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REVIEW

A systematic review of the health effects of prenatal exposure to disaster

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Abstract
Objectives The aim of this study was to determine the health effects of prenatal exposure to disaster, based on a systematic review of existing research.
Methods A literature search of scientific databases was conducted in February 2015 for articles on prenatal exposure to a natural or man-made disaster. Data was extracted from all articles that met the inclusion criteria, and we systematically analyzed contents based on type of disaster, health outcome, target group and time after birth.
Results Prenatal exposure to famine or war was found to be associated with mental health, cardiovascular or metabolic outcomes, with varying degrees of significance. The majority of the studies showed limited or weak associations between exposures and outcomes.
Conclusions Due to the lack of variety in type of events studied, as well as large methodological variation, it is difficult to draw firm conclusions from existing literature. However, our systematic review highlights the potential of evaluating secondary data, both to accentuate research gaps in the field and to increase the understanding of what effects various types of disasters potentially have on the unborn child.

Keywords Prenatal exposure · Natural disasters · Man-made disasters

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Introduction

Disasters, both natural and man-made, affect millions of people worldwide every year and cause widespread economic damage (Guha-Sapir et al. 2015). Pregnant women are at increased risk for adverse health effects both during and after a disaster event due to their condition (Harville et al. 2010; Nour 2011). Psychological and physiological stress, trauma, reduced access to health facilities and to medication, and disruption in prenatal services are some potential risk factors for pregnant women from disasters, and these adverse effects are likely to also affect the unborn child. Several research studies and reviews have investigated the health effects of various disasters on both directly and indirectly affected people (Doocy 2013a, b, c, d, e). To our knowledge, there have been no efforts to systematically examine the existing research to summarize what effect prenatal exposure to disaster has on the health outcomes of the unborn child.

We hypothesize that the effect of prenatal exposure to disaster is extensive and an important determinant for health for the unborn child, at birth and also later in life. The aim of this study, therefore, is to determine the short-term and long-term health effects of prenatal exposure to disaster, based on a systematic review of the existing research. We expect this review to be an important first step in bridging the knowledge gap on the effect that

prenatal exposure to various disaster situations has on the health outcome of the unborn child.

Methods

A literature search using PubMed, CINAHL SCOPUS, and Web of Science was conducted in February 2015. The choice of search engines was based on methodologies from existing literature reviews on similar topics, on consultations with experienced librarians, and on pilot searches in considered databases. A combination of keywords on prenatal exposure, disasters, and mass casualties was used for each search (Fig. 1).

The common definition of a disaster is "a serious disruption of the functioning of a community or a society involving widespread human, material, economic or environmental losses and impacts, which exceeds the ability of the affected community or society to cope using its own resources" (United Nations International Strategy for Disaster Reduction 2009). In this study, however, we focused on the first part of the definition, since coping capacity has less relevance for the actual prenatal effects. We therefore included events that might not meet the UN definition for a disaster, but that required a scaled-up response in order to avoid excessive adverse health effects in the affected population. We defined events as either natural disasters [*storms, heat waves, freezes, fires, landslides, droughts, floods, cyclones* (*hurricanes and typhoons*)*, tornadoes, tsunamis, volcanoes, or earthquakes*] or man-made disasters (*war, nuclear explosions, famine, hazardous material exposures, explosions, collisions, ship wreck, structural collapse, transportation accidents*). We defined health effects as a change in body function or cell structure that, if adverse, led to disease or health problems.

The search was limited to the primary criteria of peer-reviewed journal articles in English, with an abstract, and on humans. No limit was set on date of publication, time of disasters, or geographic location of disasters.

The initial searches produced 459 articles. The abstracts of each article were then reviewed to meet the inclusion criteria, as defined in Table 1. The authors critically reviewed the remaining studies and the two authors performed all review steps independently. In case of discrepancies about which studies to include, these were first discussed, and if needed, a second opinion was sought until consensus was reached (Fig. 2).

Articles were organized in EndNote X7, and extracted data were entered into a word processing file developed for the purpose by the authors. The following information was collected from each critically reviewed study: type of disaster; date of disaster; location of disaster; time between

1. ("prenatal exposure*" OR "pre-natal exposure*" OR "prenatal injur*" OR "pre-natal injur*") AND ("disaster*" OR "natural disaster*" OR "man-made disaster*" OR "manmade disaster*" OR "mass casualty incident")
2. ("prenatal exposure*" OR "pre-natal exposure*" OR "prenatal injur*" OR "pre-natal injur*") AND ("storm*" OR "heat wave*" OR "heatwave*" OR "freeze*" OR "cold spell*" OR "landslide*" OR "land slide*" OR "drought*" OR "flood*" OR "cyclone*" OR "hurricane*" OR "typhoon*" OR "tornado*" OR "tsunami*" OR "volcano*" OR "earthquake*")
3. ("prenatal exposure*" OR "pre-natal exposure*" OR "prenatal injur*" OR "pre-natal injur*") AND ("war*" OR "nuclear explosion*" OR "nuclear event*" OR "fire*" OR "hazardous material*" OR "explosion*" OR "collision*" OR "ship wreck*" OR "shipwreck*" OR "structural collapse*" OR "transportation accident*" OR "famine*")

Fig. 1 Search strategy for any articles on the health effects of prenatal exposure to disasters

Table 1 The required criteria for journal articles for inclusion in the review

Criteria for inclusion	Criteria for exclusion
An epidemiologic study	Review articles
Outcome was a clearly defined health effect that, if adverse, led to disease or health problems	Did not explicitly measure a disaster exposure or health outcome
Mothers were directly exposed to one or more disaster while subjects were in utero	Unable to limit period of exposure to only time spent in utero; exposure included postnatal period
Effects were studied at a population level	The health outcome under study was a precursor to or risk factor for disease or health problems
	Maternal stress without direct exposure to a disaster

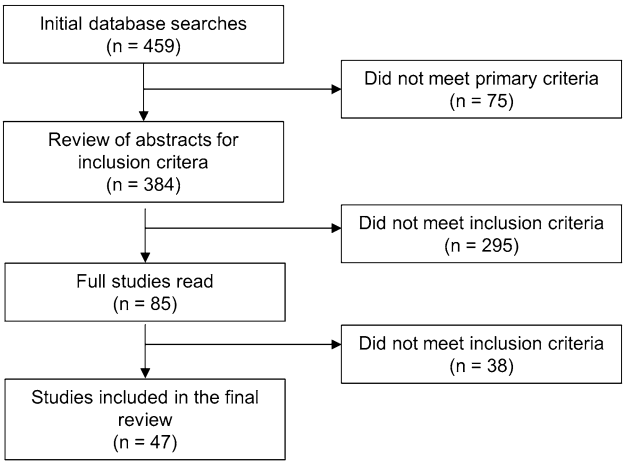

Fig. 2 Review process for the articles produced from the initial search on the health effects of prenatal exposure to disasters

Table 2 The number of articles included in the review by type of disaster exposure

Type of disaster	*N*
Natural disasters	
Extreme cold weather events	4
Extreme heat events	1
Floods or storms	4
Man-made disasters	
Chemical exposure	1
Nuclear radiation	2
Famine	27
War[a]	8
Total	47

[a] Includes military occupation, military attacks

the disaster and the study; health outcome(s) measured; length of time between birth and study; maternal population; child population; sex and age disaggregated data; overview of methods; results.

Forty-seven studies were included in the final analysis. The studies that were read but removed from the final analysis did not meet the inclusion criteria (Table 1).

Results

The types of disasters were varied; the majority (80 %) focused on man-made disaster exposures (Table 2). Over half of the articles studied a single population cohort from a particular disaster, the Dutch famine/Dutch Hunger Winter between 1944 and 1945 ($N = 25$). The next largest proportion of the remaining articles used war disasters as an exposure (17 %), involving military occupation and

Table 3 The number of articles included in the review by health outcomes

Health outcome	*N*
Birth and reproductive outcomes[a]	9
Mental health or illness	14
Mortality	4
Metabolic outcomes	4
Cardiovascular disease	8
Cancer	1
Other[b]	7
Total	47

[a] Birth and reproductive outcomes included spontaneous abortion, stillbirth, perinatal mortality, selective miscarriage, sex ratio, and reproductive health

[b] Other outcomes included asthma, irritable bowel syndrome, fetal distress, fetal iron status, congenital neural defects, obstructive airway disease, and general health

military attacks. We saw a large variation in the health outcomes under investigation (Table 3); mental illness was the most frequently studied outcome, although the specific aspects of mental illness that were studied differed, followed by birth and reproductive outcomes and cardiovascular diseases.

Some evidence for links between prenatal exposure and health effects came from the mental health and cardiovascular system outcome studies. Six studies found strong links between disaster exposure and schizophrenia or affective disorders, although it was unclear how gender affected risk. Children exposed to war during the second trimester had a raised incidence of schizophrenia [relative risk (RR) 2.3, 95 % confidence interval (CI) 1.1, 4.7], and females had an almost threefold raised incidence compared to males (RR 4.3, 95 % CI 1.7, 10.7 vs. RR 1.2, 95 % CI 0.4, 3.8) (Malaspina et al. 2008). Females exposed to severe famine showed an increased trend of hospitalization for schizophrenia (RR 2.17, 95 % CI 1.38, 3.41 to RR 2.56, 95 % CI 1.41, 4.65, dependent on type of diagnosis) (Susser and Lin 1992), which was not seen in males. However, a study of only men exposed to famine in the first trimester still found an increased risk of schizoid personality disorder (RR 2.01, 95 % CI 1.03, 3.94) (Hoek et al. 1996), and a similar study on famine exposure found a significantly increased risk of affective psychosis only in males exposed in the second trimester (Brown et al. 1995). Susser et al. (1996) showed a significant, twofold increase in risk for schizophrenia when children were conceived at the height of famine severity (RR 2.0, 95 % CI 1.2, 3.4), which remained significant when adjusted for sex. While major affective disorders significantly increased for children exposed to famine during the second (RR 1.5, 95 % CI 1.19, 1.9) and third (RR 1.45, 95 % CI 1.17, 1.81)

trimester, women were only significantly affected if they were exposed in the third trimester (Brown et al. 2000). Two other studies found no increased risk for schizophrenia for children exposed to war (Selten et al. 2003) or flooding (Selten et al. 1999).

The remaining papers on mental health all found at least weak links between exposure and outcome. The incidence of autism in children exposed to hurricanes, floods or tropical storms was 13.32/10,000 live births, compared to an incidence of 4.49/10,000 live births in unexposed children ($p < 0.001$); the prevalence of autism increased with severe exposure during the middle or end of gestation (OR 3.83, 95 % CI 1.98, 7.42) (Kinney et al. 2008). An increased incidence of hospitalization for mood disorders was found in children exposed to war (RR 3.01, 95 % CI 1.68, 5.39) (Kleinhaus et al. 2013) and an increased risk of antisocial personality disorder in male children exposed to famine [odds ratio (OR) 2.5, 95 % CI 1.15, 4.2] (Neugebauer et al. 1999). Weaker evidence came from a study on children exposed to an ice storm who scored higher on an autism spectrum screening questionnaire at age 6.5 years than the unexposed (Walder et al. 2014). de Rooij et al. (2011) found no difference in depression or anxiety symptom scores between those exposed and unexposed to famine. A related study from the same famine found a slight increase in depression score for the exposed group, although it was not significant (0.96 points, 95 % CI 0.09, 1.88) (Stein et al. 2009).

In terms of cardiovascular outcomes, exposure to famine in utero was associated with an increased risk of hypertension (OR 2.5, 95 % CI 1.19, 5.26) (Hult et al. 2010), a higher cumulative incidence of coronary heart disease [hazard ratio (HR) 13 %, 95 % CI 1.0, 3.8] and an earlier onset, at 47 years for the exposed and 50 years for the unexposed (Painter et al. 2006b). Another study on famine exposure found a higher prevalence of coronary artery disease among both genders after early gestation exposure (8.8 vs. 3.2 %) (Roseboom et al. 2000). A study on exposure to war and self-reported health problems found increased odds of hypertension (OR 2.2, 95 % CI 1.2, 3.8), dyslipidemia (OR 3.1, 95 % CI 1.7, 5.7) or any cardiovascular disease (OR 2.6, 95 % CI 1.4, 4.7) for exposed children (Bercovich et al. 2014). Conversely, there was also evidence to suggest no association. Schreier et al. found a protective effect from exposure to war and coronary heart disease: exposed women between 63 and 80 years and men between 50 and 54 years of age had higher survival rates than the unexposed (Schreier et al. 2011). Other studies of famine found no increase in coronary artery disease (Lumey et al. 2012), no effect on blood pressure (Roseboom et al. 1999), no increased cardiovascular mortality (Ekamper et al. 2015), and a weak but significant increase in hypertension prevalence among the exposed (OR 1.44, 95 % CI 1.04, 2.0) (Stein et al. 2006).

Most of the studies on birth and reproductive outcomes showed mixed associations between exposure and outcome. Exposure to famine had no effect on sex ratio at birth (Hernandez-Julian et al. 2014; Stein et al. 2004). A study by Yarde et al. (2013) found no evidence of famine exposure on fertility later in life. Exposure to war showed both no increased perinatal mortality (Wilcox et al. 1994) and a significant increase from 23.3/1,000 live births in the prewar period to 25.8/1,000 during the war ($p < 0.001$) (Skokic et al. 2006). Exposure to nuclear radiation showed a significant decline in male births after exposure in the first trimester (Peterka et al. 2004), but also no change from baseline in the incidence of spontaneous abortion (Goldhaber et al. 1983). A study on exposure to dioxin after a factory explosion found no increase in odds for birth outcomes (Eskenazi et al. 2003).

Of the studies on adult mortality, van Abeelen et al. (2012) found a significant association between females exposed to famine and increased overall mortality (HR 1.9, 95 % CI 1.1, 3.4). The remainder found no association (Roseboom et al. 2001), or a slight increase in mortality after famine exposure in the first trimester (HR 1.12, 95 % CI 1.01, 1.24) (Ekamper et al. 2014) and an increased risk of death from natural (HR 1.24, 95 % CI 1.03, 1.43) or external (HR 1.46, 95 % CI 1.09, 1.97) causes (Ekamper et al. 2015).

Another area of consistent but insufficiently conclusive evidence was the association between exposure and metabolic outcomes. Children exposed to an ice storm had an increased risk of obesity at age 5.5 years (OR 1.37, 95 % CI 1.06, 1.77) (Dancause et al. 2012), and there was a positive correlation between maternal distress and insulin secretion in the same children at age 13.5 years ($p < 0.01$) (Dancause et al. 2013). Exposure to famine increased the risk of glucose intolerance (OR 1.65, 95 % CI 1.02, 2.69) and overweight (OR 1.41, 95 % CI 1.03, 1.93) (Hult et al. 2010). Furthermore, females exposed to famine during early gestation had a 7.4 % higher BMI (95 % CI 0.7 %, 14.5 %) than unexposed women, though the same effect was not seen in men (Ravelli et al. 1999). Finally, a study of children exposed to hurricanes found a 22 % higher incidence of diabetes than in the unexposed group (Sotomayor 2013). The outlier was de Rooij et al. (2007), who found no significant association between prenatal exposure to famine and the prevalence of metabolic syndrome.

Less common outcomes included an increased prevalence of spina bifida in males exposed to famine (2.58/1,000 live births vs. 0.98/1,000 in the unexposed), but a lower prevalence in exposed females (0.94/1,000 vs. 1.61/1,000 in the unexposed) (Brown and Susser 1997), and increased fetal distress after exposure to a hurricane during the second trimester (OR 1.26, 95 % CI 1.08, 1.33) and third trimester (OR 1.26, 95 % CI 1.15, 1.38) (Zahran et al. 2010).

The remaining studies found either very weak or no associations between exposure and outcome. Findings include a weak association of congenital heart defects and ambient temperatures (Agay-Shay et al. 2013) and lower levels of cord blood ferritin in mothers exposed to war compared to non-exposed mothers (Armony-Sivan et al. 2013). No association was found between exposure to famine and prevalence of irritable bowel syndrome (IBS) (Klooker et al. 2009), or between breast cancer and exposure to famine (Painter et al. 2006a). Louphaä et al. (2000) found a weak association between mid-gestation exposure to famine and a higher prevalence of obstructive airways disease (OR 1.7, 95 % CI 1.1, 2.6), and a study on asthma and exposure to an ice storm found a weak associated in females between high levels of subjective maternal stress and diagnosed asthma (OR 1.09, 95 % CI 1.00, 1.19) (Turcotte-Tremblay and Lim 2014). Online Resource 1 presents a brief summary of all the included papers.

Discussion

This paper presents an overview of the existing research on prenatal exposure to disasters. Prenatal exposure to famine was strongly linked to schizophrenia and affective disorder outcomes, with fluctuating significance between sexes. Exposure to famine and war were also found to be associated with other mental health, cardiovascular, or metabolic outcomes, with varying degrees of significance. Interestingly, significantly fewer males than females were born approximately 8 months after the Chernobyl nuclear accident, indicating a potentially greater negative impact on male than on female fetuses (Peterka et al. 2004).

Nevertheless, over half of the studies ($N = 25$) showed limited or weak associations between exposures and outcomes, if any were found. For instance, evidence of an increase in schizophrenia after exposure to war was found in one study but not in another study of the same war. With the limited number of studies available on prenatal exposure to disaster, it is not surprising that there is contradictory evidence. Also, due to the varied methodologies of the studies, it is difficult to compare results between studies. We were not able to perform a meta-analysis due to the small number of studies that qualified for the final review, as well as the great variety of study exposures and outcomes.

With the exception of three studies (those on nuclear radiation and chemical exposure), the common underlying determinant of health was maternal stress. The impact of this stress during pregnancy is likely to be highly dependent on individual perceptions of the disaster experience as well as level of exposure. In a review paper from 2012, King et al. (2012) mentioned three dimensions of stress: the degree of objective exposure to the stressor, the level of subjective distress and the person's physiological response to the stressor. Interestingly, the Quebec ice storm cohort studies consistently found that objective maternal stress was associated with adverse health outcomes, while subjective stress appeared to play a smaller role (Walder et al. 2014; Dancause et al. 2012, 2013).

It is close to impossible to study the effect of prenatal exposure in humans in an experimental and controlled setting, such a randomized control trial, due to the ethical difficulties of exposing pregnant women to stress. Therefore, a disaster situation can serve as an independent life event, enabling a limitation of confounding factors that would accompany less defined life events such as loss of employment or the death of a relative. However, the nature of studying disaster exposure means the studies were subject to a number of biases. Measuring exposure and identifying exposed subjects relied heavily on self-reporting. Quantifying exposure was mostly done through assumption, geographic proximity to the event(s) and objective, self-reported measures. For example, the Dutch famine studies assumed that mothers living in certain geographic areas were receiving less than a certain number of calories per day (see Online Resource 1), and the study of the Biafra famine assumed that anyone who self-reported as born in certain Nigerian provinces during the famine year was exposed (Hult et al. 2010).

Since the focus of our paper was prenatal exposure only, this necessitated the removal, during screening, of papers that also included infancy or early childhood in the exposure period. This made disaggregating prenatal and early childhood exposure difficult or impossible for disasters that occurred over a longer period of time, such as famines that lasted more than a year. A further review that includes early childhood exposure may be able to show more conclusive evidence on the health effects of early life exposure to disaster.

In the case of our systematic review, publication bias would be likely to forego studies showing weak or limited associations between prenatal exposure and adverse health outcomes. However, most of the studies found in our search and screening showed results of low statistical power. Nevertheless, we cannot exclude the possibility that there may be additional studies showing weak or no association that tend to not be published.

In many of the studies, prenatal exposure and adverse health outcomes said little about causality, and confounding factors are likely to play a large role. This is especially apparent in studies where the time between exposure and health outcome covers decades. A frequent limitation of the included studies is the poor or limited measurement of outcomes, where self-reported outcomes or record reviews were most commonly used. Furthermore, over half of the articles in our review came from one cohort exposed to one

famine. We could cautiously summarize the effects of prenatal famine exposure on health, but the narrow selection of studies on other disasters does not allow the extrapolation of the effects to other exposures. Hence, drawing firm conclusions from this review and studies with such limitations should be done carefully.

Systematic reviews are often useful for identifying gaps in existing evidence-based knowledge in the field of interest. In this study, we found the lack of diversity in the types of disasters that were studied to be an important aspect of the lack of knowledge on prenatal exposure to disasters. This is probably in part due to the inherent need for research in disaster settings to be opportunistic. Long-term events with associated birth cohort registries are over-represented in the existing literature, and while they are very useful, we want to highlight the need for other types of studies and methods as well. For example, less literature is available on the long-term effects of sudden onset disasters on the unborn child. Also, while trauma and its immediate effects on the mother and child during pregnancy is a well-studied, well-published topic, less is known on how this affects the unborn child later in life. As mentioned earlier, the underlying themes in most of the studies in this review are prenatal exposure to maternal stress or to famine; few studies investigate actual physiological exposure to disaster, rather than stress.

It is clear that a systematic approach to collecting evidence on prenatal exposure to disasters would greatly improve our knowledge within this important area of study. In comparison with data collection of direct health effects of disasters, effects of prenatal exposure should be slightly more straightforward to determine, since exposure does not have to occur in the acute phase of the disaster. Data could potentially be collected via birth registries and cohorts as well as various medical registries, and subsequently compared to existing geographic information system disaster data. Despite the lack of comprehensive studies on prenatal exposure to disasters and health outcomes of the unborn child, our systematic review highlights the potential in evaluating secondary data, both to highlight research gaps in the field and also to increase our understanding of what effects a disaster potentially has on the unborn child and how adverse health outcomes can be avoided.

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