest search was conducted in August 2013.

Study Eligibility

Cohort and case-control studies addressing health outcomes of prenatal fever exposure in humans were eligible for inclusion in the review. Studies were included only if they made direct references to fever; that is, by addressing fever directly or alternatively by addressing febrile illnesses as a proxy for fever. We excluded studies in selected populations (eg, studies addressing only preterm births) and studies in which the report was inadequate to thoroughly evaluate the methods and results. In addition, we chose to limit the review to more recent evidence, including only studies published since 1990 until August 2013. We excluded duplicate publications and studies with inadequate assessment of fever or those in which we could not distinguish prenatal fever exposure from fever in relation to labor. The criteria used to include and exclude studies in the review are illustrated in Fig 1.

Data Extraction

Information on reference, publication date, design, study population, sample size, fever assessment, exposure period of interest, outcome considered, overall effect estimates, and estimates for varying fever intensities and for antipyretic use was extracted. Because several of the studies included a variety of analyses on fever exposure, we applied the following decision rules for extraction of effect estimates. First, whenever results in case-control studies were presented for >1 comparison group, we always chose estimates from comparisons with matched control subjects over general population control subjects, and general population control subjects over malformed control subjects. Second, when both crude and adjusted measures were available, we chose adjusted measures, with the exception of the studies that were included in meta-analyses. For these, crude measures were applied to ensure comparability of studies. Finally, if a study specified a certain exposure period of interest (eg, first-trimester

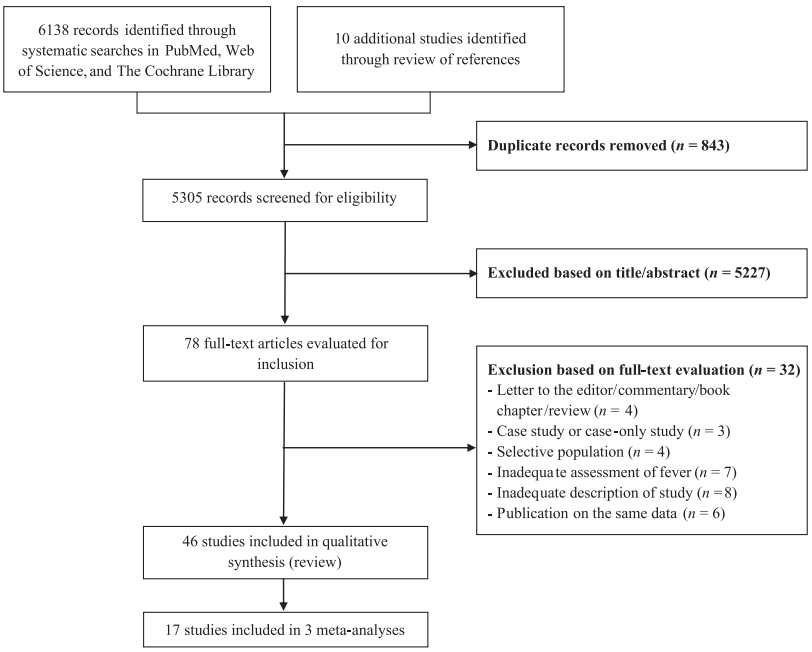

FIGURE 1
Flow diagram illustrating selection of studies.

exposure), we chose estimates pertaining to this time period.

Evidence Rating

The risk of bias of included studies was assessed by using the Newcastle-Ottawa Scale,[11] as recommended by Deeks et al.[12] Risk of bias in relation to selection, comparability, and assessment of the exposure/outcome was assessed according to 9 items by using a star allocation scheme. Stars were allocated if a study was deemed to have a low risk of bias within each item, according to the coding manual provided.[13] A study was categorized as being of low risk of bias if a total of 8 to 9 stars were allocated, medium risk of bias if 6 to 7 stars were allocated, and of high risk of bias if the study was given ≤5 stars.

Data Synthesis

To quantitatively combine results of studies addressing the same outcome, meta-analyses were performed by using Stata version 13 (Stata Corp, College Station, TX)[14] when ≥4 studies were eligible for inclusion. Statistical heterogeneity was assessed by using the Cochran's χ^2 statistic. When studies were homogeneous, we applied a Mantel-Haenszel fixed-effects model; the DerSimonian and Laird random effects model was used when studies were heterogeneous. Studies not suitable for inclusion in meta-analyses were presented in a table, according to the outcome of interest. No summary measures were calculated for these studies, however, as they were too heterogeneous in terms of methods and the outcomes addressed. Lastly, we summarized studies addressing the effects of temperature elevation as well as of antipyretic use.

RESULTS

Seventy-eight potentially eligible studies were identified through systematic searches in relevant databases or through reference reviews. Based on the full-text evaluation, 32 studies were excluded. The main reasons for exclusion were inadequate assessment or reporting of fever exposure, inadequate description of the study, and duplicate analyses across different publications. A total of 46 studies were included in the review.

The characteristics of included studies are summarized in Table 1.[6,7,15–58] Studies varied in size from ~100 to 100 000 observations, and approximately one-half of the reports were based on samples of ≥4000 observations. With 1 exception,[18] fever was measured as maternal self-reported episodes of fever or febrile illness, with or without specific subquestions concerning number of episodes, maximum temperature, duration of fever, accompanying symptoms or illness, timing of exposure, and use of antipyretic measures to treat the fever. The studies considered fever exposures from up to 3 months before conception through the entire pregnancy; however, the majority of the studies considered primarily first-trimester exposures. This choice was a reflection of the outcomes considered in the studies, as a large proportion of included studies addressed birth defects in which the critical developmental period is considered to be early in pregnancy. In general, the prospective cohort studies tended to be of lower risk of bias compared with case-control studies. Within case-control studies, the population-based studies were generally classified with a lower risk of bias compared with the nonpopulation-based studies.

Fever and Health Effects in the Child

Associations between exposure to maternal fever and a variety of health outcomes were addressed in the included studies. A substantial proportion of studies considered shorter-term health effects, such as adverse pregnancy outcomes and birth defects, whereas a smaller proportion investigated the post-neonatal health effects, such as allergic diseases, developmental outcomes, and offspring

TABLE 1 Characteristics of Included Studies

Ref.	Author	Study	*N*	Risk of Bias	Fever Measure	Exposure Period of Interest	Outcome Considered
	Prospective cohort studies						
	Denmark						
15	Streja et al, 2013	DNBC	81 066	Low (9 stars)	Fever	Gestational wk 0–32	Cerebral palsy
16	Atladóttir et al, 2012	DNBC	96 736	Low (9 stars)	Fever[a,b,c,d,e]	Gestational wk 0–32	Autism spectrum disorders
17	Sun et al, 2011	DNBC	86 810	Low (8 stars)	Fever[a,b,c,d,e]	Gestational wk 0–32	Epilepsy
7	Andersen et al, 2002	DNBC	27 432	Low (8 stars)	Fever[a,b,c,e]	Gestational wk 0–16	Fetal death
	Faroe Islands						
18	Helmsdal and Olsen, 2009	—	4208	Low (9 stars)	Fever	Whole pregnancy	Offspring mortality
	Finland						
19	Dombrowski et al, 2003	HLP	6388	Medium (6 stars)	Fever[e]	2nd trimester	Psychological and behavioral outcomes
20	Xu et al, 1999	NFBC, 1986	8088	Low (9 stars)	Fever[e]	Whole pregnancy	Asthma
21	Jones et al, 1998	NFBC, 1966	11 017	Medium (7 stars)	Fever ≥38.0°C	Whole pregnancy	Schizophrenia
	Netherlands						
22	Mommers et al, 2010	KOALA	2319	High (5 stars)	Fever ≥38.0°C	2nd and 3rd trimester	Wheezing, eczema, atopic sensitization
	Norway						
6	Morken et al, 2011,	MoBa	73 259	Low (8 stars)	Fever	Gestational wk 0–30	Spontaneous preterm delivery
	United States						
23	Mattson et al, 2003	—	124	High (5 stars)	Fever[b,c,e]	Whole pregnancy	Neurobehavioral deficits
24	Chambers et al, 1998	—	560	Medium (7 stars)	Fever[a,b,c,e] ≥38.9°C or ≥24 h	1st trimester	Adverse pregnancy outcomes
25	Milunsky et al, 1992	—	22 754	Medium (7 stars)	Fever ≥37.8°C	1st trimester	Neural tube defects
26	Little et al, 1991	—	109	Low (8 stars)	Fever ≥38.3°C for ≥24 h	1st trimester	Birth defects
	Sweden						
27	Larsson et al, 2007	DiPiS	19 756	High (5 stars)	Fever ≥38.0°C[a,e]	Whole pregnancy	High relative birth weight
	Population-based case-control studies						
	China		Case/Control Subjects				
28	Yin et al, 2011	—	246/246	Low (8 stars)	Fever	1 mo prior, to second mo	Neural tube defects
29	Wang et al, 2009	—	586/1172	Low (8 stars)	Fever	1 mo prior, to second mo	Oral clefts
30	Li et al, 2007	—	363/523	Medium (6 stars)	Fever[d,f] ≥38.5°C for ≥24 h	1 mo prior, to second mo	Neural tube defects
	Finland						
31	Kurppa et al, 1991	—	393/393	Medium (6 stars)	Fever	1st trimester	Anencephaly
32	Tikkanen and Heinonen, 1991	—	573/1055	Medium (7 stars)	Fever ≥38°C	1st trimester	Congenital heart defects
	Hungary						
33	Paput et al, 2011	HCCSCA	354/59 291	Medium (7 stars)	Febrile infections[d]	2nd and third mo of gestation	Isolated ear defects
34	Czeizel et al, 2007	HCCSCA	1349/24 354	Medium (7 stars)	Febrile infections[f]	2nd and third mo of gestation	Multiple birth defects
35	Acs et al, 2005	HCCSCA	22 843/38 151	High (5 stars)	Febrile infection[f]	2nd and third mo of gestation	Birth defects
36	Vogt et al, 2005	HCCSCA	111/60 692	High (5 stars)	Febrile infections[f]	Whole pregnancy	Congenital cataract
37	Medveczky et al, 2004	HCCSCA	1202/60 626	Medium (6 stars)	Febrile infections[d]	1st and second mo of gestation	Neural tube defects
	United States						
38	Zerbo et al, 2013	CHARGE	538/421 163/421	Medium (6 stars)	Fever in general[d,e,f]	Whole pregnancy	Autism spectrum disorders and developmental delay
39	Oster et al, 2011	BWIS	2361/3435	Medium (7 stars)	Fever[d,f] ≥38.3°C	3 mo prior, to first trimester	Congenital heart defects
40	Hashmi et al, 2010	NBDPS	2402/5821	Medium (7 stars)	Fever[b,d,f]	1st and second mo of gestation	Oral clefts
41	Cleves et al, 2008	NBDPS	3690/4760	Medium (7 stars)	Febrile infection[b]	1st trimester	Congenital heart defects
42	Suarez et al, 2004	TNTDP	225/378	Medium (6 stars)	Fever[c,d,f]	1st trimester	Neural tube defects
43	Abe et al, 2003	ABDCCS	192/3029	Low (8 stars)	Fever[d,f]	1st trimester	Renal anomalies
44	Shaw et al, 2002	—	1126/734	Medium (7 stars)	Fever ≥37.8°C	1 mo prior, to first trimester	Selected birth defects

TABLE 1 Continued

Ref.	Author	Study	*N*	Risk of Bias	Fever Measure	Exposure Period of Interest	Outcome Considered
45	Botto et al, 2001	ABDCCS	905/3029	Low (8 stars)	Fever[d]	1 mo prior, to first trimester	Congenital heart defects
46	Shaw et al, 1998	—	653/644	Low (8 stars)	Fever and febrile illnesses[f]	1st trimester	Neural tube defect
47	Lynberg et al, 1994	ABDCCS	385/6323	Medium (7 stars)	Fever and febrile infections[d,f]	1 mo prior, to first trimester	Neural tube defects
48	Erickson, 1991	ABDCCS	4929/3029	High (5 stars)	Fever	1 mo prior, to first trimester	Birth defects
	Case-control studies						
	Australia						
49	O'Callaghan et al, 2011	ACPRS	587/1154	High (5 stars)	Fever	Gestational week 21–40	Cerebral palsy
	China						
50	Zhang and Cai, 1993	—	986/1149	Medium (7 stars)	Febrile infection	1st trimester	Birth defects
	France						
51	Stoll et al, 1992	—	43/43	Medium (6 stars)	Fever	Whole pregnancy	Hydrocephalus
	Germany						
52	Wijers et al, 2010	CURE-Net	79/650	High (4 stars)	Fever ≥38.0°C	1st trimester	Congenital anorectal malformations
	Italy						
53	Calvani et al, 2004	—	338/467	Medium (6 stars)	Fever[e]	Whole pregnancy	Asthma
	Netherlands						
54	Van Rooij et al, 2010	AGORA	85/642	Medium (6 stars)	Fever ≥38.0°C	1st trimester	Congenital anorectal malformations
	Saudi Arabia						
55	al-Ansary and Babay, 1994	—	226/226	High (4 stars)	Fever	Whole pregnancy	Spontaneous abortion
	United States						
56	Wilkerson et al, 2002	—	183/209	High (3 stars)	Fever	Whole pregnancy	Autism
57	Fuller Torrey et al, 2000	—	264/528	High (2 stars)	Febrile infections[e]	Whole pregnancy	Psychosis
58	Pastore et al, 1999	—	332/357	Medium (6 stars)	Fever[e]	Whole pregnancy	Stillbirth

ACPRS, Australian Cerebral Palsy Research Study; AGORA, Etiologic Research on Genetic, Occupational and Environmental Risk Factors for Anomalies in Children; ABDCCS, Atlanta Birth Defect Case-Control Study; BWIS, Baltimore-Washington Infant Study; CHARGE, Childhood Autism Risk from Genetics and Environment; CURE-NET, German Network for Congenital Uro-Rectal Malformations; DiPiS, Diabetes Prediction in Skåne (presenting cross sectional analyses); DNBC, Danish National Birth Cohort; HCCSCA, Hungarian Case-Control Surveillance of Congenital Abnormalities; HLP, Helsinki Longitudinal Project; KOALA, KOALA Birth Cohort Study; MoBa, Norwegian Mother and Child cohort; NBDPS, National Birth Defects Prevention Study; NFBC, National Finnish Birth Cohort; TNTDP, Texas Neural Tube Defect Project.

[a] Number of exposure episodes.

[b] Temperature.

[c] Duration of exposure.

[d] Accompanying symptoms or infection.

[e] Timing of exposure.

[f] Use of antipyretic agents.

mortality. Random effects meta-analyses were conducted for case-control studies on neural tube defects (n = 9) and oral clefts (n = 5), due to statistical heterogeneity, whereas a fixed-effects meta-analysis was conducted for studies on congenital heart defects (n = 7). All of the studies included in the meta-analyses were restricted to preconceptional and first-trimester fever exposure. Results are presented in forest plots in Figs 2, 3, and 4. Maternal fever exposure was significantly associated with an increased risk of all 3 birth defects. However, the effect was strongest in relation to neural tube defects (odds ratio $[OR]_{pooled}$: 2.90 [95% confidence interval (CI): 2.22–3.79]) compared with oral clefts (OR_{pooled}: 1.94 [95% CI: 1.35–2.79]), and congenital heart defects (OR_{pooled}: 1.54 [95% CI: 1.37–1.74]). Meta-analyses were performed exclusively on case-control studies to increase homogeneity. Cohort and case-control studies differ in relation to their risk of bias due to selection and differential recall. With regard to neural tube defects, 1 cohort study was consequently not included in the meta-analysis.[25] In this study, however, a somewhat lower and insignificant increased risk of neural tube defects was reported (OR: 1.8 [95% CI: 0.8–4.1]). Furthermore, sensitivity analyses, excluding studies with high risk of bias,[35,48] showed only slightly lower pooled estimates, which remained statistically significant (data not shown).

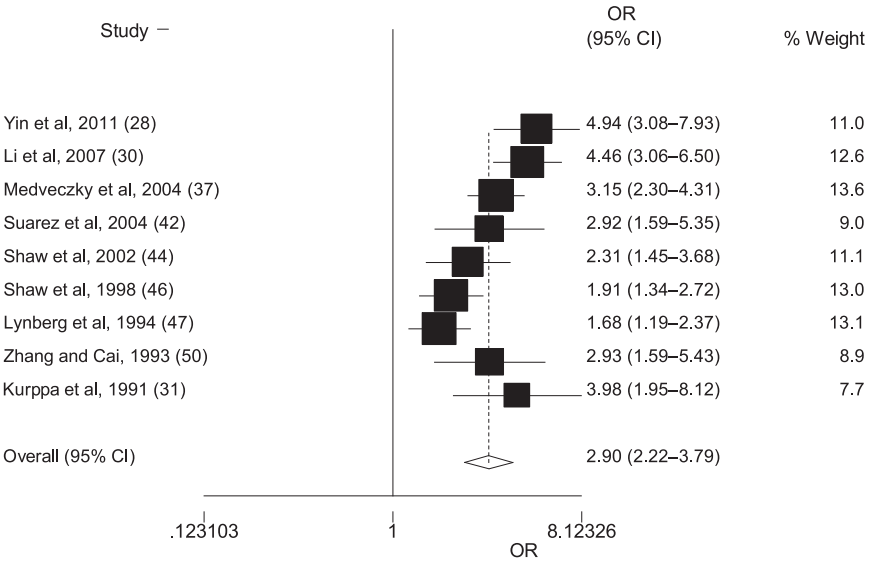

FIGURE 2
Forest plot of case-control studies considering maternal fever and risk of neural tube defects in the offspring.

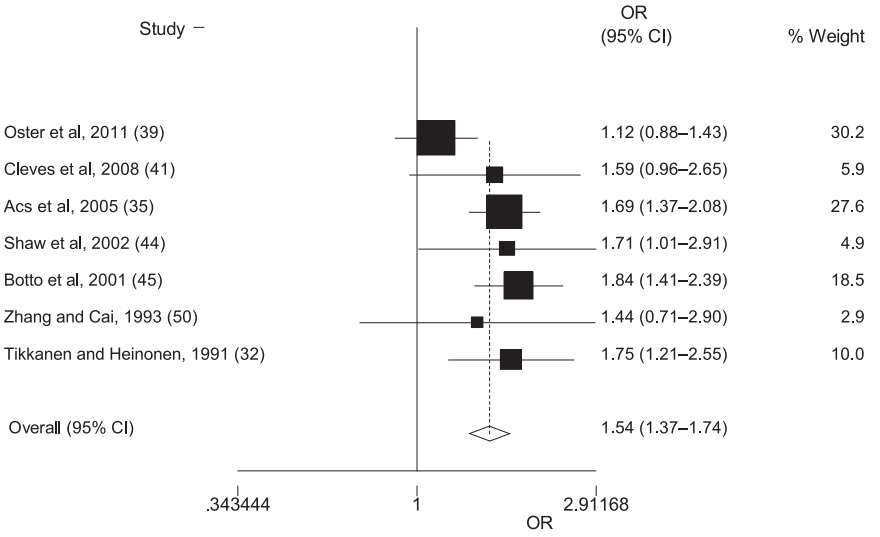

FIGURE 3
Forest plot of case-control studies considering maternal fever and risk of heart defects in the offspring.

Fewer studies were available for each remaining health outcome. The overall estimates of the impact of maternal fever exposure are presented in Table 2 for each study, ordered from short- to longer-term effects in the child. With 2 exceptions,[27,55] studies on pregnancy outcomes (ie, spontaneous abortion, stillbirth, preterm birth, birth weight) found no association with maternal fever exposure. For birth defects, conversely, several studies suggested that fever exposure is associated with excessive risk. Although Acs et al,[35] Zhang and Cai,[50] and Erickson[48] suggested that the risk of any birth defect is increased by ~40% to 60% for those children exposed to maternal fever during the first trimester, Chambers et al[24] suggested an even higher, although not significant, risk for major malformations. Although these estimates may be driven by neural tube defects, congenital heart defects, and oral clefts, as suggested by the meta-analyses, associations were also reported for several other birth defects, including ear defects,[33] anorectal malformations,[52] renal defects,[43] cataract,[36] and limb deficiencies.[44] Other studies reported no significantly increased risk for several of the same outcomes.[24,26,35,54] The evidence of an association with birth defects other than neural tube defects, congenital

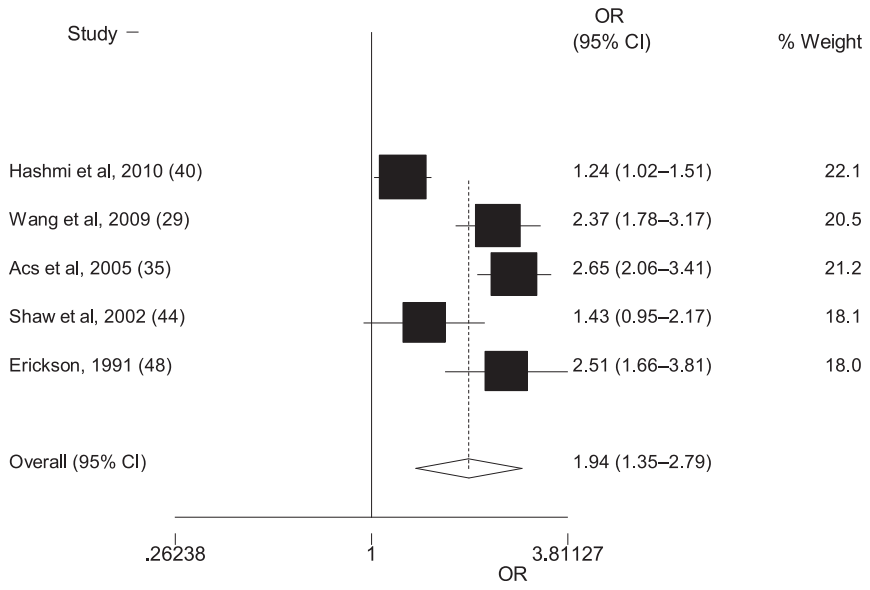

FIGURE 4
Forest plot of case-control studies considering maternal fever and risk of oral clefts in the offspring.

heart defects, and oral clefts is therefore limited, as most defects were only investigated in 1 or 2 populations, and results seemed to be inconsistent between the studies.

For allergic diseases, 2 studies report an approximately twofold increased risk of asthma in children exposed to maternal fever,[20,53] whereas another study found no association with wheezing, eczema, or atopic sensitization.[22] Significant longer-term effects on the child development of exposure to maternal fever were also reported, however, with estimates in general closer to unity. In 3 studies on childhood autism[16,56] and autism spectrum disorders,[38] an increased risk was observed in relation to fever exposure. Increased risks were also reported for cerebral palsy,[15,49] developmental delay,[38] various behavior characteristics,[19] decreased academic performance,[19] and psychosis.[57] No overall association was reported for epilepsy[17] or schizophrenia,[21] however. In addition, 1 study[23] in women infected with varicella-zoster virus found no increased risk of neurobehavioral deficits after fever in relation to the infection. Lastly, 1 study considered overall mortality and found that maternal febrile episodes significantly increased the mortality rate in the offspring in male subjects but not in female subjects.[18]

When we considered effect sizes reported across different health effects, we found that studies which were conducted prospectively were more likely to report lower risk estimates compared with studies with retrospective assessment of fever and also more likely to find no effects of fever. Likewise, studies with lower risk of bias were also more likely to report lower risk estimates compared with studies with higher risk of bias.

Risk in Relation to Level of Fever

Fever intensity, measured by the maximum temperature during a fever episode, was hypothesized in several studies to affect the strength of the association with the outcome of interest. Studies reporting estimates for different fever intensities are summarized in Table 3. Chambers et al[24] reported nonsignificant increases in the risk of several minor birth defects with increasing intensity of fever. However, none of the remaining studies[7,16,17,40,41] reported such a temperature–response relationship.

Antipyretic Medication

Studies that investigated whether the use of antipyretic medication attenuated the risk related to maternal fever exposure are presented in Table 4. One study[30] reported that use of antipyretics was associated with an increased risk of the given outcome compared with the risk observed with fever alone. This tendency is supported by another study by Wang et al[29] (not presented in Table 4; relevant numbers were not reported). In contrast, several other studies observed reductions in risk with antipyretic medication.[34,35,38–40,42,46,47] In some cases, the risk associated with fever was even eliminated.[35,36,40]

DISCUSSION

Our review shows that the available literature supports the occurrence of adverse health impacts in association with fever. The strongest evidence is available for effects on the following selected birth defects: neural tube defects, congenital heart defects, and oral clefts, in which pooled estimates suggest between a 1.5- and nearly 3-fold increased risk through exposure to maternal fever during the first trimester. Some, but not all, evidence furthermore supports an association with other birth defects, developmental deficits, and overall mortality. However, despite the numerous studies reporting associations between fever and adverse health outcomes, we found no strong evidence to suggest that these associations were subject to a dose–response relationship. In addition, we found that most studies, but not all, suggested a protective effect of antipyretic medications when used in relation to febrile episodes. To our

TABLE 2 Association Between Maternal Fever and Health Effects (Other Than Neural Tube Defects, Heart Defects, and Oral Clefts)

Ref.	Author	Study Design	With Disease: Exposed/Unexposed	With No Disease: Exposed/Unexposed	Effect	95% CI
Pregnancy outcomes						
Spontaneous abortion and still birth						
7	Andersen et al, 2002	Cohort	Not shown	Not shown	aHR = 1.0	0.8–1.1
58	Pastore et al, 1999[a]	Case-control	44/50	288/307	RR = 1.0	0.8–1.2
24	Chambers et al, 1998[a]	Cohort	23/26	239/272	RR = 1.0	0.6–1.7
55	al-Ansary and Babay, 1994	Case-control	13/213	4/222	RR = 3.4	1.0–12.5
Preterm birth						
6	Morken et al, 2011	Cohort	Not shown	Not shown	aHR = 0.9	0.8–1.2
High relative birth weight						
27	Larsson et al, 2007	Cohort	Not shown	Not shown	OR = 1.2	1.1–1.3
Birth defects						
Any birth defect						
35	Acs et al, 2005	Case-control	462/22 381	535/38 616	aOR = 1.4	1.3–1.6
24	Chambers et al, 1998	Cohort			aRR = 2.3	0.7–8.2
50	Zhang and Cai, 1993[a]	Case-control	83/903	62/928	OR = 1.4	1.0–2.0
48	Erickson, 1991	Case-control	431/4398	170/2831	OR = 1.6	1.3–1.9
26	Little et al, 1991[a]	Cohort	8/9	47/45	RR = 0.9	0.4–2.1
Multiple birth defects						
34	Czeizel et al, 2007	Case-control	Not shown	Not shown	aOR = 2.3	1.8–2.9
Limb deficiencies						
44	Shaw et al, 2002[a]	Case-control	22/134	38/426	OR = 1.8	1.1–3.2
35	Ács et al, 2005	Case-control	14/534	535/38 616	aOR = 1.9	0.8–4.5
Renal defects						
35	Acs et al, 2005	Case-control	3/102	535/38 616	aOR = 1.5	0.2–10.0
43	Abe et al, 2003	Case-control	20/172	161/2868	aOR = 1.8	1.1–3.0
Anorectal malformations						
54	Van Rooij et al, 2010	Case-control	3/82	4/642	aOR = 5.1	0.9–28.1
52	Wijers et al, 2010	Case-control	5/74	4/642	OR = 10.6	2.8–40.4
35	Ács et al, 2005	Case-control	3/217	535/38 616	aOR = 0.7	0.2–3.0
Hydrocephalus						
35	Acs et al, 2005	Case-control	11/303	535/38 616	aOR = 2.1	0.8–5.5
51	Stoll et al, 1992[a]	Case-control	6/37	5/38	OR = 1.2	0.4–4.4
Ear defects						
33	Paput et al, 2011	Case-control	32/322	13/498	aOR = 4.3	1.9–7.4
24	Chambers et al, 1998[a]	Cohort	3/8	28/165	RR = 2.1	0.6–7.5
Cataract						
36	Vogt et al, 2005	Case-control	62/49	24/87	aOR = 5.2	2.8–9.7
Allergic diseases						
Asthma						
53	Calvani et al, 2004	Case-control	34/254	30/370	aOR = 2.2	1.2–3.9
20	Xu et al, 1999	Cohort	71/212	1321/6484	aOR = 1.7	1.3–2.2
22	Mommers et al, 2010	Cohort	Not shown	Not shown	aOR = 0.8	0.5–1.2
Eczema						
22	Mommers et al, 2010	Cohort	Not shown	Not shown	aOR = 0.9	0.6–1.4
Atopic sensitization						
22	Mommers et al, 2010	Cohort	Not shown	Not shown	aOR = 1.0	0.6–1.7

TABLE 2 Continued

Ref.	Author	Study Design	With Disease: Exposed/Unexposed	With No Disease: Exposed/Unexposed	Effect	95% CI
Developmental deficits						
Infantile autism						
16	Atladottir et al, 2012	Cohort	101/241	23 027/61 241	aHR = 1.4	1.0–1.8
56	Wilkerson et al, 2002	Case-control	Not shown	Not shown	Not shown	*P* = .026
Autism spectrum disorders						
16	Atladóttir et al, 2012	Cohort	234/742	22 894/60 740	aHR = 1.0	0.9–1.2
38	Zerbo et al, 2013	Case-control	97/441	62/359	aOR = 2.1	1.2–3.8
Cerebral palsy						
15	Streja et al, 2013	Cohort	49/80	22 583/56 413	aHR = 1.5	1.1–2.2
49	O'Callaghan et al, 2011	Case-control	20/367	8/1146	OR = 5.1	2.2–11.5
Developmental delay						
38	Zerbo et al, 2013	Case-control	32/131	62/359	aOR = 2.5	1.2–5.2
Epilepsy						
17	Sun et al, 2011	Cohort	197/508	24 063/62 556	aIRR = 1.0	0.9–1.2
Behavior characteristics						
19	Dombrowski et al, 2003 (distress to novelty)	Cohort	Not shown	Not shown	aOR = 1.1	1.0–1.2
19	Dombrowski et al, 2003 (negative emotionality)	Cohort	Not shown	Not shown	aOR = 0.9	0.7–1.2
19	Dombrowski et al, 2003 (Inhibition)	Cohort	Not shown	Not shown	aOR = 1.3	1.0–1.7
19	Dombrowski et al, 2003 (Lack of task persistence)	Cohort	Not shown	Not shown	aOR = 1.3	1.0–1.5
Academic grade						
19	Dombrowski et al, 2003[b]	Cohort	Not shown	Not shown	aOR = 1.3	1.0–1.4
Psychosis						
57	Fuller Torrey et al, 2000	Case-control	Not shown	Not shown	OR = 2.8	1.6–5.1
Schizophrenia						
21	Jones et al, 1998	Cohort	2/68	8/1066	OR = 3.7	0.7–18.1
Mortality						
Offspring mortality						
18	Helmsdal and Olsen, 2009 (males)	Cohort	23/487	Not shown	aHR = 1.5	1.1–1.9
18	Helmsdal and Olsen, 2009 (females)	Cohort	3/233	Not shown	aHR = 1.0	0.1–1.8

The table shows the effect of fever exposure on several outcomes, reported as ORs, relative risks (RRs), hazard ratios (HRs), or incidence rate ratios (IRRs). Whenever adjusted effects were available, these are reported with the prefix a.

[a] Estimates are calculated based on numbers from the original article.

[b] Estimates from the original article reported odds of having better academic grade. To ensure comparability we reversed the estimate; therefore, the OR shows the risk of having a lower grade.

TABLE 3 Effect of Fever During Pregnancy According to Level of Fever

Ref.	Author	Outcome	Low Fever			High Fever			Effect of High Fever
			Definition	Estimate	95% CI	Definition	Estimate	95% CI	
Pregnancy outcomes									
7	Andersen et al, 2002	Fetal death	≤38.9°C	aHR = 0.7	0.5–1.0	>39.0°C	aHR = 0.9	0.6–1.2	No effect
24	Chambers et al, 1998[a]	Spontaneous abortion	<38.9°C or <24 h	RR = 0.9	0.5–1.8	≥38.9°C and ≥24 h	RR = 1.1	0.6–2.1	No effect
Birth defects									
40	Hashmi et al, 2010	Oral clefts	<38.5°C	aOR = 1.1	0.7–1.8	≥38.5°C	aOR = 1.3	0.8–2.1	No effect
41	Cleves et al, 2008[b]	Congenital heart defects	<38.3°C	—	—	>38.3°C	—	—	No effect
24	Chambers et al, 1998[a]	Digital anomalies	<38.9°C or <24 h	RR = 3.1	0.7–13.5	≥38.9°C and ≥24 h	RR = 6.5	2.2–19.8	↑ risk
		Palpebral fissures	<38.9°C or <24 h	RR = 2.6	0.5–8.6	≥38.9°C and ≥24 h	RR = 3.4	1.1–10.9	
		Cleft vulva	<38.9°C or <24 h	RR = 2.5	0.3–21.5	≥38.9°C and ≥24 h	RR = 8.7	2.1–35.1	
		Ear anomalies	<38.9°C or <24 h	RR = 1.4	0.2–10.1	≥38.9°C and ≥24 h	RR = 2.9	0.7–12.4	
Developmental deficits									
16	Atladóttir et al, 2012	Infantile autism	< 38.5°C	aHR = 1.3	0.7–2.3	≥38.5°C	aHR = 1.3	0.9–1.8	No effect
		Autism spectrum disorders	< 38.5°C	aHR = 1.1	0.8–1.6	≥38.5°C	aHR = 1.0	0.8–1.2	
17	Sun et al, 2011	Epilepsy	37.0–37.9°C	aIRR = 0.5	0.1–2.0	38.5–38.9°C	aIRR = 1.0	0.7–1.4	No effect
			38.0–38.4°C	aIRR = 1.2	0.8–1.8	39.0–39.5°C	aIRR = 1.2	0.9–1.7	
						>39.5°C	aIRR = 1.2	0.8–1.8	

aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; RR, relative risk.
[a] Estimates are calculated based on numbers presented in the original article.
[b] No estimates provided; only conclusion.

knowledge, this is the first review that systematically assesses and synthesizes studies on the entire spectrum of adverse health outcomes in the child after fever exposure during pregnancy.

Although there was evidence of an adverse impact of fever on several health outcomes, the strength of this evidence varied considerably. For neural tube defects, congenital heart defects, and oral clefts, several studies were available, enabling us to calculate pooled estimates based on meta-analyses. The findings of increased risks related to prenatal fever exposure remained statistically significant even when studies with a high risk of bias were excluded. For other birth defects, allergic diseases, and for developmental deficits, the evidence was limited due to fewer studies addressing each outcome, varying risk of bias, and a higher degree of inconsistency between study findings. The associations found in studies reporting an adverse effect of fever are nevertheless generally consistent with effects reported from animal studies.[1] One finding that did contrast with evidence from animal studies, however, was the fairly consistent suggestion that fever had no effect on the risk of adverse pregnancy outcomes (spontaneous abortion, stillbirth, and preterm delivery). It is unclear why no association was observed for these very short-term outcomes as these are some of the most frequently reported adverse outcomes in animal studies.[3] It may be that the extent of increased body temperature experienced by women during a fever is not sufficient to cause such severe harm that it leads to fetal death. Generally, it is suggested that maternal body core temperature can be raised by ∼2°C or more before risk of fetal death is increased.[2] This increase is equivalent to a fever of ≥39°C. However, both the study by Chambers et al[24] and that by Andersen et al[7] performed

TABLE 4 Effect of Fever During Pregnancy With or Without Use of Antipyretic Agents

Ref.	Author	Outcome	Fever Without Antipyretics		Fever With Antipyretics		Effect of Antipyretic Use
			aOR	95% CI	aOR	95% CI	
Birth defects							
30	Li et al, 2007	Neural tube defects	4.0	2.5–6.5	13.9	3.0–63.6	↑ risk
35	Acs et al, 2005	Neural tube defects	2.7	1.8–4.0	0.7	0.3–1.6	↓ risk[a]
42	Suarez et al, 2004	Neural tube defects	3.9	1.5–10.0	2.4	1.1–5.4	↓ risk
46	Shaw et al, 1998[b]	Neural tube defects	2.9	1.8–4.8	1.3	0.8–2.2	↓ risk[a]
39	Oster et al, 2011	Right-sided obstructive defects	2.4	1.3–4.3	1.5	0.9–2.4	↓ risk
35	Acs et al, 2005	Heart defects	1.7	1.3–2.2	1.4	0.9–2.1	↓ risk
40	Hashmi et al, 2010	Oral clefts	1.8	1.2–2.8	1.1	0.9–1.5	↓ risk[a]
35	Acs et al, 2005	Cleft lip ± palate	3.3	2.4–4.7	1.4	0.8–2.5	↓ risk[a]
34	Czeizel et al, 2007	Multiple congenital abnormalities	2.2	1.7–2.9	1.6	0.9–2.9	↓ risk
36	Vogt et al, 2005	Congenital cataract	11.1	5.3–23.3	0.6	0.1–4.0	↓ risk[a]
Developmental deficits							
38	Zerbo et al, 2013	Autism spectrum disorders	2.6	1.3–5.0	1.3	0.6–2.8	↓ risk
		Developmental delay	2.7	1.2–6.3	2.1	0.8–5.4	↓ risk

aOR, adjusted odds ratio.

[a] Significant differences between risk estimates for fever exposure with or without antipyretic use.

[b] Estimates are calculated based on numbers presented in the original article (crude estimates).

subanalyses restricted to women with temperatures of ≥38.9°C, but the risk remained unchanged. Another explanation could be that prospective studies addressing adverse pregnancy outcomes, such as spontaneous abortion, did not recruit the pregnant women in time to catch most of the very early pregnancy losses and consequently found no overall effect.

In the reviewed studies, we also found little evidence to support a dose–response relationship with temperature. This evidence was based on studies assessed to be of low and medium risk of bias. The absence of a dose–response relationship contrasts with findings from animal studies and also seems counterintuitive if a causal relationship between fever and adverse health outcomes exists. It could possibly be explained by the fact that the studies used self-reported measures of the maximum temperature during a febrile event, and such a measure is likely to be imprecise several weeks or even months after the episode occurred. Furthermore, thermal dose is not only defined by the elevation of temperature but also by the duration of the exposure. It might therefore be necessary to consider both temperature elevation and fever duration in combination when looking for a dose–response relationship. This theory is supported in the study by Chambers et al,[24] who defined a high fever group by using both temperature elevation and duration. This study was the only 1 of 6 reported in Table 3 that found a dose–response relationship for several minor birth defects. An increased risk by increasing duration of the fever alone (ie, without considering temperature elevation) was also reported by Atladóttir et al[16] and Suarez et al[42] but not by Sun et al[17] or Andersen et al.[7]

On the basis of studies with varying risks of bias, we also found evidence to suggest that antipyretic use seemed to attenuate the risks associated with fever exposure. Only 2 of 10 studies reported increased risk associated with antipyretic use in relation to a febrile episode.[29,30] Nevertheless, substantially more studies reported results suggesting that antipyretic use decreased the risk associated with fever exposure. Differences between study findings may be due to differences in the type of antipyretic agents commonly used, as this use can vary between countries.[30] The fact that a reduction or removal of the fever generally seems to decrease the risk of a given outcome supports the notion that fever itself carries a risk and, furthermore, that this risk is distinct from a potential risk associated with the infection causing the fever. It also provides the possibility of preventing occurrence of adverse health effects in the child, if fever is readily treated in pregnant women. Nevertheless, some antipyretic agents have also been suspected of having detrimental effects on the fetus,[59] and more research is needed to be able to identify safe choices of antipyretics and to estimate if potential risks of antipyretic use outweigh the benefits of reduced temperature. One potential concern about the studies investigating the effect of antipyretic use was that several studies did not specify whether the antipyretic medication was taken as a measure to treat fever. Most antipyretic medications have other purposes in addition to fever management, and it is possible that they were used as analgesics instead. If the antipyretics were generally used in relation to the underlying infection and not at the time of the fever, it would dilute the measure of effect. Only 3 studies[30,38,46] clearly stated that the antipyretics were taken

as a measure to treat the fever; however, no systematic differences in effect estimates or SEs were seen between these and the remaining studies.

There are several mechanisms through which fever has been proposed to interfere with fetal development. When infection in pregnancy occurs, the maternal immune system is mobilized, causing changes in the level of cytokines in the fetal environment. Some cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor-α, are pyrogenic, causing hyperthermia to occur through alteration of the set point in the hypothalamus.[60] Hypothesized effects of the increased body temperature include interruption of protein synthesis and enzyme production, which results in cellular processes (eg, proliferation, migration, differentiation, apoptosis) becoming altered or dysfunctional.[4,60] In addition, as a reaction to the fever, the heat shock response is induced.[2] The response acts as a survival mechanism, and the expression of heat shock proteins is increased to enhance cellular resistance to thermal stress.[60] The heat shock response takes precedence over other cellular activities, resulting in inhibition of protein synthesis and cell proliferation.[4] It is consequently believed that these mechanisms may disturb or harm the fetal development if they coincide with specific windows of vulnerability.

From animal studies, we know that different defects hold unique windows of vulnerability. Although some of the studies included in the review considered fever exposure in specific periods of the pregnancy, others considered the entire pregnancy. Detrimental effects of prenatal exposure to fever might be diluted if too-broad time intervals of exposure are used in the analyses. Czeizel et al[61] suggested that future research in this area should consider critical exposure periods as specific as possible to the outcome of interest and not rely only on commonly used indicators of time, such as trimesters. We found most evidence to support a harmful effect of fever in the early stages of pregnancy. The majority of the studies, however, also only considered these early exposures, which were related to their outcomes of interest (namely, birth defects). Whether exposure later in pregnancy is harmful was less studied. Both the studies by Dombrowski et al[19] and by Calvani et al,[53] however, suggest that exposures in middle and late pregnancy may lead to longer-term adverse effects in the child. Nevertheless, the current evidence is insufficient to conclude whether fever might be harmful in all stages of pregnancy.

It is well established that several infections, such as the TORCH complex (toxoplasmosis, other vertically transmitted infections, rubella, cytomegalovirus, herpes simplex virus 2), have teratogenic effects.[62,63] In addition, a range of other infections (eg influenza,[64] Q fever,[65,66] HIV[67]) are suspected of having detrimental effects on the child. Because fever occurs as a response to infection, it is problematic to distinguish the effects of fever from those of an underlying infection and also from the potential treatment of the infection or the fever. These concerns should be kept in mind when interpreting the findings of the present review. However, because the aim was to summarize studies discussing prenatal exposure to fever as a potential threat to the child, we have not included studies on infections only. Instead, only studies with a direct reference to fever were considered. Consequently, we included studies that defined fever by using specific questions on fever but also whenever authors defined an infection as being a febrile illness. The concept of a febrile infection is only vaguely defined, however, and studies considered infections from influenza, in which ~90%[35] experience fever, to infections such as the common cold, in which fever might only be present in ~50%[68] of cases. If an infection in which fever only occurs in one-half of the cases is used as a proxy for fever, it would lead to substantial misclassification of the fever exposure. Because this misclassification is most likely unrelated to the outcomes, it would be unsystematic (nondifferential), suggesting that studies using febrile infections as a measure of fever would, in most cases, underestimate the impact of fever.

Another concern in systematic reviews is the potential for publication bias, and we cannot exclude the possibility that this factor could have affected the findings of this review. In addition, a number of studies were found to have a medium or high risk of bias, when assessed by using the Newcastle-Ottawa Scale. A general problem for a large proportion of the studies was the potential for bias in the assessment of fever. Several of the findings were based on case-control studies that have assessed fever exposure only after the presence or absence of the outcome was recognized. Compared with cohort studies, case-control studies are more prone to biases originating from differential recall for case and control mothers as well as from selection. We observed that, across different health outcomes, studies using a retrospective design were more likely to report higher risks compared with studies using a prospective design, which could suggest that pooled estimates from the meta-analyses, as well as individual results of case-control studies, were subject to positive bias. Several of the case-control studies did also try to overcome problems in relation to selection bias, by using a population-based design, to ensure that control

subjects reflected the population that gave rise to the cases. Some studies also performed sensitivity analyses by using malformed control subjects to assess the extent of recall bias. Li et al,[30] Lynberg et al,[47] and Medveczky et al[37] found smaller effects when they used a malformed comparison group; however, the associations were always in the same direction and remained statistically significant.

CONCLUSIONS

We found substantial evidence to support an adverse impact of maternal fever during pregnancy. The harmful effects seemed to cover both some short- and longer-term health outcomes. With this review, we do not have adequate evidence, however, to rule out or confirm associations with many of the investigated outcomes. Prospective studies are therefore now required to investigate whether the findings from case-control studies on birth defects remain valid when the exposure to fever is assessed before the outcome occurs. Research on longer-term health impacts is also still in its infancy, but several of the studies included in the review indicate that this is a relevant area of further research. In addition, we suggest that further research aspires to clarify the impact of timing, duration, and extent of fever, as well as the potential role of antipyretic agents.

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