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Review article

Systematic review of ambient temperature exposure during pregnancy and stillbirth: Methods and evidence

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ABSTRACT

Background: Associations between ambient temperature exposure during pregnancy and stillbirth have been reviewed and described in the literature. However, there is no existing review of environmental and epidemiologic methods applied to measure stillbirths resulting from exposure to ambient temperatures during pregnancy. The objective of this study is to systematically review published methods, data sources, and data linkage practices to characterize associations between ambient temperature and stillbirth to inform stillbirth prevention and risk management strategies.
Methods: A systematic review of published studies that assess the association between ambient temperature exposure during pregnancy using any measures or approach and stillbirth was undertaken in Cochrane Library, PubMed, Medline, Scopus, Embase, and Web of Science of studies (2000–2020, inclusive). Selection of studies were assessed by pre-specified eligibility criteria and documented using PRISMA. Citations were managed using EndNote X8 whilst selection, reviewing, and data extraction were performed using Covidence. The screening, selection, and data extraction process consisted of two blind, independent reviews followed by a tertiary independent review. An adapted Critical Appraisal Skills Program (CASP) checklist was used to assess quality and bias. The main findings and characteristics of all studies was extracted and summarized. Where appropriate, a meta-analysis will be performed for measures of association.
Results: Among 538 original records, 12 eligible articles were identified that analysed associations between ambient temperature exposure and stillbirth for 42,848 stillbirths among 3.4 million births across seven countries. Varied definitions of stillbirth were reported based on gestational age, birthweight, both, or neither. The overall rate of stillbirth ranged from 1.9 to 38.4 per 1000 among six high-income countries and one low-middle-income country. All study designs were retrospective and included ten cohort studies, three case-crossover studies, and two additional case-control subgroup analysis. Exposure data for ambient temperature was mostly derived from standard municipal or country-level monitors based on weather stations (66.6%) or a forecasting model (16.7%); otherwise, not reported (16.7%). Results were not statistically pooled for a meta-analysis due to heterogeneity of methods and models among included studies. All studies reported associations of increased risk of stillbirth with ambient temperature exposures throughout pregnancy, particularly in late pregnancy. One study estimates 17–19% (PAR) of stillbirths are potentially attributable to chronic exposure to hot and cold ambient temperatures during pregnancy. Overall, risk of stillbirth was observed to increase below 15 °C and above 23.4 °C, where highest risk is above 29.4 °C.
Conclusion: Exposure to hot and cold temperatures during pregnancy may increase the risk of stillbirth, although a clear causative mechanism remains unknown. Despite lack of causal evidence, existing evidence across diverse settings observed similar effects of increased risk of stillbirth using a variety of statistical and methodological approaches for exposure assessments, exposure windows, and data linkage. Managing exposure to ambient temperatures during pregnancy could potentially decrease risk of stillbirth, particularly among women in low-resource settings where access to safe antenatal and obstetric care is challenging. To fully understand the effects or dose-response relationship of maternal exposure to ambient temperatures and stillbirth, future studies

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should focus on biological mechanisms and contributing factors in addition to improving measurement of ambient temperature exposure.

1. Introduction

Stillbirth causes a substantial emotional and economic burden to society with nearly 2 million babies stillborn each year worldwide (United Nations Inter-agen, 2020). Certain maternal conditions, lifestyle factors, and pregnancy conditions have established epidemiologic associations with stillbirth as an adverse pregnancy outcome, yet neither the causal role or mechanism has been explained (Strand et al., 2011; Lawn et al., 2016; Goldstein et al., 2016; Flenady et al., 2016). Currently, there are several probable assumptions and little empirical evidence of the associations between ambient temperature exposure during pregnancy and stillbirth (Strand et al., 2011). In a time of heightened concern for health impacts due to climate change, there has been mounting interest and subsequent increase in studies surrounding ambient temperature exposures and stillbirth. In the context of reducing the incidence of stillbirth globally, it is important to understand the relationship between ambient temperature thresholds, exposure periods during pregnancy, and stillbirth (Intergovernmental Panel o, 2007).

A previous systematic review published in 2017 identified ecological ($n = 17$) and retrospective cohort studies ($n = 19$) that described associations between temperature and gestational age, temperature and preterm birth, impact of temperature on birth weight, and temperature and stillbirth (Zhang et al., 2017). Among these studies, only four included stillbirths as an outcome of interest (Strand et al., 2012a; Arroyo et al., 2016; Basu et al., 2016). Since 2017, key papers have been published that focus on stillbirth and ambient temperature exposure during pregnancy as well as severe pregnancy-related emergencies that result in stillbirth (Weng et al., 2018a; Li et al., 2018a; Wang et al., 2019; Rammah et al., 2019; Kanner et al., 2020). These recent studies have found that both cold (Ha et al., 2017; Auger et al., 2017a; Bruckner et al., 2014; Li et al., 2018b) and hot temperatures (Strand et al., 2012a; Ha et al., 2017; Li et al., 2018b; Asamoah et al., 2018a) increase risk of stillbirth, although with varied methods and results. As such, the independent association between stillbirth and exposure to ambient temperatures during pregnancy remains unclear. By including most recent evidence with an expanded scope to consider statistical and environmental methods, this review provides novel context to the relationship between ambient temperature and stillbirth for clinical management and obstetric practice considerations as well as recommendations for environmental data collection and linkage.

The main objective of this study is to undertake a systematic review and metanalysis to assess published associations between ambient temperature exposure during pregnancy and stillbirth. A secondary objective is to explore the quality and variation of environmental data collection methods for ambient temperature exposure and data linkage methods to identify the most accurate methodological approach for measuring risk of stillbirth resulting from pregnancy exposure to ambient temperatures.

2. Methods

A systematic review of published English-language clinical trials, ecological studies, and cohort studies that report associations between stillbirth and ambient temperature exposure during pregnancy was undertaken for all years 2000–2020, inclusive. Literature reviews, systematic reviews, and Cochrane reviews were hand-searched and screened for potential studies. EndNote citation management software was used to manage citations while screening and extraction took place using Covidence systematic review software (Clarivate Analytics EndNo; Veritas Health Innovation). Eligible studies from 2000 to 2020, inclusive, or setting must have included stillbirths as an outcome of interest in the context of adverse pregnancy outcomes resulting from or associated with the exposure of interest. The exposure of interest is ambient temperature exposure during pregnancy. A full registered protocol is available online via PROSPERO (#CRD42020141765) (Sexton et al., 2019).

2.1. Search strategy

A search strategy was applied to The Cochrane Library, PubMed, Medline, Scopus, Embase, and Web of Science on July 3, 2019 and updated on January 20, 2021. The review was restricted to peer-reviewed English language articles excluding animal studies. A combination of MeSH terms and keywords were used including 'pregnant women', 'pregnancy', 'ambient temperature', 'hot or cold temperature', 'stillbirth', and 'fetal death' in the search. References of relevant papers and existing reviews were examined for additional studies to include.

Selection of eligible studies and extraction was performed by two blind, independent reviewers via a three-step screen process using Covidence and documented via a PRISMA flow diagram (Fig. 1) (Veritas Health Innovation). First, studies identified from the database searches were screened for relevance. The following criteria were used to screen abstracts for relevance: (1) publication type, (2) quantitative inclusion of ambient temperature exposure during pregnancy and (3) inclusion of stillbirth as an outcome. Animal studies, non-English studies, grey literature, and/or conference proceedings, and studies that did not include stillbirths or ambient temperature exposure were excluded at this stage. Full texts of relevant studies were then reviewed for eligibility. Studies where stillbirth was coded as a composite outcome or where early pregnancy losses (<20 weeks gestation) were classified as stillbirths were excluded. Data extraction was performed for studies selected for inclusion in Covidence using a customised data collection tool. Data was extracted by two blind, independent reviewers. All conflicts were resolved by co-tertiary reviewers via Covidence (Veritas Health Innovation).

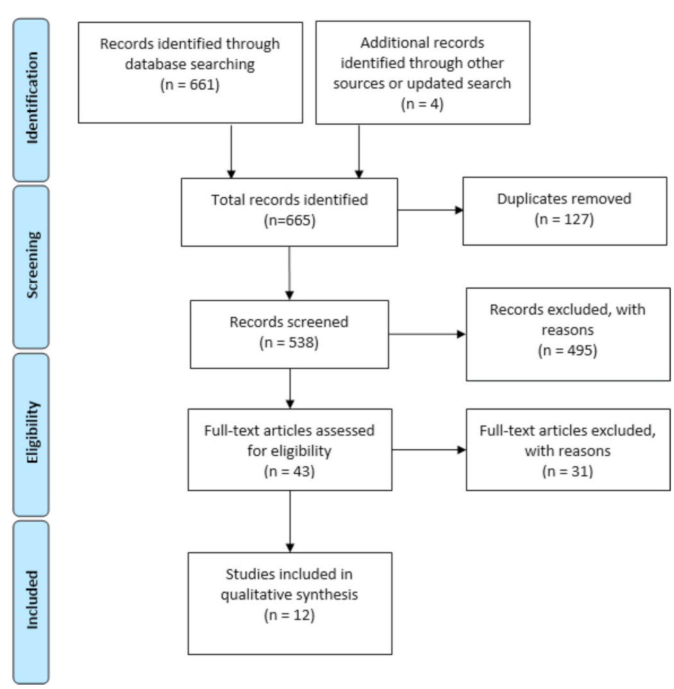

Fig. 1. PRISMA study selection flow diagram.

2.2. Quality assessment

A quality assessment was performed based on an adapted version of the Critical Appraisal Skills Program (CASP) appraisal tool for systematic reviews previously published by Zhang et al. (Zhang et al., 2017; Oxford Centre for Triple Value Healthcare Ltd). Eligible studies were assessed for validity, ethics, and bias using a checklist of questions and scored accordingly with 'yes' or 'no' (one point award per question for 'yes'; minimum score: 0; maximum score: 14). The quality score is reported in tabular format with corresponding study information (Box 1).

2.3. Data management and analysis

A customized electronic database was used to extract data points from all studies by two blind, independent investigators (JS, CA). Any conflicts or queries were raised to an independent, tertiary investigator (SL). Data extraction can be grouped into three main areas: general information, statistical approach, and environmental measures. General study information was extracted from all studies including administrative details, population characteristics, setting, eligibility criteria, and definition(s) of stillbirth. Data for statistical measures included study design, software used, data sources, methods, output measure, weeks gestation analysed, covariates (where appropriate), estimates reported, and consideration of confounders. Further data was collected for environmental measures including exposure data source and definition(s), exposure timing, data linkage methods, other environmental measures considered, and whether the environmental data was subject to any quality assessment prior to transformation for analysis. Where information cannot be found in any published material related to the study (main text, figures, tables, appendices, supplements), missing information is recorded as "Not Reported" (NR).

3. Results

Among 538 original records, 12 eligible articles were identified that analysed associations between ambient temperature exposure during pregnancy and stillbirth for 42,848 stillbirths among 3.4 million births (Table 1). Due to lack of relevance, 495 studies were excluded and a further 31 were excluded due to missing or misclassifying stillbirths, composite outcomes, or missing ambient temperature as an exposure. The CASP quality assessment ranged from 9 to 14 ($\bar{x} = 12.5$) where studies most frequently failed to report clinical practice implications, ethical issues, conflict of interest, and confounding factors.

The overall rate of stillbirth ranged from 1.4 to 28.2 stillbirths per 1000 births. In high-income countries, the observed or reported stillbirth rate varied from 1.4 to 26.2 stillbirths per 1000 births as compared to 28.1 stillbirths per 1000 births in one low-middle-income country. All studies included a definition of stillbirth adopted from the World Health Organisation's recommended definition of stillbirth, which is a baby born with no signs of life at or after 28 weeks' gestation. Most definitions (83%) included either gestational age and/or birth weight. The majority of studies that reported gestational age recognized a stillbirth at 20 weeks gestation and/or birth weight from 400 g. One study reported "born dead" (Asamoah et al., 2018a).

All 12 studies were retrospective and included nine cohort studies (Arroyo et al., 2016; Weng et al., 2018a; Li et al., 2018a; Wang et al., 2019; Kanner et al., 2020; Ha et al., 2017; Bruckner et al., 2014; Asamoah et al., 2018b; Strand et al., 2012b), three case-crossover studies (Basu et al., 2016; Rammah et al., 2019; Auger et al., 2017a), and two additional case-control subgroup analyses (Kanner et al., 2020; Ha et al., 2017). There were no clinical trials or prospective studies.

3.1. Exposure data, analysis, and linkage

Exposure data for ambient temperature was mostly derived from municipal or country-level monitors based on weather stations (67%) or a forecasting model (17%)[16]; otherwise, not reported (Wang et al., 2019; Li et al., 2018b) (Table 2). Clinical data was linked to environmental exposure data (mean/maximum monthly/daily ambient temperature) most frequently by defined exposure window or lag day in a given catchment area (e.g., county-level area). The defined exposure window varied from any point during pregnancy to day-of-delivery to continuous daily measures throughout pregnancy, which could have major practice implications for results interpretation. One study utilized geocoding to link post-code level exposure to place of usual residence (Rammah et al., 2019). Statistical software programs were used for all analysis including R Studio, Stata, SAS, or SPSS and none used geospatial software programs such as ESRI ArcMaps or QGIS (Table 3). Maternal movement patterns or ambient temperature exposure type (e.g., indoor, outdoor, occupational, city, rural) were not considered.

3.2. Quality and bias scores

Study quality scores assessed by the CASP guidelines and adapted tool ranged from 4 to 14, out of a maximum of 14 points. More recent studies and studies that employed a time-to-event methodological approach demonstrated higher quality scores as compared to older, retrospective ecological studies. For three studies where the population

Box 1
Adapted CASP guidelines quality assessment for studies included in the systematic review.

1. Did the review address a clearly focused question?
2. Was the patient cohort recruited in an acceptable way?
3. Was the exposure accurately measured to minimize bias?
4. Was the outcome accurately measured to minimize bias?
5. Have the authors identified all important confounding factors?
6. Have the authors adjusted for important confounding factors?
7. Are the results of this study demonstrated clearly?
8. Are the results precise?
9. Are the results consistent with other available evidence?
10. Has the smdy considered practice implications?
11. Is the study design and analytic methodology appropriate?
12. Was the data analysis sufficient rigorous?
13. Have ethical issues been taken into consideration?
14. Have potential conflicts of interested been disclosed and sufficiently addressed?

Table 1
Study characteristics on ambient temperature and stillbirth.

Study	Country	Setting	Study years	Study design	SBs[a] (n)	Total births (n)	SBR[b]	Definition of stillbirth	Gestational age analysed (weeks)	Quality score (0–14)
Arroyo et al., 2016	Spain	HIC	2001–2009	Retrospective cohort	1,214	298,705	4.06	Stillbirths and/or live births that died in the first 24 h of life, late foetal death (LFD)	≤37	9
Asamoah 2018	Ghana	LMIC	2004–2007	Retrospective cohort	32	1,136	28.17	"Born dead"	All	9
Auger 2017	Canada	HIC	1981–2011	Retrospective case-crossover	5,047	5,315	1.92[28]	Stillborn fetus weighing 500 g or more regardless of gestational age	All	14
Basu et al., 2016	United States	HIC	1999–2009	Retrospective time-stratified case-crossover	8,510	8,542	1.41[29]	Death of a fetus whose development has advanced to the 20th week of gestation or beyond, prior to complete expulsion or extraction from the mother	≥20	13
Bruckner et al., 2014	Sweden	HIC	1915–1929	Retrospective cohort	359	13,657	26.29	Fetal death irrespective of the duration of pregnancy ≥ 24 weeks gestation	24+	13
Ha et al., 2017	United States	HIC	2002–2008	Retrospective cohort; additional case-control analysis	992	228,438	4.34	Fetal death ≥23 weeks gestation as reported in electronic medical record (EMR) supplemented by ICD-9 codes in discharge summaries	23+	14
Kanner et al., 2020	United States	HIC	2002–2010	Retrospective cohort	500	112,005	4.5	Any fetal death ≥ 20 weeks gestation	≥20	13
Li 2018	Australia	HIC	1994–2013	Retrospective cohort	1,783	289,351	6.16	Loss of fetus who shows no signs of life at birth and is at least 20 weeks in gestation or 400 g in birthweight if gestation is unknown	20+	13
Rammah et al., 2019	United States	HIC	2008–2013	Retrospective case-crossover	1,599	1,874	6.00[29]	At least 20 weeks gestation or birthweight ≥350 g	20–44	13
Strand 2012	Australia	HIC	2005–2009	Retrospective cohort	653	101,870	6.41	Death occurring before delivery at more than 20 weeks of gestation or birthweight ≥400 g	20+	13
Wang et al., 2019	Australia	HIC	2000–2010	Retrospective cohort	1,684	277,149	6.08	Fetal death after 20 weeks of gestational age or birthweight ≥400 g	20+	13
Weng 2018	Taiwan	HIC	2001–2010	Retrospective cohort	20,475	2,123,781	9.64	Death of a fetus ≥20 weeks gestation	20+	13

[a] SB: Stillbirth.
[b] SBR: Stillbirth rate defined as stillbirths per 1000 births.

stillbirth rate was not reported (Basu et al., 2016; Rammah et al., 2019; Auger et al., 2017a), an estimated rate is provided based on most appropriate available report representing the study population and time period (Table 1).

3.3. *Ambient temperature exposure and stillbirth*

Seasonal changes in number of stillbirths were observed and suggested to result from heat-related or cold-related stress, where statistically significant differences were observed between cold or hot months and reference months on average (Ha et al., 2017). Due to heterogeneity of included studies in study design and measures, a meta-analysis was not feasible. One study reported ambient temperature measures in Fahrenheit units while all other reported Celsius units. An impact on late fetal death were observed for fine particulate matter ($PM_{2.5}$) and minimum temperature in the third trimester and ozone (O_3) in second trimester (Arroyo et al., 2016). Another study observed an increase in odds of stillbirth by 12–15% for every 1 °C increase in the range of 23–27 °C (Asamoah et al., 2018a). According to Auger et al., odds of late-pregnancy stillbirth for temperature 28 °C the day before death were 1.16 times greater relative to 20 °C (Auger et al., 2017a). While results appeared protective (HR 0.92, 95% CI 0.86–0.996), a linear model showed that temperatures accelerated risk of stillbirth (Bruckner et al., 2014). Independent of maternal ambient air pollutant exposure, evidence of association between apparent temperature increases (10 °F) in the week preceding birth (lag days 1–6) and risk of stillbirth was demonstrated where risks further elevated among Hispanic and non-Hispanic Black women from June to August (Rammah et al., 2019).

In Strand et al., higher ambient temperatures in the last four weeks of pregnancy increased risk of stillbirth (Strand et al., 2012a). In Kanner

Table 2
Summary of environmental exposure data and analysis characteristics.

Study	Measurement	Timing	Linkage method	Source	Data collection	Other measures reported
Arroyo et al., 2016	Spatially aggregated weekly averages (°C)	37 weeks preceding a full-term birth	Lag weeks gestation for assumed equal exposure for all women in population	Madrid Municipal Air Quality Monitoring Grid, Madrid Permanent Acoustic Pollution Monitoring Grid	Weekly average	Pollen exposure
Asamoah 2018	Yearly average and monthly average temperature (°C)	Month and year estimate of the outcome; first 1–3 months of that pregnancy	Region where outcome occurred	Climate Research Unit (CRU) via HOTHAPS database	Grid-cell weather station data	NR
Auger 2017	Continuous maximum daily temperature (°C)	1–6 days prior to death	Not explained; Hospital region and date???	Environment Canada	18 representative meteorological stations in provincial Quebec	Relative humidity
Basu et al., 2016	Apparent daily temperature (relative humidity and ambient temp) (°C)	Daily preceding death (by lag days)	Maternal zip codes to climate zone linked to date	California Irrigation Management Information System, US EPA, National Climatic Data Center	Weather station daily temperatures	CO, NO_2, O_3, SO_2
Bruckner et al., 2014	Daily temperature (C°) as mean of hourly temperature	Average weekly temperature over the gestation as a time-dependent variable	Average weekly temperature to week gestation	SMHI Stockholm	Instrument-based surface temperature	NR
Ha et al., 2017	Average ambient temperature (°C) over varying time periods	Three-month preconception period, first trimester, and whole pregnancy	15 distinct hospital-referral regions were used as a proxy for maternal residence and local mobility; Average temperatures during exposure period	Weather Research and Forecasting (WRF) model for temperature and relative humidity; Community Multiscale Air Quality models (CMAQ) for ozone	Hourly temperature data from WRF model averaged for each referral region	Relative humidity, ozone, particulate matter
Kanner et al., 2020	Ambient temperature <10th centile (cold) and >90th centile (hot) where 10–90th centile is reference (control) (°C)	Average ambient temperature across pregnancy for chronic exposure; odds associated with temperature during the last week of pregnancy for acute exposure	Hospital referral region	Weather Research and Forecasting (WRF) model for temperature and relative humidity; Community Multiscale Air Quality models (CMAQ) for ozone	Hourly temperature data from WRF model averaged for each referral region	Relative humidity, $PM_{2.5}$, NO_2, O_3
Li 2018	Daily mean temperature, maximum temperature, minimum temperature, mean relative humidity (°C)	Trimesters: week 1–12; week 13–28; week 29-birth	Not explained: Assume week gestation with temperature, humidity	Queensland Department of Environment and Heritage Protection	NR	Relative humidity
Rammah et al., 2019	Mean daily temperature (°F)	Lag days 1–6	Weather station(s) closest to mothers geocoded address on lag days of exposure	National Climatic Data Center	Mean daily temperature calculated from hourly ambient and dew point temperature from weather station(s) closest to mothers geocoded address	$PM_{2.5}$, NO_2, O_3
Strand 2012	Hourly ambient temperature (°C), relative humidity, and air pollution converted to weekly means	15 weeks to birth	Gestational week from 15 weeks	Queensland Department of Environment and Resource Management	Pollution stations (n = 5)	Humidity, PM_{10}, $PM_{2.5}$, NO_2, O_3, CO
Wang et al., 2019	Monthly ambient temperature (°C) in six heat waves defined as a combination of 90–95th percentile temperature measurements	All gestations	Gestational month	Australia Bureau of Meteorology	NR	Relative humidity (%), air pressure (kPa), PM_{10}, CO, SO_2, O_3, NO_2
Weng 2018	Mean daily outdoor temperature in 9 categories (°C)	Ambient temperature on day of delivery ("at birth")	Ambient temperature on day of birth was extracted and assigned to individual newborns at a county-area level	Central Weather Bureau	14 weather stations selected around Taiwan	NR

et al., the risk of stillbirth across whole pregnancy versus acute exposure with a seven-day lag to day-of-delivery was comparable at 7% increased risk for acute exposure and adjusted odds of 7.22 and 6.79 for cold and hot exposure throughout pregnancy (Kanner et al., 2020). The hazard ratio for stillbirth was 0.3 at 12 °C relative to 21 °C (reference temperature) in Strand et al. (2012a). The temperature effect was greatest at less than 36 weeks gestation. Other factors reported include maternal smoking (HR 1.27, 95% CI 1.54–1.68), Indigenous status (HR 1.58, 95% CI 1.06–2.37), and pre-eclampsia or pregnancy-induced hypertension (HR 1.42, 95% CI 1.03–1.95).

There was a significant correlation of temperature with stillbirth over 23.4 °C compared to reference temperature (21.1 °C) (Weng et al., 2018b), particularly during defined heat waves (Wang et al., 2019). However, one case control analysis found 32% increased odds of stillbirth (95% CI 1.17–1.49) above 20 °C. This evidence suggests an inflection point for prevention may exist between 20.0 °C and 23.4 °C where risk of stillbirth begins to increase significantly compared to mild temperatures. An inverse U-shaped seasonal pattern in stillbirth incidence was observed overall, with highest incidence in summer and winter months in seasonal climates (Weng et al., 2018b). Overall,

Table 3
Statistical methods and results.

Study	Software	Method	Model or main descriptive analysis	Covariates adjusted for (if relevant)	Estimate	
Arroyo et al., 2016	SPSS, Stata	Poisson time-series autoregression	Tmax (lag 20)	Chemical pollution, acoustic pollution, max and min daily temperatures	RR	1.01 ($p < 0.00001$)
			Tmin (lag 2)		RR	1.04 ($p < 0.00001$)
Asamoah 2018	SPSS	Multivariable logistic regression	Ambient heat yearly distributions for 10 administrative regions	Not applicable	Crude OR (95% CI)	1.15 (0.92–1.42)
			Model 1: Ambient heat yearly distributions for 10 administrative regions	Maternal age	aOR (95% CI)	1.12 (0.90–1.39)
			Model 2: Ambient heat yearly distributions for 10 administrative regions	Total number of pregnancies	aOR (95% CI)	1.00 (0.80–1.25)
			Ambient heat yearly distributions for 4 administrative regions	Not applicable	Crude OR (95% CI)	1.42 (1.00–2.03)
			Model 1: Ambient heat yearly distributions for 4 administrative regions	Maternal age	aOR (95% CI)	1.36 (0.95–1.95)
			Model 2: Ambient heat yearly distributions for 4 administrative regions	Total number of pregnancies	aOR (95% CI)	1.27 (0.89–1.81)
Auger 2017	SAS	Conditional multivariable logistic regression	Stillbirth the day before death at 28 °C	Relative humidity	aOR (95% CI)	1.16 (1.02–1.33)
			Stillbirth the day before death at 30 °C		aOR (95% CI)	1.22 (1.02–1.46)
			Stillbirth the day before death at 32 °C		aOR (95% CI)	1.28 (1.03–1.60)
Basu et al., 2016	SAS, R	Simple linear regression	For every 10 °F increase in apparent temperature (average of lags 2–6 days)	Not applicable	Percent change (95% CI)	10.4% (4.4–16.8)
			For every 10 °F increase in apparent temperature (average of lags 2–6 days) among mothers <25 years		Percent change (95% CI)	11.8% (1.5–23.2)
			For every 10 °F increase in apparent temperature (average of lags 2–6 days) among mothers with a high school education or less		Percent change (95% CI)	10.6% (2.9–18.8)
			For every 10 °F increase in apparent temperature (average of lags 2–6 days) among Hispanic mothers		Percent change (95% CI)	10.5% (2.1–19.5)
			For every 10 °F increase in apparent temperature (average of lags 2–6 days) among male fetuses		Percent change (95% CI)	13.3% (4.8–22.4)
Bruckner et al., 2014	NR	Cox proportional hazards	Ambient temperature (1 °C increase)	Not applicable	Hazard ratio (95% CI)	0.92 (0.86–0.996)
Ha et al., 2017	SAS	Conditional logistic regression	Whole pregnancy exposure to cold and hot temperatures for stillbirth risk	Clustering, study site, infant sex, maternal age, race, marital status, parity, pre-pregnancy body mass index, hypertensive disorders, insurance status, humidity, season, particulate matter <2.5 μm and ozone	aOR (95% CI) 'cold' aOR (95% CI) 'hot'	4.75 (3.96–5.71) 3.71 (3.07–4.47)
			Percent increase for every 1 °C during week preceding delivery		Percent increase	6% increase in stillbirth risk May–September
Kanner et al., 2020	SAS	Conditional multivariable logistic regression	Whole pregnancy chronic exposure model	Maternal age, race, parity, pre-pregnancy BMI, marital status, insurance status, alcohol use, smoking during pregnancy, infant sex, season of conception, gestational age, delivery hospital, hypertensive disorders, gestational diabetes	Cold (<10th) aOR (95% CI) Moderate Hot (>90th) aOR (95% CI)	4.42 (3.43–5.69) Ref. 5.06 (3.34–7.68)
			Whole pregnancy case-control model		Cold (<10th) aOR (95% CI) Moderate Hot (>90th) aOR (95% CI)	7.22 (5.03–10.37) Ref. 6.79 (4.61–9.99)
			Acute case-crossover model	Air pollutants and relative humidity	Percent (%) change daily odds of stillbirth for 1 °C (95% CI)	6% (1.02–1.10) cold season 7% (1.03–1.11) warm season 32% (1.17–1.49) ≥20 °C

(continued on next page)

Table 3 (*continued*)

Study	Software	Method	Model or main descriptive analysis	Covariates adjusted for (if relevant)	Estimate	
Li 2018	R	Cox proportional hazards	Hazard ratios of stillbirth associated with mean daily temperature during three trimesters of pregnancy	Sex of baby, number of births, previous pregnancy, maternal conditions, maternal age at admission, and smoking status	HR (95% CI) (low temperature)	1.21 (1.16–1.27)
					HR (95%C I) (high temperature)	1.21 (1.16–1.26)
Rammah et al., 2019	SAS	Conditional logistic regression (Case-crossover)	Maternal exposure to daily average apparent temperature over days preceding birth (lag days 1 through 6)	Fine particulate matter (PM2.5), nitrogen dioxide (NO2), and ozone (O3); maternal race/ethnicity	aOR (95% CI)	1.45 (1.18–1.77)
Strand 2012	R	Cox proportional hazards	Hazard ratios of stillbirth associated with month of birth	Temperature, humidity, sulphur dioxide levels in the last 4 weeks, maternal age, and secular trends in livebirth and stillbirth	HR (95% CI) (minimum: March)	0.54 (0.36–0.82)
					HR (95% CI) (maximum: July)	1.13 (0.50–2.56)
			Splines for stillbirth and livebirth for before 36 weeks' gestation of temperature exposure before and after adjustment	Sulphur dioxide	HR and temperature (°C) (low)	0.96 at 15 °C
					HR and temperature (°C) (high)	1.02 at 25 °C
Wang et al., 2019	NR	Cox proportional hazards	Heat wave exposure during pregnancy (Definition 2)	Maternal age, marital status, Indigenous status, parity, baby's gender, socioeconomic disadvantage, air pollutants, cold temperature exposure	HR (95% CI) first month	1.54 (1.27–1.87)
					HR (95% CI) sixth month	1.75 (1.44–2.12)
			Heat wave exposure during pregnancy (Definition 6)		HR (95% CI) eighth month	1.52 (1.11–2.09)
Weng 2018	SPSS	Generalized linear model	Maternal exposure to temperatures above 23.5 °C and stillbirth	Congenital anomalies, neonatal death, sex at birth, APGAR score, delivery mode, gestational age, birth weight, birth region (north vs. south), obstetric complications, parity, birth year, maternal ethnicity	RR (95% CI) 23.5–25.4 °C	1.08 (1.01–1.14)
					RR (95% CI) 25.5–27.4 °C	1.09 (1.03–1.15)
					RR (95% CI) 27.5–29.4 °C	1.16 (1.10–1.22)
					RR (95% CI) 29.5–30.8 °C	1.17 (1.09–1.26)
		Descriptive	Incidence	Not applicable	Percent (%) and temperature	1.30% at 29.4 °C

incidence of stillbirths highest above 29.4 °C (1.30% PAR) (Weng et al., 2018b).

4. Discussion

Exposure to ambient heat and cold during pregnancy is associated with increased risk of adverse pregnancy outcomes, including stillbirth (Asamoah et al., 2018a). Among the twelve studies reviewed, all found an increased risk of stillbirth associated with exposure to hot and cold ambient temperatures throughout pregnancy and in the week preceding delivery.

Measuring stillbirth risk as a result of exposure to ambient temperatures without an explanatory physiological mechanism is tremendously difficult. There is wide variation in methodology in existing literature and lack of confirmatory evidence, mostly explained by insufficient methodology and ambiguous data linkage practices. All study results included in this review should be interpreted conservatively due to an inability to generalize data for individual-level risk. To accurately assess individual-level risks of stillbirth, environmental exposures would ideally be captured and linked uniquely to the mother. In existing studies, linking clinical data by place of usual residence to environmental data retrospectively appears to demonstrate the most sensitive effect using average weekly daily temperature recorded from ground weather stations (Rammah et al., 2019). However, this approach does not account for individual-level variation in movement patterns during pregnancy, home environment (open air dwelling vs. climate controlled house), indoor air quality, or outdoor exposures unique to the mother. Due to an absence of prospective studies and infeasibility of a randomized control trial, it is not yet possible to describe a causal or dose-response association between ambient temperature exposure during pregnancy and stillbirth. Future studies should focus on understanding competing risk factors in the context of environmental exposures and consider potential effect modification or mechanisms that may impact body temperature regulation during pregnancy (Naimi and Auger, 2016; Smith and White, 2016). Examples include other recent studies that indicate a high level of stillbirth risk in the presence of other ecological risk factors including air and water quality, occupational health (in the context of occupational hazards), socioeconomic status, access to health services, and access to affordable high-quality foods (Sohi et al., 2014; Walker et al., 2010; Hager et al., 2017). In one study, household (indoor) air quality was independently associated with 1.22 times risk (95% CI 1.06–1.14) of stillbirth and could potentially interact with ambient temperature exposures among other lifestyle and clinical risk factors (Lee et al., 2020).

Future studies should focus on data that includes specific geographical information for maternal health and pregnancy outcomes is needed. Kanner et al. discussed a need to analyse population-level data in larger, more diverse populations as a next step for understanding temperature and stillbirth (Kanner et al., 2020). However, a key challenge with population-level studies that often use registry data is lack of granularity and privacy concerns for maternal residential data. The limitations in existing studies resulting from linkage of climate data to generalized geographic regions is likely to persist with larger datasets. In Australia, the most granular level of data available for stillbirths is currently Statistical Area 2 (SA2) and is arguably unsuitable for a detailed geographic analysis. SA2 is approximately three levels larger than the randomised mesh block, which is the smallest captured geographic area and unavailable for research use due to important privacy protections (Australian Bureau of Statistics (ABS), 1011). Rather than exploring large-scale studies, it may be more beneficial to focus on highly sensitive hospital-level datasets for retrospective studies or prospective studies with consent to geocode maternal residential address for linkage of climate data. Geocoded address and travel range data during pregnancy can be linked to remote sensing data and may provide a more realistic estimate of exposure while accounting for spatial clustering among other effects (Basu et al., 2016).

In the Australian setting as characterized by Strand et al., there would be 353 stillbirths per 100,000 pregnancies at 15 °C, compared with 610 stillbirths per 100,000 pregnancies at 23 °C or warmer (Strand et al., 2011). Although these results should be interpreted with caution due to high degree of uncertainty, the population attributable risk (PAR) of stillbirth among pregnant mothers exposed to hot and cold ambient temperatures could potentially explain 17–19% of preventable stillbirths according to one study (Ha et al., 2017). Ambient temperature exposure may have chronic and acute effects on stillbirth risk, even in temperate zones. In a similar study, low and high temperatures in the 2nd trimester of pregnancy were associated with stillbirth (Li et al., 2018b). The effects of low temperature became stronger, whereas effects of high temperature became weaker from 1994 to 2014 (Li et al., 2018b). According to a report published jointly by Energy Efficient Strategies and Australian Bureau of Statistics, actual and forecasted trends of household and population air conditioning has increased by a minimum of 9% every year since 1996 and was expected to continue to increase (Energy Efficient Strategi, 2006). Compared to other Australian cities, Brisbane reported the second highest cooling hours (600 h) and second lowest heating hours (100 h) (Energy Efficient Strategi, 2006), suggesting potential vulnerabilities at both hot and cold ambient temperature for pregnant women. Further household-level analyses are needed to better understand whether 'adaptation' to high temperatures is confounded by an increase in air conditioner units or improved access to residential HVAC. Impact of socioeconomic status and rurality need to be carefully considered in the context of environmental exposures, especially where access issues to household climate control arise.

The biological mechanism of ambient heat exposure during pregnancy and impact of exposure windows with stillbirth remains unclear. This evidence indicates a need to explore opportunity and feasibility for stillbirth risk management, particularly among preventable stillbirths and stillbirths occurring in LMIC where risk is highest and resources are most limited (United Nations Inter-agen, 2020). There is currently no clinical guideline that describes any preventive measures or risk management interventions for stillbirth among women who may be exposed to ambient temperatures during pregnancy. Higher ambient temperatures have also been associated with pre-term delivery (Cox et al., 2016) and risk of neural tube defects (Auger et al., 2017b), with little mechanistic understanding. The highest rate of stillbirth was observed at very early preterm gestations (under 28 weeks) in one LMIC setting (Asamoah et al., 2018b), where stillbirth rates are already elevated compared to HIC settings (Flenady et al., 2011).In a study examining all-cause mortality and temperature events in the United States, longer-lasting heat days resulted in elevated mortality and cold-related risk was higher in warmer ('southerly') locations (Allen and Sheridan, 2018). It seems logical that a failure to regulate body temperature (hyper- or hypothermia) during pregnancy may result from hot and cold ambient temperature exposure, however, existing studies have focused on distinct pathways and conditions that demonstrate similar physiological stresses resulting from infectious diseases and chronic conditions. When considering SARS-CoV-2 infection and vertical transmission, 56% of mothers testing positive presented with fever where gestational complications reached as high as 33% including a 35% rate of preterm delivery and 2.5% rate of stillbirth (Chamseddine et al., 2020). Among TORCH pathogens (infectious pathogens causative of congenital infections), fever is an established symptom and contributing risk factor for poor pregnancy outcomes (Vouga et al., 2019). Further, the role of dehydration in the context of stillbirth among pregnant women exposed to ambient temperature has yet to be explored. Current studies that examine the effects of dehydration and stillbirth focus on diarrheal diseases (Schillberg et al., 2016) or maternal conditions such as hyperemesis gravidarum (Dinberu et al., 2019). To understand the effects of maternal exposure to ambient temperatures, future studies should focus on biological mechanisms and contributing factors.

4.1. Limitations

While the quality scores based on the adapted CASP assessment were generally high, the studies included in the review are potentially vulnerable to publication and reporting bias. Most studies used routine, retrospective data and would be less likely to publish if no significant effect was found. Published study protocols were not found for any of the included studies and no pre-specified cut-points or definitions were described in any methods sections. Therefore, it is possible that certain outcomes, gestational age groups, exposure thresholds, or linkage approaches (lag period) might have been selected due to effect size or significance and contributed to model selection. Study findings should be interpreted conservatively due to lack of individual-level data linkage, which assumes similar risk exposure for all women in a defined catchment (e.g., postcode or hospital region).

Study results are further limited by a lack of meta-analysis to estimate effective size ambient temperature exposure and stillbirth or vibration of effects assessment to quantify the variability of results (Patel et al., 2015). The studies included in this review are heterogenous: High variability in model selection and statistical methods was observed. Among studies that applied survival analyses methods, each study managed time-varying covariates uniquely. For these reasons, pooling of results was not feasible or clinically appropriate. Lastly, no study considered important potential confounders such as maternal pregnancy conditions, sleep position during pregnancy (Gordon et al., 2015), personal movement patterns, home environment, variation in type of ambient temperature exposure, or food access indicators in any statistical model. Lifestyle factors, pre-existing and pregnancy-related health conditions, and other environmental indicators for quality of life should be considered in future studies.

5. Conclusion

Exposure to hot and cold ambient temperatures is associated with increased risk of stillbirth and should not be ignored. Where possible, pregnant women should protect themselves against high and low ambient temperatures during pregnancy, especially during late pregnancy. Clinicians and policy makers should consider developing appropriate clinical practices guidelines to better accommodate susceptible women during pregnancy to avoid potential stillbirth resulting from exposure to environmental factors. Existing studies across LMIC and HIC settings demonstrate similar effects of increased risk of stillbirth using a variety of methodological approaches for exposure assessments, exposure windows (including lag time), and data linkage strategies. Ambient temperature exposure and other environmental exposures should be further investigated and considered for risk modelling and risk management during pregnancy as a strategy to reduce stillbirth. In the context of temperature exposure, the roles of other socioeconomic, lifestyle, and clinical factors should be further evaluated. To fully understand the effects of maternal exposure to ambient temperatures, future studies should focus on biological mechanisms and contributing factors in addition to improving measurement of ambient temperature exposure.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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