A

DISSERTATION REPORT

ON

IMPACTS OF ENVIRONMENTAL RISK FACTORS ON PREGNANCY AND PREGNANCY-RELATED BIRTH OUTCOMES:

A SYSTEMATIC REVIEW

By

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Under the Guidance of

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Completion of Dissertation from respective organization

The certificate is awarded to

MUSKAN GUPTA

in recognition of having successfully completed his/her

Internship in the department of

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Public Health

has successfully completed her Project on

IMPACTS OF ENVIRONMENTAL RISK FACTORS ON PREGNANCY AND PREGNANCY RELATED BIRTH OUTCOMES

From 1^{ST} MARCH TO 10^{TH} JUNE 2021

The INCLEN Trust International, New Delhi

She comes across as a committed, sincere & diligent person who has a strong drive & zeal for learning.

We wish him/her all the best for future endeavors.

Training & Development

Dr. Manoj Kumar Das

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TO WHOMSOEVER IT MAY CONCERN

This is to certify that **Muskan Gupta** student of PGDM (Hospital & Health Management) from International Institute of Health Management Research, New Delhi has undergone internship training at **The INCLEN Trust International**, **New Delhi** from 1st May 2021 to 10th June 2021..

The Candidate has successfully carried out the study designated to him during internship training and his/her approach to the study has been sincere, scientific and analytical.

The Internship is in fulfilment of the course requirements.

I wish him all success in all his/her future endeavors.

Ms. Divya Aggarwal	Mentor
Associate Dean, Academic and Student Affairs	Dr. Nitish Dogra
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CERTIFICATE OF APPROVAL

The following dissertation titled **"IMPACTS OF ENVIRONMENTAL RISK FACTORS ON PREGNANCY AND PREGNANCY RELATED BIRTH OUTCOMES"** at **"The INCLEN Trust International, New Delhi"** is hereby approved as a certified study in management carried out and presented in a manner satisfactorily to warrant its acceptance as a prerequisite for the award of **PGDM (Hospital & Health Management)** for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the dissertation only for the purpose it is submitted.

Dissertation Examination Committee for evaluation of dissertation.

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CERTIFICATE FROM DISSERTATION ADVISORY COMMITTEE

This is to certify that **Ms. Muskan Gupta,** a graduate student of the **PGDM (Hospital & Health Management)** has worked under our guidance and supervision of Dr. Nitish Dogra. She is submitting this dissertation titled "**IMPACTS OF ENVIRONMENTAL RISK FACTORS ON PREGNANCY AND PREGNANCY RELATED BIRTH OUTCOMES**" at "**The INCLEN Trust International**" in partial fulfillment of the requirements for the award of the **PGDM (Hospital & Health Management).**

This dissertation has the requisite standard and to the best of our knowledge no part of it has been reproduced from any other dissertation, monograph, report or book.

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **Impacts of environmental risk factors on pregnancy and pregnancy related birth outcomes** and submitted by **Muskan Gupta,** Enrollment No. **PG/19/047** under the supervision of **Dr. Nitish Dogra** for award of PGDM (Hospital & Health Management) of the Institute carried out during the period from **1st March to 10th June 2021**, embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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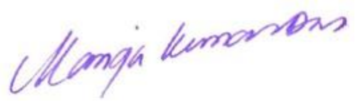

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Date: 9th June 2021

Place: New Delhi, India

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I hereby certify that the report has been solely prepared by me under the guidance of my guide from The Inclen Trust International. Before starting the project report, earlier I had obtained and attached hereto a written permission from my guide duly signed by him and included in my dissertation.

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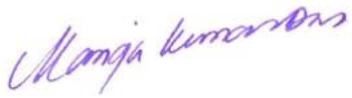

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Contents

ABBREVIATIONS

PM	Particulate matter
MAT	Maximum apparent temperature
AQI	Air quality index
PTB	Preterm birth
LBW	Low birth weight
SGA	Small gestational age
O3	Ozone
NO2	Nitrogen dioxide

ABSTRACT

Background and Rationale

Environmental factors have adversely shown impacts on pregnancy and pregnancy related outcomes. Air pollution and rising temperature are the most common facets of the environment that are causing adverse impacts on birth related outcomes thus increasing the infant mortality ratio. This study is conducted to determine the impacts of environmental factors on pregnancy and related adverse birth outcomes (stillbirth, low birth weight, preterm birth, & congenital anomalies).

Problem statement/ Research Question

To study the pregnancy related adverse birth outcomes in relation to climate/environmental factors. Air pollution level and rising temperature have been seen as the potential environmental factors to cause adverse birth outcomes. The report will therefore identify the repercussions of above stated environmental factors and their impact on adverse pregnancy related outcomes. The outcomes taken in reference for study are stillbirth, low birth weight, preterm birth, and congenital anomalies.

Objectives:

1) To study the impact of air pollution in terms of AQI (PM<2.5) and ambient temperature conditions (ambient heat, heat stress, cold spells) as the environmental factors responsible for pregnancy/birth related adverse outcomes including stillbirths, low birth weight (LBW), Preterm births (PTB) and neonatal deaths.

2) To systematically review the association between air pollution & temperature conditions with birth outcomes as stillbirths, low birth weight, preterm birth, neonatal mortality.

Methodology:

Electronic databases and bibliographies of articles selected are reviewed systematically. The articles identified are in English language with studies reporting adverse birth outcomes. The databases searched are PubMed and Cochrane. Major keywords used are pregnant women, pregnancy, infants, neonates, air pollution, PM <_2.5, PM10, ambient heat, ambient temperature, heat stress, preterm birth/PTB, stillbirth, LBW, and neonatal death.

Results

34 published peer reviewed manuscripts which examines the impact of environmental factors such as air pollution, specifically PM<_2.5, PM 10, ambient temperature including cold spells & heat stress on birth outcomes**.** Exposure to the responsible factors i.e., high temperature conditions during the entire pregnancy or in the last trimester of the delivery results in small gestational age/ PTB, Stillbirth. Also temperature and air pollution have been seen as the factors responsible for PTB and LBW, if the prenatal exposure during the 4th month and 3rd trimester of the pregnancy is more. However, no significant impact of air pollution and temperature have been seen for neonatal mortalities.

Conclusion:

The study will further strengthen the existing recorded data related to the problem statement thus will help in decreasing the maternal and child mortalities, and will improve the outcomes. Important future recommendations and directions include developing methods to detect the duration of exposure along with the intensity the women could tolerate to avoid the resultant adverse birth outcomes.

Keywords: pregnant women, pregnancy, infants, neonates, air pollution, PM <_2.5, PM10, ambient heat, ambient temperature, heat stress, preterm birth/PTB, stillbirth, low birth weight /LBW, and congenital anomalies.

Chapter I – Introduction

Background: Environmental factors have adversely shown impacts on pregnancy and pregnancy related outcomes. Air pollution and rising temperature are the most common facets of the environment that are causing adverse impacts on birth related outcomes thus increasing the neonatal and child mortality ratio. Adverse birth outcomes and fetal growth has become an important emerging field of environmental epidemiology. During recent years, a limited number of studies have been performed giving evidence of association between prenatal exposure to air pollution and changing temperature conditions. Several outcomes have been related to exposure to high AQI during pregnancy which includes stillbirth, congenital anomalies, low birth weight, preterm birth, and pregnancy loss.
Purpose: Therefore, this study is being conducted to systematically review the association between the exposure and outcomes where exposure is air pollution levels and changing temperature conditions during the prenatal period and outcomes measured are adverse birth outcomes stated above.

Pregnancy and birth related outcomes have been adversely affected by environmental factors. A number of factors are responsible for producing the undesirable consequences related to pregnancy and childbirth [1,2]. Exposure to air pollution, rising temperature conditions, environmental chemicals such as persistent organic pollutants (POPs), PM<2.5, PM 10, NO2, O3, Heat stress, Cold spells have their implication in adverse pregnancy-related outcomes. As suggested and reported in a number of reviews and studies, air pollution and adverse temperature conditions are considered as the major facets to create inimical impacts to a larger extent [1,2]. Outcomes such as stillbirth, congenital anomalies, low birth weight, preterm birth, and pregnancy loss have been associated with the rising air pollution levels and adverse temperature conditions, however effects are not seen as consistent in studies [2].

Air pollution since the beginning is largely recognised as a risk factor for a number of diseases and disorders. It is associated with the increased mortality, increased emergency visits and hospital admissions for many of the respiratory diseases and CVDs. Impacts are observed largely in those populations who are in the tail of the age distribution i.e., the infants and elderly [2]. In relation to environmental epidemiology, the study of fetal growth, stillbirths, congenital anomalies and birth related other outcomes have become a focussed area and an important emerging field of study. Pregnant women and fetuses in early age respond differently to environmental factors as compared to other age group populations [3].

Prolonged exposure to changed temperature conditions leads to physical immaturity [6] which is related to low-birth-weight infants. Also, assessing the individual pregnant women exposure to air pollution and temperature conditions is often in demand but requires extensive resources [3]. Therefore, other methods to determine the exposure level and outcomes have been used to estimate the desired results. For mapping the exposure of air pollution and rising temperature conditions during pregnancy (starting from initial trimester till delivery of baby), a number of methods have been used. Most studies have assessed the exposure level using the outdoor air pollution monitoring station data [3, 4].

Chapter II - Background Statement:

Review of Literature

This literature review has been drafted to garner the understanding about the background of the problem statement which is association of the environmental factors and pregnancy outcomes. This literature review section is conducted using explorative search on Medline, PubMed and Springer databases. Research papers published related to the problem statement are considered for extracting the information for this literature review. Key terms used to conduct the study are – Low birth weight, stillbirths, preterm birth, environmental factors, air pollution, temperature, PM 2.5, congenital anomalies, neonatal/ infant deaths.

Studies suggested that ambient air pollution has also an impact on the pregnancy outcomes. Number of studies have published evidence showing the possibility of association between the air pollution levels and adverse pregnancy outcomes [5,6]. Several studies also have kept their focus on the changing temperature conditions along with the air pollution level as the environmental factors which have an adverse impact on the pregnancy and related outcomes. Now these outcomes could be in terms of maternal health, infant and child mortalities, low birth weight related issues, preterm delivery and stillbirths [7, 8].

Low birth weight (LBW) and preterm birth have become the leading causes of infant and neonatal mortality as well as the maternal deaths and long-term morbidities also [9]. And environmental factors and changing conditions are contributing to the disparities in pregnancy outcomes and related impacts [9]. Preterm birth and LBW infants have shown an increased risk of short-term life (less than 1 year) and long-term health and developmental complications. Therefore, it is of immense importance that we first understand the conditions the women should not be in during the whole pre-pregnancy phase. Then subsequently intervening to prevent such conditions to overall improve the health of the nation [9,10].

Preterm birth (PTB): Elevated physical environmental risk factors also increase the risk of adverse pregnancy outcomes. Some review studies have shown the relationship between the environmental factors and preterm birth [12] as the adverse pregnancy outcomes but none offers the framework for understanding the association within the larger context of pregnant host and risk factors [9].

Stillbirths and perinatal maternal deaths are also the major health concerns. Stillbirth rate is majorly counted as the fetal death in >_20 week of gestation. Air pollution and temperature conditions are also found to be responsible environmental factors for increasing the stillbirth rates. Airborne pollutants and PM are a complex mixture of extremely small particles and liquid droplets with acids, soil and dust particles along with metal particles and organic chemicals that are harmful for the body when inhaled. These micro particles measure <2.5 µm and can pass through the lungs, impacting the multiple organs of the body [12]. In pregnant women, these PM can even cross the placenta through respiratory tract and blood streams. And causes fetal health complications to both foetus and mother [11]. Few studies have reported the association of stillbirth and PM 2.5 air pollutants [12].

Pregnant women are more at risk due to air pollution exposure than the non-pregnant women and leading to neonatal deaths [11]. Effects of air pollution have also been seen to increase the congenital anomalies and malfunctions. Few studies have given an idea that exposure to PM <_2.5 can also trigger the autoimmune disorders but not much evidence has been produced regarding the same [11].

Therefore, this study is focussed on producing the evidence which would relate the association between air pollution, temperature with pregnancy and related outcomes.

Chapter III - Methodology

3. Methodology

This section is designed to describe the procedures adopted in this research.

3.1 Search strategy and article selection

In this study, we conducted a systematic review of the journal articles selected and referenced above. Meta-analysis of observational studies in Epidemiology (MOOSE) criteria is followed for reporting.

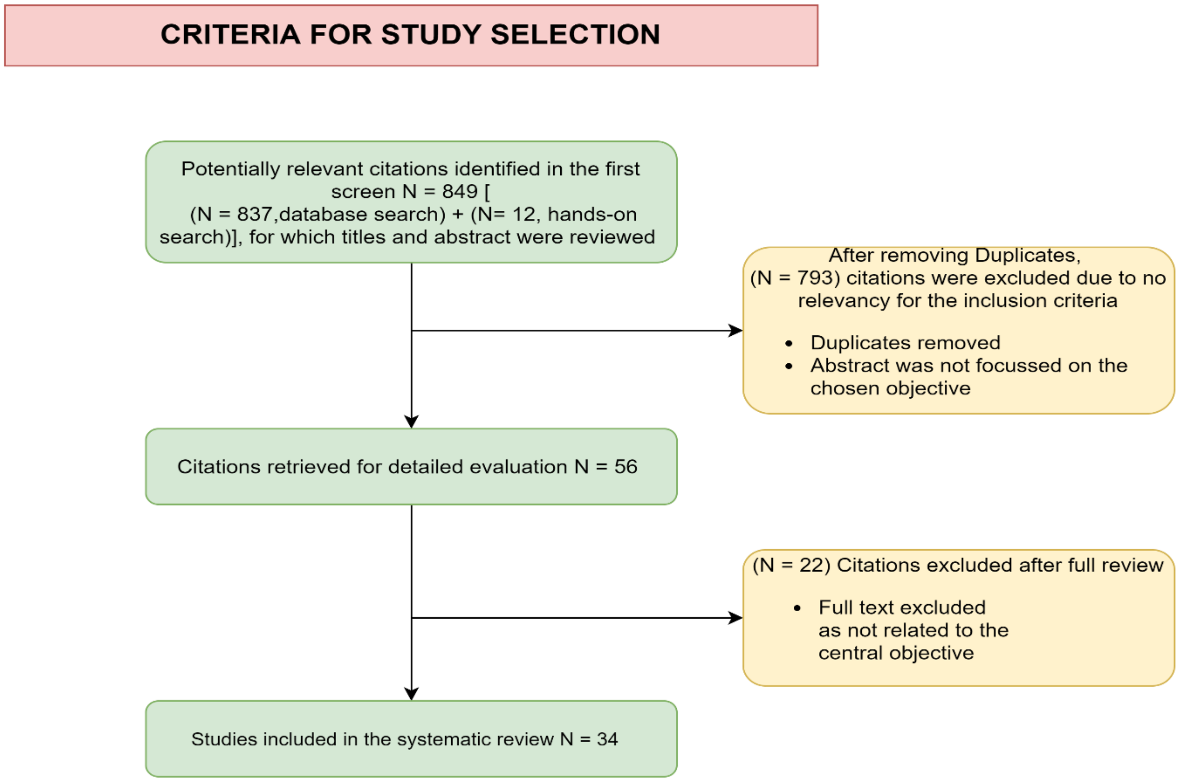
Epidemiologic literature published in the recent peer reviewed journals are assessed and selected for conducting the systematic review and electronic databases including PubMed and Cochrane are searched for the defined objective. Time restriction has also been maintained in our search for a decade only i.e., we reviewed the recent articles published between January 2011 to January 2021. Also, the bibliographies of the selected articles are reviewed systematically including some hands-on search results to make the study comprehensive. The articles identified are in English language with studies reporting adverse birth outcomes. We used the following keywords or their combinations in the search strategies: ‘air pollution’, ‘PM <_2.5’, ‘PM 10’, ‘ambient temperature’, ‘ambient heat’, ‘heat stress’, ‘adverse birth outcomes’, ‘preterm birth’, ‘stillbirth’, ‘LBW’, and ‘congenital anomalies’. The data is extracted from already published manuscripts therefore no ethical considerations were necessary.

3.2 Study question

To assess the adverse birth outcomes of pregnant women to air pollution (PM<_2.5 & PM 10) and temperature conditions (hot heat waves and cold spells, and heat stress).

3.3 Criteria for selecting studies

In this review only original articles have been included which directly assessed the relationship between environmental factors (eg: air pollution, PM<2.5, PM10, ambient temperature including extremely hot heat waves and cold spells, and heat stress) adverse birth outcomes (eg; preterm birth, LBW, stillbirth and congenital anomalies). Also, if the studies have provided enough information on the association of exposure (pregnant women/ maternal) and outcome of interest were considered as eligible for the inclusion criteria. No additional data/information has been gathered by any contact with any of the primary sources. In exclusion criteria, we kept the studies which do not define the association of the subjects (pregnant women) to exposure (environmental factors) and the outcome of interest (stillbirths, congenital anomalies, LBW, preterm birth (PTB), neonatal mortality).



Out of 849 articles selected, 793 citations were removed followed by removal of duplicates and no relevancy of the content in abstract and title to be included in the study. 53 studies were included for full text review out of which 24 excluded as they fall under exclusion criteria mentioned above. After excluding the non-relevant studies, 34 studies have been included finally.

3.4 Type of studies incorporated

Cohort studies including prospective and retrospective analysis, Time series analysis, Time-to-event studies and cross-sectional studies are reviewed. No review/ unpublished studies have been included.

3.5 Types of participants

Studies with subjects as pregnant women exposed to air pollution and temperature conditions during pregnancy are included.

3.6 Assessment of exposure

Data regarding maternal exposure to temperature conditions and air pollutants (PM<2.5, PM 10, O3, NO2) obtained via sources were eligible to fit in the inclusion criteria thus included.

3.7 Outcomes of interest

Studies which reported the final outcomes as any of the following were included:

1. Stillbirth: death in <20 weeks of conception
2. LBW (Low birth weight): neonates with <2.5 kg of birth weight
3. PTB (preterm birth): birth/ gestational age <37 weeks
4. Congenital anomalies/ malformation
5. Neonatal mortality: deaths during 28 completed days after birth

3.8 Methods of review

3.8.1 Data extraction:

Data was extracted from the existing and included manuscripts/ studies by the second author. No modifications have been made in the original data.

3.8.2 Data synthesis & analysis:

Due to heterogeneities of the studies incorporated in this review and measure of outcomes (air pollution and temperature conditions taken altogether) taken against the subject selected (pregnant women), a decision has been taken to conduct a systematic review and not meta-analyses.

❖ **Study Quality Scope:** Tool used for assessing the quality of studies is CASP guidelines

CASP guidelines	Score 0/1
Q1. Did the study address a clearly focused issue?	0/1
Q2. Did the authors use an appropriate method to answer their question?	0/1
Q3. Was the cohort recruited in an acceptable way?	0/1
Q4. Was the exposure accurately measured to minimise bias? (maternal age)	0/1
Q5. Was the outcome accurately measured to minimise bias? (maternal/perinatal/ outcome)	0/1
Q6. a. Have the authors identified all important confounding factors?	0/1
b. Have they taken account of the confounding factors in the design and/or analysis?	0/1
Q7. a. Was the follow up of subjects complete enough?	N/A
b. Was the follow up of subjects long enough?	
Q8. What are the results of this study? (Are they communicated clearly?)	0/1
Q9. How precise are the results?	0/1
Q10. Do you believe the results? (How believable are the results?)	0/1
Q11. Can the results be applied to the local population?	N/A
Q12. Do the results of this study fit with other available evidence?	0/1
Q13. Was the study representative of the entire population from which subjects were recruited?	0/1

Table 1 (a): Characteristics of included studies on association between Temperature/ Heat Stress and preterm birth and Low birth weight (LBW)

S.NO.	Study & Year	Location	Type of study	Duration of study	No. of participants (Sample size)		Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	Wang. Y. Y., Li. Q., et al. (2020) [13]	China	Cohort Study	Dec 2013	Nov. 2014	12,81,859 Singleton live birth cohort	Recorded daily mean temperature from 824 weather stations in China	**Preterm birth**- Overall preterm birth rate was 8.1% (104,493 preterm births). Exposure to relatively low or high temperatures during the entire pregnancy significantly increase the risk of preterm birth, with hazard ratios (HRs) [95% confidence intervals (CIs)] of 1.03 (95%CI: 1.02, 1.04) for relatively low (9.1 °C) temperature and 1.55 (95%CI: 1.48, 1.61) for relatively high (23.0 °C) temperature	Cox proportional hazard regression models	Gestational week & specific hazard ratios associated with increase in temperature conditions	HR low temperature = 1.02 (95% CI, 1.00, 1.03) HR for high temperature = 1.90 (95% CI, 1.00, 1.03)	11
2	Ranjbaran. M., Mohammadi. R., et al. 2020 [15]	Tehran, Iran	Time series analysis	March 2015	March 2018	542,492 births	daily data of preterm birth, air pollution and min., max., & mean temperature were recorded	**Preterm birth** - Highest RR for extreme (26.9 °C) and moderate (24.8 °C) heat of minimum temperature (RR = 1.17) & (RR = 1.15) respectively. - Each 10-unit increase in PM2.5 in Lag 0 (RR = 1.008; 1.001–1.014) and lag 1 (RR = 1.004; 1.001–1.007) had significant effects.	Distributed lag Non-Linear model RR calculated (DLNM)	RR calculated for extreme, moderate and mild heat and for each 10-unit increase in air pollutants	RR extreme temperature =1.17 (95% CI) RR moderate temperature =1.15 (95% CI) for each 10 unit rise in air pollutants level RR = 1.008 (95% CI)	9

3	Bruckner. T. A., Modin. B., et al, 2014 [16]	Uppsala, Sweden	Cohort Study	1915	1929	14000 deliveries	daily ambient temperature series	**Preterm birth-** Risk of stillbirth rose as ambient temperature during pregnancy fell (hazard ratio for a 1°C decrease in temperature, 1.08; 95% confidence interval, 1.00 to 1.17)		Linear regression model & Cox proportional hazards	stillbirth and specific hazard ratio is associated with each degree rise in temperature	HR for 1 °C rise in temperature = 0.92 (95% CI, 0.86 to 0.996) HR for a 1°C decrease in temperature = 1.08; (95% CI, 1.00 to 1.17)	11
4	Mohammadi. D., et al., 2019 [17]	Sabzevar, Iran	Time series analysis	2011	2017		Data obtained from meteorological station in the city	**Preterm birth-** RR with the extremely hot mean temperature showed the highest risk increase for both main model and air pollution-adjusted model (RR 1.60; 95% CI 1.37: 1.86)		Quasi-Poisson distribution wit DLNM		RR extreme cold temperature = 1.83 (95% CI, 1.61 to 2.09) RR extreme hot temperature = 1.60; (95% CI 1.37: 1.86)	8
5	Liu. X., et al, 2020 [18]	Guangzhou, China	Cohort Study	2016	2020	4928 pregnant women birth cohort	Data obtained from hospital setting	**Preterm birth-** Maternal exposures to higher temperatures during pregnancy may increase the risk of PTB, and lower temperatures may decrease the risk of PTB.		DLNM model with Cox proportional hazard model	Gestational week & specific hazard ratios associated with increase in temperature conditions	Peak effect was found during the 6th week (HR = 1.79, 95% CI: 1.26, 2.54) and 24th week (HR = 1.83, 95% CI: 1.27, 2.62).	11
6	Mathew. S., Mathur. D., (2020) [18]	Australia	Cohort Study	January 1986	2013	26460 singleton births	Data obtained from NT Department of Health	**Preterm birth** - Reported 1401 births (8.3%) of the total sample taken after applying exclusion criteria. Delayed effects are also observed closer to 3 weeks before delivery & Immediate risks to preterm birth are also observed for cold temperature exposures (0 to –6 °C), with an increased relative risk of up to 10%.		Poisson Generalised Additive Model with DLNM and Lag specific RR calculated	Percentage change during heat waves and each 2 degree C rise in MAT	RR at median temperature (41 - 45 °C) = 1.05 (8.3%) at (95% CI, 1.03 - 1.15) An immediate increase in RRs (at day of delivery & 2 to 3 week before delivery) of up to 2% & 4.5 % observed respectively RR low temperature (0 to -6 °C) = 7.2% (95% CI: 1.018 to 1.130) and 36.7%	12

												(95% CI: 1.023 to 1.824) respectively	
7	Schifano. P., Lallo. A., et al., (2013) [19]	Rome	Time series analysis	2001	2010	132,691 births	Certificate of Delivery Care Registry	**Preterm births** - reported 7259 (5.5%) of the total sample taken after applying exclusion criteria		Poisson Generalised Additive Model with DLNM and Lag specific RR calculated	Percentage change during heat waves and each 1 degree C rise in MAT	percent change of 1.87% (95% confidence interval (CI) 0.86– 2.87) in the rate of preterm births per 1 °C increase in MAT RR at warm temperature (20.4 - 30.6 °C) = 1.93% change, (95% CI 0.88–2.98) RR at cold temperature (3.0 - 8.8 °C) = 0.85% change (95% CI, −0.14, 1.85) RR at PM 10 = 0.33% change for 1 μg/m3 (95% CI 0.01–0.66)	11
8	Zhong. K., Lu. C., (2018) [20]	Changsha, China	Cohort Study	Sept. 2011	Jan 2012	3509 preschool children	Questionnaire	**Preterm birth** - Prevalence of PTB (4.1%) was associated with outdoor temperature. t heat exposure was related to an elevated risk of PTB, with higher risk of PTB for nocturnal exposure and warm seasons.		Linear regression model	Association calculation between mothers exposed to outdoor air temperature during three trimesters and for 24 hr in different seasons of pregnancy	ORs (95% CI) = 1.34 (1.11–1.62) for increase of 1 °C in temperature exposure during pregnancy Risk increases during the 2nd trimester, with ORs exposure to temperature = 1.03 (95% CI, 1.00–1.06) and ORs extreme heat stress = 1.01 (95% CI, 1.00–1.02)	12

9	Sun. S., Weinberger. K. R., et al., (2019) [21]	403 countries of US	Retrospective Time series analysis	1989	2002	32 million (31,921,046) singleton births	US Centers for Disease Control and Prevention's National Centre for Health Statistics	**Preterm birth** - Days of extreme heat, but not extreme cold, are associated with higher risk of preterm birth in the contiguous US.		DLNM model with quassi - poisson time series model	Daily mean ambient temperature using PRISM and its association with exposure look up	RR extreme heat = 1.025 (95% CI: 1.015, 1.036) RR extreme cold = 0.985 [95% CI: 0.976, 0.993]). Days of extreme and moderate heat accounted for = 154 (95% eCI: 127, 173) and 586 (95% eCI: 457, 693) preterm births per million pregnancies in the study population, respectively	12
10	Weng. Y.H., Yang. C. Y., (2017) [22]	Taiwan	Retrospective cohort study	2001	2010	2 million (2,123,751) births	MAT data obtained from Central Weather Bureau, Taiwan Maternal and neonatal data were derived from the Birth Notification System (BNS), a database of Ministry of Health and Welfare, Taiwan	**Preterm birth** - Maternal exposures to temperature extremes carry greater risks for adverse neonatal outcomes – including stillbirth, preterm birth, and low birth weight. optimal ambient temperatures to minimize adverse neonatal outcomes are 21.5~25.4 °C		Log-binomial model	Correlation between ambient temperature conditions at birth and adverse neonatal outcomes.	IR preterm birth = 7.38% (95% CI, p<0.05) W shaped curve, highest ambient temperature conditions taken are 29.4 °C - 30.8 °C	12
11	Walfisch, A., Kabakov, E. et al., (2016) [23]	Israel	Retrospective Time	1988	2012	263,709 deliveries	Meteorological data were collected from the Israeli	**Preterm birth** - Increased outdoor temperature has a significant effect		Poisson regression model with time -	Correlation between ambient temperature	IRR (Incidence rate ratio) Summer = 2.8 (95% CI 2.2 – 3.7; p <0.001) Elevation in one heat	10

			series analysis				Meteorological Service & pregnancy data from Soroka University Medical Center (SUMC)	on the incidence of spontaneous, but not induced, PTD.		harmonic model	conditions at birth and adverse birth outcomes as preterm birth.	stress unit was associated with a 6.3% higher risk IRR Winters = 1.2 (95% CI, 0.9 – 1.6; p< 0.184)	
12	Strand. L., et al., (2012) [25]	Australi a	Cohort Study	2005	2009	101,870 births	Hourly data on temperature, relative humidity, and air pollution, provided by the Queensland Department of Environment and Resource Management for 5 pollution stations.	**Preterm birth-** Association between increased temperature and increased risk of stillbirth and shorter gestation.		Cox proportional hazards model	Gestational week & specific hazard ratios associated with increase in temperature conditions	HR for a live preterm infant (28–36 weeks) = 1.20 at 27°C (High temperature) HR for a live preterm infant (28–36 weeks) = 0.97 to 1.00 at 16°C to 21°C (Median temperature)	10
13	Orryo.V., Diaz. J., et al., (2016) [26]	MAdrid, Spain	Time series analysis	2001	2009	298,705 singleton births	Daily mean concentrations (μg/m3) of PM2.5 and PM10, O3 and NO2, Leqd for measuring acoustic pollution and Maximum and Minimum daily temperature	**Preterm birth** - PM2.5, diurnal noise levels and O3 have a short-term impact on total births and heat temperatures on preterm births		Time-series analysis with DLNM	Daily mean ambient temperature using PRISM and its association with exposure look up	RR at PM2.5 = 1.020 (95% CI, .008 - 1.03 RR O3 concentrations = 1.012, (95% CI, 1.002 - 1.022) RR Leqd for noise = 1.139 (95% CI, 1.124 - 1.154) for the total number of births, and	9

							(°C), mean Humidity in the air (%) and Atmospheric Pressure (HPa), for temperature conditions					RR heat temperatures at Lag 1 = 1.055, (95% CI, (1.018 - 1.092	
14	Cheng. P., Peng.L., et al., (2021) [27]	Xuzhou, China	Time series analysis	2016	2019	103,876 singleton deliveries		**Preterm birth -** low ambient temperatures may lead to preterm birth, suggesting that women should stay away from low temperatures during pregnancy		Quasi-Poisson model with distributed lag nonlinear models (DLNM)		RR Extreme cold temperature (− 2.8 °C) = 1.659 (95% CI, 1.177–2.338) and RR moderate cold temperature (6.8 °C) = 1.456 (95% CI 1.183–1.790)	8
15	Yu. X., Feric. X., et al., (2018) [28]	Puerto Rico	Exploratory time series analysis	1994	2012	1,005,340 singleton birth	National Oceanic and Atmospheric Administration	No Significant outcome- weather factors do not explain the marked increase and decrease in PTB rate,		Distributed lag non-linear model (DLNM)	Association of lagged effect of temperature on birth outcome over monthly timescales	RR recorded = 1 for 32 °C in this tropical island	11
16	Changchang. L., Bloom. M.S., (2021), [29]	Shenzhen, China	Time-to-event analysis	2003	2012	1,388,994 live singleton births	Shenzhen meteorological data	**Preterm birth** - Sharp Temperature variation is a likely risk factor for PTB		Cox proportional hazards model	Percentage change during heat waves and each 2 degree C rise in MAT	RR Max DTR (17 °C) = 5.8% (95%CI: 3.3%, 8.3%), RR temperature increase (8 °C) = 23.7% (95%CI: 19.6%, 27.9%), and RR temperature decrease (11°C) = 4.4% (95%CI: 1.8%, 7.1%)	9

17	Gou. Y., Wang. T., et al., (2018) [30]	132 cities of China	Cohort Study		2013	1,020,471 pregnant women		**Preterm birth** - Acute and chronic exposure to extreme temperatures may affect the risk of preterm birth. Extreme heat is a risk factor for preterm birth and extreme cold is a protective factor.		Logistic regression model	association between exposure and outcomes	OR heat exposure = 1.229, (95% CI, 1.166–1.295) 3 months before pregnancy OR Cold exposure = 0.784, (95% CI, 0.734–0.832) 3 months before pregnancy	11
18	Zhou, G., Yang, M et al., (2021) [31]	Henan, China	Time series analysis	2013	2016	1,231,715 pregnant women	Mean temperature data obtained from China Meteorological Data Sharing Service System	**Preterm birth** - the risk of PTB was susceptible to PAT changes within 2 weeks or longer before conception.		Pearson's correlation	Correlation between PTB and PAT (preconception ambient temperature)	Exposure to extreme heat within 2 weeks - RR = 1.470, (95% CI: 1.132 - 1.910, P < 0.05) Exposure to extreme heat within 3 weeks RR = 1.375, (95% CI: 1.068 - 1.770, P < 0.05) before conception could increase the risk of PTB	9
19	Spolter, F., Kloog, I., et al., (2020) [32]	Israel	Time series analysis	2004	2013	62,547 pregnant women	sensors inside meteorological monitoring stations	**Preterm birth** - Exposure to high ambient temperature during pregnancy is associated with a higher risk of preterm and early term birth		Cox proportional hazard regression models	Gestational week & specific hazard ratios associated with increase in temperature conditions	HR (5th quirtile) = 1.31 (95% CI = 1.11–1.56) and HR (4th quirtile) = 1.13 (95% CI = 0.98–1.29) where Temperature range of 5th quirtile is 25.6 to 36.5 and temperature range of 4th quirtile is22.2–25.4	10
20	Li, S., Wang, J.,et al., (2018), [34]	Queensland, Australia	Prospective Cohort	2001	2010	237,585 pregnant women	relevant government agencies	**Preterm birth/ gestational age**- optimal temperature range during pregnancy for reducing the risk of preterm birth and low birthweight is advised		ANOVA & linear regression models	Gestational week & specific hazard ratios associated with increase	OR (during last 4 weeks of delivery Tat max. temperature: >30 °C) = 0.007 (95% CI, 0.004 - 0.016, p<0.001)	8

											in ambient temperature		
21	Ha, S., Zhu, Y. et al., (2017), [35]	12 sites of US	observational Prospective cohort	2002	2008	220,572 singleton births	site-specific distributions of daily temperature over three-month preconception, each trimester, and whole-pregnancy	**Small gestational age/ preterm birth** - prenatal exposures to extreme ambient temperature relative to usual environment may increase tLBW risk		Poisson regression model + Spearman correlation coefficients	Correlation between air pollution PM<_10 & ambient temperature conditions at birth and adverse birth outcomes as LBW and preterm birth.	RR cold exposure during trimester 2 = 1.21 (95% CI, 1.05–1.38)], trimester 3 [RR: 1.18 (1.03–1.36)], and whole-pregnancy [RR: 2.57 (2.27–2.91)] & RR hot exposure during trimester 3 [RR: 1.31 (1.15–1.50)] and whole-pregnancy [RR: 2.49 (2.20–2.83)] Carbon associated with a 4% increase in SGA while dust particles increased tLBW by 10%. PM ≤10 µm in the second trimester and whole pregnancy also appeared related to tLBW	11

Table 2: Characteristics of included studies on association between Air Pollution and Preterm Birth and low birth weight

S.NO.	Study & Year	Location	Type of study	Duration of study		No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	Stieb.D. M., Levigne. E., et al. 2019 [14]	24 cities of Canada	Time- to-event analysis	1999	2008	1,001,700 singleton births occurring between 1999 and 2008	Daily air pollution level data and temperature conditions recorded from NAPS (Canada) and Canada's meteorology data archive respectively.	**Preterm birth**- Overall prevalence of preterm birth is 6.34%. Pooled estimates across 24 cities indicated that an IQR increase in ozone (O_3, 13.3 ppb) 0–3 days prior to delivery was associated with a hazard ratio of 1.036 (95% CI 1.005, 1.067) for preterm birth.	Cox proportional hazard model, Expressed per IQR with distributed lag model for analysis	Gestational age in days as the time scale of each air pollutant.	HR ratio showed significant association with the air pollutants. Significant positive associations were observed ranging from HR = 1.005 (95% CI 1.005, 1.111) to HR = 1.131 (95% CI 1.035, 1.236).	12
2	Ranjbaran. M., Mohammadi. R., et al. 2020 [15]	Tehran, Iran	Time series analysis	March 2015	March 2018	542,492 births	daily data of preterm birth, air pollution and min., max., & mean temperature were recorded	**Preterm birth** - Highest RR for extreme (26.9 °C) and moderate (24.8 °C) heat of minimum temperature (RR = 1.17) & (RR = 1.15) respectively. - Each 10-unit increase in PM2.5 in Lag 0 (RR = 1.008; 1.001–1.014) and lag 1 (RR = 1.004; 1.001–1.007) had significant effects.	Distributed lag Non-Linear model RR calculated (DLNM)	RR calculated for extreme, moderate and mild heat and for each 10-unit increase in air pollutants	RR extreme temperature =1.17 (95% CI) RR moderate temperature =1.15 (95% CI) for each 10 unit rise in air pollutants level RR = 1.008 (95% CI)	9

3	Schifano. P., Lallo. A., et al., (2013) [19]	Rome	Time series analysis	2001	2010	132,691 births	Certificate of Delivery Care Registry	**Preterm births** - reported 7259 (5.5%) of the total sample taken after applying exclusion criteria		Poisson Generalised Additive Model with DLNM and Lag specific RR calculated	Percentage change during heat waves and each 1 degree C rise in MAT	RR at PM 10 = 0.33% change for 1 µg/m3 (95% CI 0.01–0.66)	11
4	Alman. B.L., et al., (2019) [24]	US	Cohort Study	1999	2006	2839 births	US EPA's Air Quality Systems (AQS) data & NBDPS data for births	**Preterm birth** - Results add to literature on associations between PM2.5 and PTB.		Bayesian two-level hierarchical model	Correlation between aerodynamic diameter (PM2.5) & preterm birth	OR during 3rd month = 1.00 (95% CI, 0.35, 2.15) to 1.49 (95% CI, 0.82, 2.68) OR during 4th month of pregnancy = 1.31 (95% CI, 0.56, 2.91) to 1.62 (95% CI, 0.7 - 3.32) OR during 7th month = 0.82 (95% CI, 0.25, 1.82)	11
5	Orryo.V., Diaz. J., et al., (2016) [26]	MAdrid , Spain	Time series analysis	2001	2009	298,705 singleton births	Daily mean concentrations (µg/m3) of PM2.5 and PM10, O3 and NO2, Leqd for measuring acoustic pollution and Maximum and Minimum daily temperature (°C), mean Humidity in the air (%) and Atmospheric Pressure (HPa), for temperature conditions	**Preterm birth** - PM2.5, diurnal noise levels and O3 have a short-term impact on total births and heat temperatures on preterm births		Time-series analysis with DLNM	Daily mean ambient temperature using PRISM and its association with exposure look up	RR at PM2.5 = 1.020 (95% CI, .008 - 1.03 RR O3 concentrations = 1.012, (95% CI, 1.002 - 1.022) RR Leqd for noise = 1.139 (95% CI, 1.124 - 1.154) for the total number of births, and RR heat temperatures at Lag 1 = 1.055, (95% CI, (1.018 - 1.092	9

6	Ha, S., Zhu, Y. et al., (2017), [35]	12 sites of US	observational Prospective cohort	2002	2008	220,572 singleton births	site-specific distributions of daily temperature over three-month preconception, each trimester, and whole-pregnancy	**Small gestational age/ preterm birth** - prenatal exposures to extreme ambient temperature relative to usual environment may increase tLBW risk		Poisson regression model + Spearman correlation coefficients	Correlation between air pollution PM<_10 & ambient temperature conditions at birth and adverse birth outcomes as LBW and preterm birth.	RR cold exposure during trimester 2 = 1.21 (95% CI, 1.05–1.38)], trimester 3 [RR: 1.18 (1.03–1.36)], and whole-pregnancy [RR: 2.57 (2.27–2.91)] & RR hot exposure during trimester 3 [RR: 1.31 (1.15–1.50)] and whole-pregnancy [RR: 2.49 (2.20–2.83)] Carbon was associated with a 4% increase in SGA while dust particles increased tLBW by 10%. PM ≤10 µm in the second trimester and whole pregnancy also appeared related to tLBW	11
7	Chen, G., Guo, Y et al., (2018) [37]	Brisbane, Australia	Cohort Study	2003	2013	13,994 PTB and 10,708 LBW were recorded	relevant government agencies	**Preterm birth** - Exposures to low-level air pollutants are related to adverse birth outcomes		Cox proportional hazards models	correlation between air pollution and birth outcomes	**Risk of PTB** during the whole pregnancy IQR HR PM 2.5 = 1.05 (95% CI, 1.02, 1.08), HR SO2 = 1.12 (95% CI, 1.09, 1.16), HR NO2 = 1.07 (95% CI, 1.01, 1.13), and HR O3 = 1.13 (95%PM2.5, Also, SO2, NO2, and O3 in the whole pregnancy were associated with **increased risk of LBW** [IQR HR and 95% CI: 1.06 (1.02, 1.10), 1.12 (1.08, 1.16), 1.11 (1.03, 1.18), and 1.13 (1.09, 1.17), respectively] CI, 1.10, 1.16), respectively	12

8	Chen, J., Fang, J et al., (2021) [38]	China	Cohort Study	2014	2016	10960 pregnant women	Chinese Air Quality Reanalysis datasets. high-resolution CAQRA datasets	**Preterm birth**- ambient air pollution increases the risks of adverse pregnancy outcomes	Cox proportional hazards regression models	proportions of days with daily average of variates taken	For PTB risk HR PM<2.5 = 1.58, or 58% at (95% CI, 1.43-1.75, p <0.05) and HR PM 10 = 1.83, or 83% at (95% CI, 1.65-2.22, p <0.05) For LBW risk HR PM<2.5 = 2.00 or 100% (95% CI, 1.47-2.74) and HR PM 10 = 1.82 or 82%, (95% CI, 1.45-2.27)	11
9	Shang, L., Huang, L et al., (2021) [39]	Shaanxi, China	Retrospective population based cohort study	2015	2018	321521 term newborns	Ministry of Ecology and Environment of the People's Republic of China	**PTB & Term Low birth weight** - prenatal exposure to air pollution might cause adverse impacts on term birth weight	2-level binary logistic regression models	Correlation	OR at 95%CI & p<0.05 values are - OR for PM 2.5 = 1.025 (1.005–1.045), OR for PM 10 = 1.035 (1.020–1.049), OR for SO2 = 1.034 (1.004–1.065), and OR for CO exposure = 1.013 (1.004–1.023), respectively).	9
10	Mueller, W et al., (2021) [40]	Thailand	Time series analysis	2015	2018	83,931 eligible births		LBW - study supports the outcome	semi-ecological analysis;		OR at PM10 = -6.81 g per 10 µg/m3 (95% CI, -12.52 to -1.10]) and OR of biomass burning = -6.34 g per 1 SD increase in fires/km2 [95% CI = -11.35 to -1.34])	
11	Sarizadeh, R et al., (2020) [41]	Ahvaz, Iran	Time series analysis	2008	2018	150766 pregnant women	Environmental Protection Agency	**PTB & LBW** - Results indicate the effect of air pollutants on low birth weight and preterm labor	Descriptive statistics including mean, standard deviation	Correlation between exposure and outcome	Correlation b/w PM10 and low birth weight at RR 0 lag day =1.003 (95% CI:1.001–1.004)), RR 1 =1.002, (1.000–1.004), RR 2 = 1.003 (1.002–1.005), RR 3 =1.004 (1.002–1.005), RR 4 = 1.002 (1.001–	10

												1.004)), RR 5 =1.002 (1.001–1.004)) and RR 6 = 1.002 (1.001 – 1.004)	
12	Zhang, X et al., (2020) [42]	Wuhan, China	Cross-sectional study	2013	2014	2101 singleton births	AQI Index calculated from Wuhan Environmental Protection Bureau website.	**Risk of PTB** - Maternal exposure to PM2.5 increased the risk of PTB		logistic regression model	Correlation between exposure and outcome	OR first trimester = 1.052 (95% CI: 1.002, 1.101)	9
13	Qian, Z., et al., (2016) [43[	China	Prospective Cohort	2011	2013	95,911 live births	relevant government agencies	**PTB** - association between air pollutants and PTB.		logistic regression model	Correlation between exposure and outcome	OR at PM 2.5 = 3% or 1.03; (95% CI: 1.02, 1.05), OR at PM 10 = 2% or 1.02; (95% CI: 1.02, 1.03), OR for 100-µg/m3 increase in CO concentrations = 15% or 1.15; (95% CI: 1.11, 1.19), and OR for 100-µg/m3 increase in O3 concentrations = 5% 1.05; (95% CI: 1.02, 1.07)	11

Table 2 (a): Characteristics of included studies on association between Temperature/ Heat Stress and stillbirth

S.NO.	Study & Year	Location	Type of study	Duration of study		No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	Bruckner. T. A., Modin. B., et al, 2014 [16]	Uppsala, Sweden	Cohort Study	1915	1929	14000 deliveries	daily ambient temperature series	**Stillbirth-** Risk of stillbirth rose as ambient temperature during pregnancy fell (hazard ratio for a 1°C decrease in temperature, 1.08; 95% confidence interval, 1.00 to 1.17)	Linear regression model & Cox proportional hazards	stillbirth and specific hazard ratio is associated with each degree rise in temperature	HR for 1 °C rise in temperature = 0.92 (95% CI, 0.86 to 0.996)	11
2	Weng. Y.H., Yang. C. Y., (2017) [22]	Taiwan	Retrospective cohort study	2001	2010	2 million (2,123,751) births	MAT data obtained from Central Weather Bureau, Taiwan Maternal and neonatal data were derived from the Birth Notification System (BNS), a database of Ministry of Health and Welfare, Taiwan	**Stillbirth,** Maternal exposures to temperature extremes carry greater risks for adverse neonatal outcomes – including stillbirth, preterm birth, and low birth weight. optimal ambient temperatures to minimize adverse neonatal outcomes are 21.5~25.4 °C	Log-binomial model	Correlation between ambient temperature conditions at birth and adverse neonatal outcomes.	IR (Incidence rate) stillbirth = 1.30% (95% CI, p<0.05) U shaped curved, ambient temperature conditions taken are 29.4 °C	12
3	Strand. L., et al., (2012) [25]	Australia	Cohort Study	2005	2009	101,870 births	Hourly data on temperature, relative humidity, and air pollution, provided	**Stillbirth & preterm birth-** Association between increased temperature and	Cox proportion	Gestational week & specific hazard ratios associated with	HR (hazard ratio) for stillbirth at 12°C = 0.3 HR for stillbirths at 15 °C = 0.96	10

							by the Queensland Department of Environment and Resource Management for 5 pollution stations.	increased risk of stillbirth and shorter gestation.		al hazards model	increase in temperature conditions	HR for stillbirths at 25°C =1.02	
4	Basu, R., et al., (2016) [33]	California	cohort study	1999	2009	8,510 fetal deaths	Meteorological data were provided by the California Irrigation Management Information System, the US Environmental Protection Agency, and the National Climatic Data Center, while the California Department of Public Health provided stillbirth data	**Stillbirth** - highest risks were observed during gestational weeks 20–25 and 31–33 with every 10 degree F increase in temperature.		Time-stratified case-crossover study design	Percentage change during heat waves and each 10 °F rise in MAT Pearson's correlation	RR = 10.4% (95% CI, 4.4 - 16.8) For every 10°F increase in apparent temperature r = 0.44 is for correlation between apparent temperature and O3 r = 0.73 is for CO and NO2	
5	Li, S., Wang, J.,et al., (2018), [34]	Queensland, Australia	Prospective Cohort	2001	2010	237,585 pregnant women	relevant government agencies	**Stillbirth** - optimal temperature range during pregnancy for reducing the risk of preterm birth and low birthweight is advised		ANOVA & linear regression models	Gestational week & specific hazard ratios associated with increase in ambient temperature	OR (during last 4 weeks of delivery Tat max. temperature: >30 °C) = 0.007 (95% CI, 0.004 - 0.016, p<0.001)	8

Table 2 (b): Characteristics of included studies on impact of Air pollution on Stillbirth

S.NO.	Study & Year	Location	Type of study	Duration of study		No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	DeFranco, E et al., (2015) [44]	Ohio	Cohort Study	2006	2010	349,188 live births and 1,848 stillbirths	via 57 monitoring stations across Ohio	**Stillbirth** - Exposure to high levels of fine particulate air pollution in the third trimester of pregnancy is associated with increased stillbirth risk	Chi-square test with logit link function	Daily measures of PM2.5 & adverse outcome	Mean PM2.5 level in Ohio was 13.3 µg/m3 [±1.8 SD, IQR(Q1: 12.1, Q3: 14.4, IQR: 2.3)	10

Table 3 (a): Characteristics of included studies on association between Temperature/ Heat Stress and Low birth weight (LBW)

S.NO.	Study & Year	Location	Type of study	Duration of study		No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	Weng. Y.H., Yang. C. Y., (2017) [22]	Taiwan	Retrospective cohort study	2001	2010	2 million (2,123,751) births	MAT data obtained from Central Weather Bureau, Taiwan Maternal and neonatal data were derived from the Birth Notification System (BNS), a database of Ministry of Health and Welfare, Taiwan	**Low birth weight** Maternal exposures to temperature extremes carry greater risks for adverse neonatal outcomes – including stillbirth, preterm birth, and low birth weight. optimal ambient temperatures to minimize adverse neonatal outcomes are 21.5~25.4 °C	Log-binomial model	Correlation between ambient temperature conditions at birth and adverse neonatal outcomes.	IR Low birth weight = 6.09% (95% CI, p<0.05) W shaped curve, highest ambient temperature conditions taken are 29.5 °C - 30.8 °C	12
2	Strand. L., et al., (2012) [25]	Australia	Cohort Study	2005	2009	101,870 births	Hourly data on temperature, relative humidity, and air pollution, provided by the Queensland Department of Environment and Resource Management for 5 pollution stations.	**Low birth weight-** Association between increased temperature and increased risk of stillbirth and shorter gestation.	Cox proportional hazards model	Gestational week & specific hazard ratios associated with increase in temperature conditions	HR (hazard ratio) for stillbirth at 12°C = 0.3 HR for stillbirths at 15 °C = 0.96 HR for stillbirths at 25°C =1.02	10

3	Li, S., Wang, J.,et al., (2018), [34]	Queensland, Australia	Prospective Cohort	2001	2010	237,585 pregnant women	relevant government agencies	**Low birth weight -** optimal temperature range during pregnancy for reducing the risk of preterm birth and low birthweight is advised		ANOVA & linear regression models	Gestational week & specific hazard ratios associated with increase in ambient temperature	OR (during last 4 weeks of delivery Tat max. temperature: >30 °C) = 0.007 (95% CI, 0.004 - 0.016, p<0.001)	8
4	Ha, S., Zhu, Y. et al., (2017), [35]	12 sites of US	observational Prospective cohort	2002	2008	220,572 singleton births	site-specific distributions of daily temperature over three-month preconception, each trimester, and whole-pregnancy	**Low birth weight** - prenatal exposures to extreme ambient temperature relative to usual environment may increase tLBW risk		Poisson regression model + Spearman correlation coefficients	Correlation between air pollution PM<_10 & ambient temperature conditions at birth and adverse birth outcomes as LBW and preterm birth.	RR cold exposure during trimester 2 = 1.21 (95% CI, 1.05–1.38)], trimester 3 [RR: 1.18 (1.03–1.36)], and whole-pregnancy [RR: 2.57 (2.27–2.91)] & RR hot exposure during trimester 3 [RR: 1.31 (1.15–1.50)] and whole-pregnancy [RR: 2.49 (2.20–2.83)] Carbon was associated with a 4% increase in SGA while dust particles increased tLBW by 10%. PM ≤10 µm in the second trimester and whole pregnancy also appeared related to tLBW	11

Table 3 (b): Characteristics of included studies on association between Air pollution and Low birth weight (LBW)

S.NO.	Study & Year	Location	Type of study	Duration of study: Entry point	Duration of study: End point	No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results: Statistical method	Statistic	Estimates	Study Quality Score (0-12)
1	Ha, S., Zhu, Y. et al., (2017), [35]	12 sites of US	observational Prospective cohort	2002	2008	220,572 singleton births	site-specific distributions of daily temperature over three-month preconception, each trimester, and whole-pregnancy	**Low birth weight** - prenatal exposures to extreme ambient temperature relative to usual environment may increase tLBW risk	Poisson regression model + Spearman correlation coefficients	Correlation between air pollution PM<_10 & ambient temperature conditions at birth and adverse birth outcomes as LBW and preterm birth.	RR cold exposure during trimester 2 = 1.21 (95% CI, 1.05–1.38)], trimester 3 [RR: 1.18 (1.03–1.36)], and whole-pregnancy [RR: 2.57 (2.27–2.91)] & RR hot exposure during trimester 3 [RR: 1.31 (1.15–1.50)] and whole-pregnancy [RR: 2.49 (2.20–2.83)] Carbon associated with a 4% increase in SGA while dust particles increased tLBW by 10%. PM ≤10 µm in the second trimester and whole pregnancy also appeared related to tLBW	11
2	Chen, G., Guo, Y et al., (2018) [37]	Brisbane, Australia	Cohort Study	2003	2013	13,994 PTB and 10,708 LBW were recorded	relevant government agencies	**Low birth weight** - Exposures to low-level air pollutants are related to adverse birth outcomes	Cox proportional hazards models	correlation between air pollution and birth outcomes	**Risk of PTB** during the whole pregnancy IQR HR PM 2.5 = 1.05 (95% CI, 1.02, 1.08), HR SO2 = 1.12 (95% CI, 1.09, 1.16), HR NO2 = 1.07 (95% CI, 1.01, 1.13), and HR O3 = 1.13 (95%PM2.5, Also, SO2, NO2, and O3 in the whole pregnancy were associated with	12

											increased risk of LBW [IQR HR and 95% CI: 1.06 (1.02, 1.10), 1.12 (1.08, 1.16), 1.11 (1.03, 1.18), and 1.13 (1.09, 1.17), respectively] CI, 1.10, 1.16), respectively	
3	Chen, J., Fang, J et al., (2021) [38]	China	Cohort Study	2014	2016	10960 pregnant women	Chinese Air Quality Reanalysis datasets. high-resolution CAQRA datasets	**Low birth weight** - ambient air pollution increases the risks of adverse pregnancy outcomes	Cox proportional hazards regression models	proportions of days with daily average of variates taken	For PTB risk HR PM<2.5 = 1.58, or 58% at (95% CI, 1.43-1.75, p <0.05) and HR PM 10 = 1.83, or 83% at (95% CI, 1.65-2.22, p <0.05) For LBW risk HR PM<2.5 = 2.00 or 100% (95% CI, 1.47-2.74) and HR PM 10 = 1.82 or 82%, (95% CI, 1.45-2.27)	11
4	Shang, L., Huang, L et al., (2021) [39]	Shaanxi, China	Retrospective population based cohort study	2015	2018	321521 term newborn	Ministry of Ecology and Environment of the People's Republic of China	**Term Low birth weight -** prenatal exposure to air pollution might cause adverse impacts on term birth weight	2-level binary logistic regression models	Correlation	OR at 95%CI & p<0.05 values are - OR for PM 2.5 = 1.025 (1.005–1.045), OR for PM 10 = 1.035 (1.020–1.049), OR for SO2 = 1.034 (1.004–1.065), and OR for CO exposure = 1.013 (1.004–1.023), respectively).	9
5	Mueller, W et al., (2021) [40]	Thailand	Time series analysis	2015	2018	83,931 eligible births		LBW - study supports the outcome	semi-ecological analysis;		OR at PM10 = -6.81 g per 10 µg/m3 (95% CI, -12.52 to -1.10]) and OR of biomass burning = -6.34 g per 1 SD increase in fires/km2 [95% CI = -11.35 to -1.34])	
6	Sarizadeh, R et al.,	Ahvaz, Iran	Time series analysis	2008	2018	150766 pregnant women	Environmental Protection Agency	**PTB & LBW** - Results indicate the effect of air pollutants on low birth	Descriptive statistics including mean,	Correlation between exposure and outcome	Correlation b/w PM10 and low birth weight at RR 0 lag day =1.003 (95% CI:1.001–1.004)), RR 1 =1.002, (1.000–1.004), RR	10

	(2020) [41]							weight and preterm labor	standard deviation		2 = 1.003 (1.002–1.005), RR 3 =1.004 (1.002–1.005), RR 4 = 1.002 (1.001–1.004)), RR 5 =1.002 (1.001–1.004)) and RR 6 = 1.002 (1.001 – 1.004)	

Table 4 (a): Characteristics of included studies on association between Temperature/ Heat Stress and Neonatal death

S.NO.	Study & Year	Location	Type of study	Duration of study		No. of participants (Sample size)	Exposure measurement	Adverse Outcomes Reported (Findings)	Statistical method and results			Study Quality Score (0-12)
				Entry point	End point				Statistical method	Statistic	Estimates	
1	Weng. Y.H., Yang. C. Y., (2017) [22]	Taiwan	Retrospective cohort study	2001	2010	2 million (2,123,751) births	MAT data obtained from Central Weather Bureau, Taiwan Maternal and neonatal data were derived from the Birth Notification System (BNS), a database of Ministry of Health and Welfare, Taiwan	**Neonatal Death** Maternal exposures to temperature extremes carry greater risks for adverse neonatal outcomes – including stillbirth, preterm birth, and low birth weight. optimal ambient temperatures to minimize adverse neonatal outcomes are 21.5~25.4 °C	Log-binomial model	Correlation between ambient temperature conditions at birth and adverse neonatal outcomes.	IR neonatal death = No data shown	12

4. Results

4.1 Study identification, distribution and quality score

In this systematic review we have identified 34 published peer reviewed manuscripts which examines the impact of environmental factors such as air pollution specifically PM<_2.5, PM 10, ambient temperature including cold spells & heat stress on birth outcomes. We have limited our search to certain adverse birth outcomes such as low birth weight, stillbirth, preterm birth, congenital anomalies and neonatal death. Most of the selected studies are conducted in developed countries along with some of the LMICs. As the search criteria were defined and restricted to 10 years only (January 2011 to January 2021), we have got limited studies on the neonatal death as the adverse birth outcome. Listing the studies selected in perspective of study designs, 15 studies used cohort methodology (including 12 retrospective cohort and 3 prospective cohort), 2 studies used time-to-event analysis, and 14 studies used ecological designs (including 12 time-series analysis, 1 exploratory time-series analysis and 1 cross-sectional design).

In respect to the study topic and outcomes reported, 30 studies have investigated the relationship between environmental factors including the environmental air pollution level (air pollutants like PM <_2.5, PM10, NO2 & O3) along with the temperature conditions playing its role in between (including heat stress, hot waves & cold spells) and preterm birth/ small gestational age (SGA). 6 studies have demonstrated the impact of these environmental factors on stillbirth, 9 studies reported the relationship between air pollution and temperature conditions and low birth weight (LBW) as resultant adverse birth outcome, and only 1 study signifies the impact of environmental air pollution and rising temperature due to global warming issue on neonatal death. Emphasis has been put on preterm birth and LBW & have been reported as the most occurring adverse birth outcomes.

Study quality scores have been taken into consideration in the context of documenting the quality of the studies selected. Quality scores have been assessed using CASP guidelines which ranged from 8 to 12, out of total 12 possible quality checklist points. More recent studies have shown higher quality scores in terms of all possible points.

Studies selected have a large variance in terms of their years of conduct, varying from 1 year (as minimum period of study) [13] to 14, 24 [23] years and as long as 27 years [18].

4.2 Prenatal exposure to air pollution and ambient temperature and risk of preterm birth/SGA

Table 1 represents the characteristics and main results of the studies included which investigates the association between prenatal exposure of the pregnant women and air pollution and ambient temperature conditions. Out of the studies reviewed, 18 studies have been conducted in Asia (11 in China, 3 in Iran, 2 from Israel, and single studies from Taiwan and Thailand), 5 Studies from Australia, 3 from Europe (Rome, Spain & Sweden), and 5 were conducted in America (US, Puerto Rico). Variations in study period have been noticed as some of them persisted from within 1 year [42, Zhang, X et al., (2020)] to more than 10 years [19, Schifano. P., Lallo. A., et al., (2013)], or >20 years even [18] Mathew. S., Mathur. D., (2020), [23] Walfisch, A., Kabakov, E. et al., (2016)]. Sample size of the studies reviewed in context of preterm birth and air pollution varies from 2100 singleton births [42, Zhang, X et al., (2020)] to 1 lac births [41, Sarizadeh, R et al., (2020)] and 2 million [22, Weng. Y.H., Yang. C. Y., (2017)] or even 32 million [21, Sun. S., Weinberger. K. R., et al., (2019)].

Study results were presented differently in each of the studies. The overall prevalence of the outcome is expressed in percentage and number of preterm births. Table 1 shows the impact of temperature both heat strokes, heat stress and cold spells on the outcome recorded. Exposure to the responsible factors i.e., high temperature conditions during the entire pregnancy or in the last trimester of the delivery results in small gestational age [13, Wang. Y. Y., Li. Q., et al. (2020)] & [35, Ha, S., Zhu, Y. et al., (2017)] or preterm birth [15, Ranjbaran. M., Mohammadi. R., et al. 2020)]. Relatively high and low temperature conditions significantly increase the risk [13]. Some studies have also suggested that high temperature conditions have increased the risk of preterm birth while maintaining a lower temperature during pregnancy may decrease the risk [18, Liu. X., et al, 2020]. Air pollution on the other end, has also an impact on the outcome recorded [17, Mohammadi. D., et al., 2019]. Immediate risks to preterm birth are also observed for cold temperature exposures (0 to –6 °C), with an increased relative risk of up to 10% [18, Mathew. S., Mathur. D., (2020)]. One study reported the elevated risk of PTB for nocturnal and warm seasons as compared to very cold temperature [20, Zhong. K., Lu. C., (2018)]. Primarily the impact of O3 and PM<2.5 and PM 10 have been seen to exert a greater impact on the outcome [26, Orryo.V., Diaz. J., et al., (2016)]. The duration of earlier weeks (4th and 5th week) of pregnancy and then the time of last trimester has suggested as crucial for the pregnant women [28, Yu. X., Feric. X., et al., (2018)]. Mean humidity and atmospheric pressure (HPa) altogether have also created an adverse impact on the pregnancy or birth outcomes [39, Shang, L., Huang, L et al., (2021)] & [43, Qian, Z., et al., (2016)].

4.3 Prenatal exposure to air pollution and ambient temperature and risk of stillbirth

Table 2 represents the characteristics and main results of the studies included which investigates the association between prenatal exposure of pregnant women and air pollution and ambient temperature conditions results in stillbirth.

4.4 Prenatal exposure to air pollution and ambient temperature and risk of Low birth weight

Table 3 represents the characteristics and main results of the studies included which investigates the association between prenatal exposure of pregnant women and air pollution and ambient temperature conditions resulting in low birth weight.

4.5 Prenatal exposure to air pollution and ambient temperature and risk of neonatal death

Table 4 represents the characteristics and main results of the studies included which investigates the association between prenatal exposure of the pregnant women and air pollution and ambient temperature conditions results in Neonatal death.

Confounders added:

Maternal age, social and demographic factors, educational status, physical activity, lifestyle factors.

LEGENDS USED FOR ANALYSIS

HR	Hazard Ratio
RR	Relative Risk
OR	Odds Ratio
IRR	Incidence rate ratio
Percentage	%

SUMMARY TABLE FOR EXPOSURES AND OUTCOMES

Table 5: Summary Table for Temperature (exposure) estimates and pregnancy and neonatal outcomes													
Range	**Studies**	**HR**		**Studies**	**OR**		**Studies**	**RR**		**Studies**	**RR in %**	
		low	high		low	high		low	high		low	high
Heat stress and preterm birth	Wang. Y. Y., Li. Q., et al. (2020) [13], Bruckner. T. A., Modin. B., et al, 2014 [16]	0.92	1.9	Gou. Y., Wang. T., et al., (2018) [30]	0.7	1.2	Mohammadi. D., et al., 2019 [17]	0.98	1.83	Schifano. P., Lallo. A., et al., (2013) [19]	7.20%	8.30%
Heat stress and stillbirth	Bruckner. T. A., Modin. B., et al, 2014 [16]	0.3	1.08	Li, S., Wang, J.,et al., (2018), [34]	0.007	0.016	Li, S., Wang, J.,et al., (2018), [34]	0.007	0.016	Basu, R., et al., (2016) [33]	6.80%	10%
Heat stress and low birth weight	Strand. L., et al., (2012) [25]	0.3	1.02	Li, S., Wang, J.,et al., (2018), [34]	0.007	0.016	Ha, S., Zhu, Y. et al., (2017), [35]	1.18	1.31	Weng. Y.H., Yang. C. Y., (2017) [22]	6.09%	
Heat stress and neonatal death	Weng. Y.H., Yang. C. Y., (2017) [22]											1.30%

HR: Hazard Ratio; OR: Odds ratio; RR: Relative risk

Table 5 (b): Summary Table for Air pollution (exposure) estimates and different outcomes

Range	Studies	HR		Studies	OR		Studies	RR		Studies	RR in %	
		low	high		low	high		low	high		low	high
Air pollution PM<2.5 and Preterm birth	Chen, J., Fang, J et al., (2021) [38]	1.005	1.58	Alman. B.L., et al., (2019) [24] During 4th month of pregnancy	1.31	1.62	Orryo.V., Diaz. J., et al., (2016) [26]	1.008	1.02	Qian, Z., et al., (2016) [43[	3%	
Air pollution PM 10 and Preterm birth	Stieb.D.M., Levigne. E., et al. 2019 [14]	1.131	1.83		1.025	1.035	Sarizadeh, R et al., (2020) [41]	0.003	1.003	Ha, S., Zhu, Y. et al., (2017), [35]	2%	10%
Air pollution PM<2.5 and stillbirth	DeFranco, E et al., (2015) [44]	1.33	1.46		-			-			-	
Air pollution PM 10 and stillbirth												
Air pollution PM<2.5 and low birth weight			2	Shang, L., Huang, L et al., (2021) [39]		1.025			0.003		-	
Air pollution PM 10 and low birth weight			1.82			1.035						
Air pollution and neonatal death		NA	NA		NA	NA		NA	NA		NA	NA

HR: Hazzard Ratio; OR: Odds ratio; RR: Relative risk

5. Discussion

In the study presented, we have reviewed the most recent publications and epidemiologic evidence for the objective selected as the research window has kept up to 10 years (studies published from 2011 to 2021). The evidence shows the relationship and statistical association between the exposure and outcome where the exposure taken is impact of air pollution with PM<2.5 & PM10 and changing temperature conditions onto adverse birth outcomes. The outcomes that have been taken into consideration are stillbirth, preterm birth (PTB)/ Small gestational age (SGA), Low birth weight (LBW), congenital anomalies, and neonatal death.

Since global climate changes are there in existence which cannot be bypassed when we talk about public health. Therefore, taking the background of global climate change, the findings recorded will have a great implication in public health decision making regarding the maternal and child health of any nation. In India, the current infant mortality rate is 31.4 per 1000 live births and maternal mortality ratio is 130 per 1,00,000 live births. Out of which preterm birth (birth before 37 weeks of pregnancy) has been the leading cause of neonates, infant and child mortality [ ]. A decade ago (around 2010), the overall rate of PTB mortality was 11.1% [ ] which now must have increased. One of the reasons for PTB, stillbirths, LBW and other adverse outcomes, we could frame here is due to changes in climatic conditions given the evidences above from the research and epidemiologic studies [Table 1, 2, 3, 4].

However more well-structured and defined studies are needed in order to represent the problem statement more in an elaborated form and could be taken into account for future considerations.

5.1 Study design and statistical approach

Several designs and statistical approaches have been used to study the impact of exposure and outcome selected. To study the impact of air pollution, air pollutants PM<2.5, 10, heat strokes, rising temperature conditions and birth outcomes, Time series analysis, Time-to-event analysis, Retrospective cohorts along with prospective cohort designs, multivariate regression models, chi-square test, Case-crossover and Cox proportional hazard ratio have been used.

Earlier simple statistical tools and methods had been used like t-test, simple correlation and ANOVA. Recent studies have used more advanced set of methodologies using retrospective and prospective cohort analysis, Cox regression hazard models, Poisson regression model [35, Ha, S., Zhu, Y. et al., (2017)] and Time-stratified case-crossover study design [33, Basu, R., et al., (2016)]. Time-to-event analysis has also been used in some of the studies with gestational age as the survival rate and outcomes as the adverse birth outcomes [14, Stieb.D.M., Levigne. E., et al. (2019)].

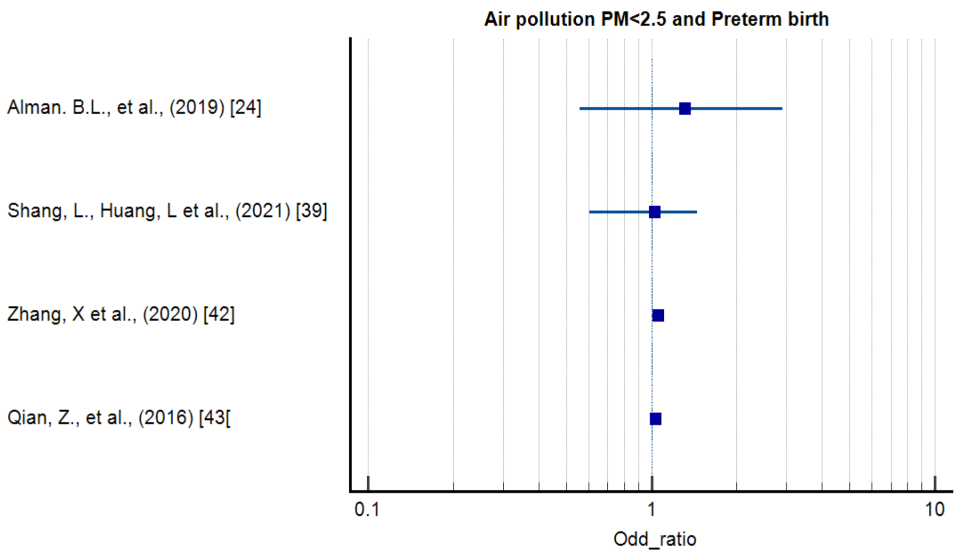
Statistics recorded also varied depending upon the tool and method of analyses used. Ranging from simple correlation between the exposure and outcomes, mapping the gestational weeks with specific hazard ratio with each degree rise in temperature [22, Weng. Y.H., Yang. C. Y., (2017)] to percentage change during heat waves and rise in maximum apparent temperature (MAT) [33, Basu, R., et al., (2016)]. This indicates that these studies have defined the correlation between exposure and outcomes quantitatively. Some studies have reported the birth outcomes associated with each 1 °C or 10 °F rise in the temperature [33, Basu, R., et al., (2016)] & [29, Changchang. L., Bloom. M.S., (2021)]. Further population-based studies have also their implications on the outcome in this current review study. Cohort method used for determining the impact of air pollution level in the setting/ country on birth outcomes [44, DeFranco, E et al., (2015)]. Generally, the exposure was measured by mapping the data on air pollution, relative humidity, atmospheric pressure and temperature through the meteorological departments of each respective country [25, Strand. L., et al., (2012)]. Apart from this, the dept. of environment has also played a role in collecting data [25, Strand. L., et al., (2012)].

Hazard risks/Odds ratio/ Relative risk have been used to measure the outcomes. With respect to different exposure level (eg; cold exposure, hot exposure, exposure within 2/ 3 weeks prior pregnancy/ during 3rd trimester, temperature increase, decrease) all the studies included shows a positive association and correlation between the exposure and outcomes [30, Gou. Y., Wang. T., et al., (2018)], [31, Zhou, G., Yang, M et al., (2021)] & [32, Spolter, F., Kloog, I., et al., (2020) [32].

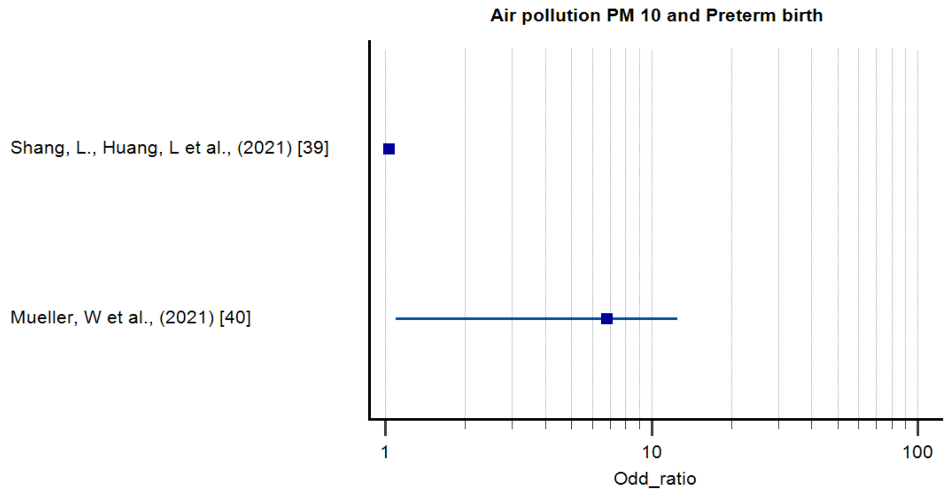
Time series analysis has been seen as the flexible method for conducting the studies in the future for emerging epidemiological studies. As the method helps in maintaining a clean set of data by filtering out the noise thus helps in finding out the ‘true signal’ in a dataset. Also, time series analysis is suggested as it filters out the outliers and applying a number of averages helps in gaining overall perspective of the data recorded. On the other hand, for assessing the individual level data and developing the relationship between exposure and outcomes, retrospective cohorts are advisable to carry with. In terms of ecological aspects and population characteristics, cohort studies are advisable. Generally, cohort studies evaluate the HR linked with each degree change in exposure conditions. For estimating the results HR & RR are advisable to calculate the risk of getting into the outcome as HR describes the relative risk of complications by comparing the event rates. And RR gives the risk ratio.

Forest Plots:

Exposure	Studies	OR	Lower	Higher
Air pollution PM<2.5 and Preterm birth	Alman. B.L., et al., (2019) [24] During 4th month of pregnancy	1.31	0.56,	2.91
	Shang, L., Huang, L et al., (2021) [39]	1.025	1.005	1.045
	Zhang, X et al., (2020) [42]	1.052	1.002	1.101
	Qian, Z., et al., (2016) [43[	1.03	1.02	1.05

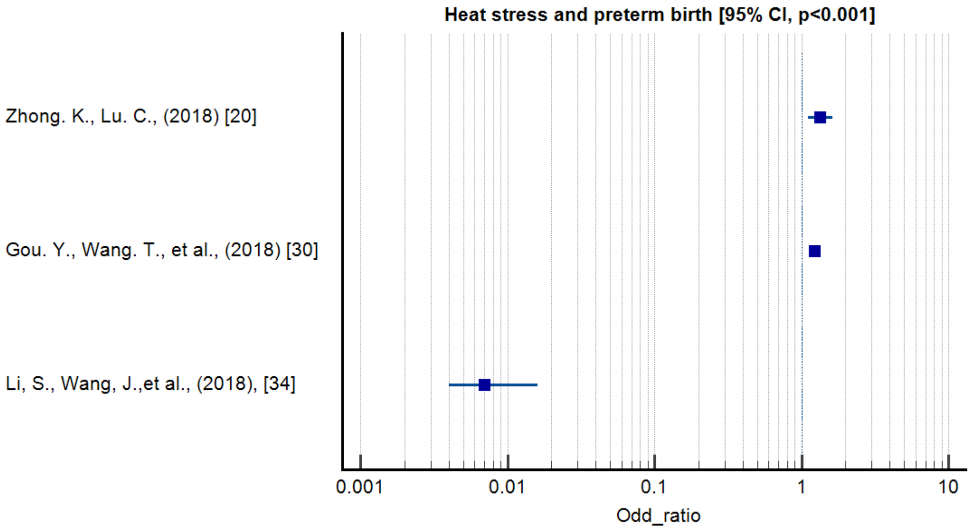


	Studies	OR	Lower	Higher
Air pollution PM 10 and Preterm birth	Shang, L., Huang, L et al., (2021) [39]	1.035	1.02	1.049
	Mueller, W et al., (2021) [40]	-6.81	-12.52	-1.1

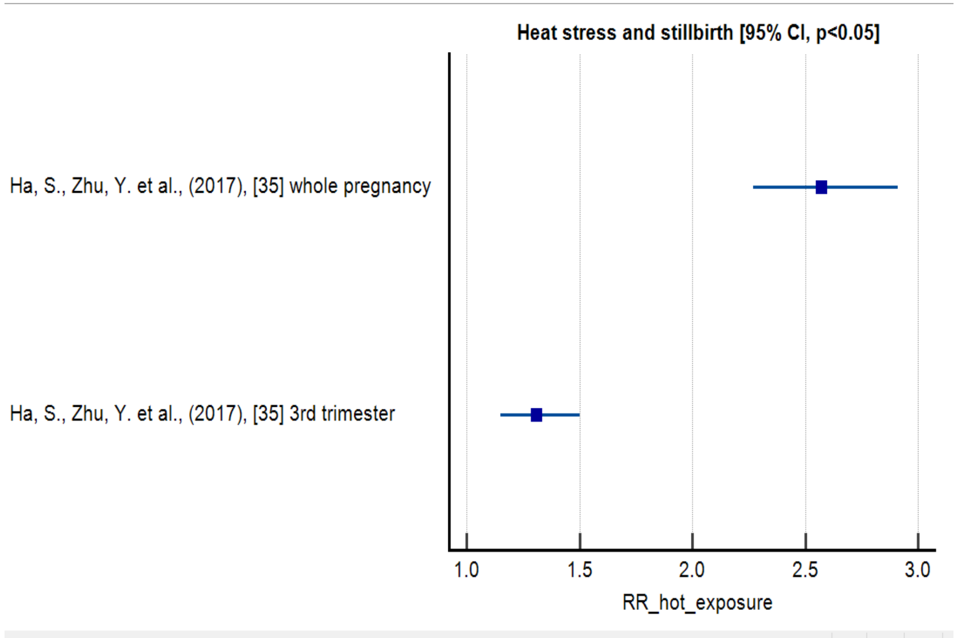


Heat stress and PTB

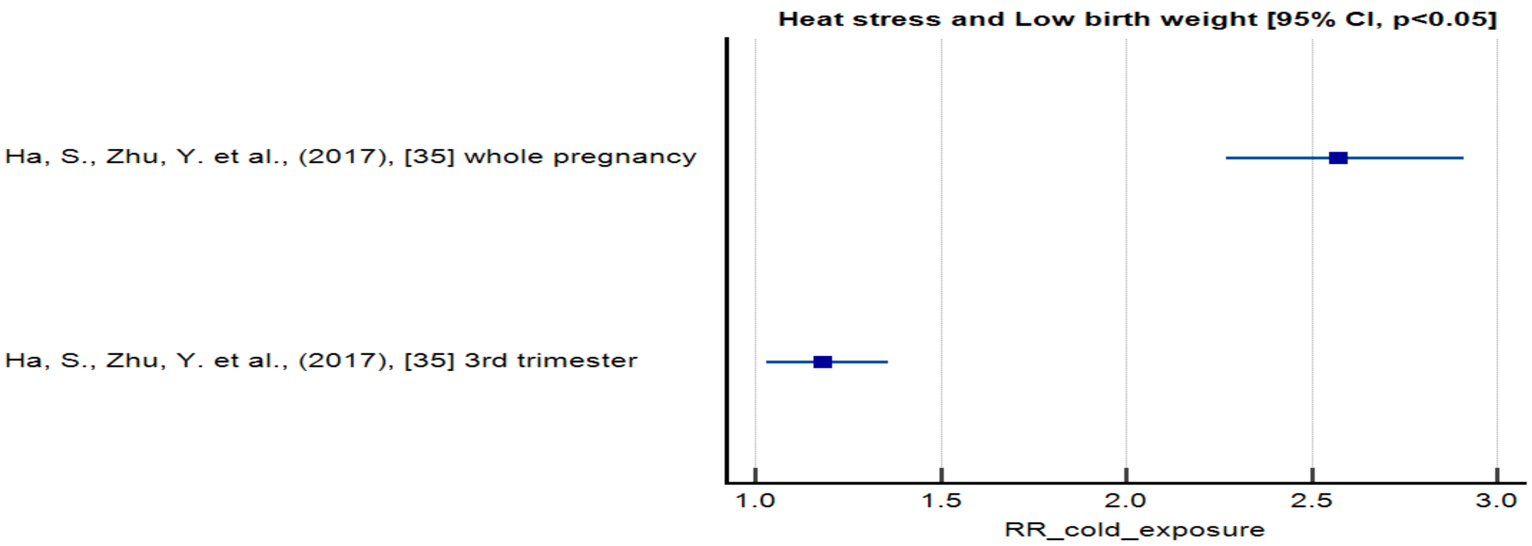
Exposure	Studies	OR	Lower	Higher
Heat stress & PTB	Zhong. K., Lu. C., (2018) [20]	1.34	1.11	1.62
	Gou. Y., Wang. T., et al., (2018) [30]	1.229	1.166	1.295
	Li, S., Wang, J.,et al., (2018), [34]	0.007	0.004	0.016



Exposure	Studies	RR_hot exposure	Lower	Higher
Heat stress & stillbirth	Ha, S., Zhu, Y. et al., (2017), [35] whole pregnancy	2.57	2.27	2.91
	Ha, S., Zhu, Y. et al., (2017), [35] 3rd trimester	1.31	1.15	1.5



Exposure	Studies	RR_cold exposure	Lower	Higher
Heat stress and LBW	Ha, S., Zhu, Y. et al., (2017), [35] whole pregnancy	2.57	2.27	2.91
	Ha, S., Zhu, Y. et al., (2017), [35] 3rd trimester	1.18	1.03	1.36



Conclusion:

Due to the high ratio of maternal and child deaths globally, an increased attention has been paid to the research works relating to adverse birth outcomes. Association of adverse birth outcomes and prenatal exposure to air pollution and changing temperature conditions have a large impact on the overall development of any country or nation.

In the current review, a number of studies have been reviewed with large variation in their study designs and methodologies, and varied air pollution level with number of pollutants included and temperature indicators for assessing the outcomes. Also, time windows of exposure level to the subjects selected varied considerably from study to study. despite of variations in the study research aspects, this review suggests the association between major environmental factors as air pollution, temperature and adverse birth outcomes. The review also implied solid indications about the correlation between the exposure and the outcomes. The major areas the study identified are parts of Europe, Australia, Parts of US and North America and Asia. Consequently, more studies are needed to be conducted worldwide with diversified environmental conditions to analyse the outcomes against the same objective. So as to further ascertain the association between environmental factors as air pollution PM<2.5, ambient temperature, heat stress and cold spells and adverse birth outcomes.

Implications for Practice: The study reports the relationship/association between the environmental exposures and adverse pregnancy related outcomes. It also indicates the air pollution levels and changing temperature conditions impacting maternal and child health and is responsible for increasing neonatal and child mortality rates.

Implications for Research: The study further strengthens the existing unrecorded data related to the problem statement thus will improve the outcomes. Also, the study will help in decision making related to public health interventions and strategies to reduce the adverse birth outcomes and improve the maternal and child health.

Conflicts of interest

I as the author of this study declare that I have no competing financial interests.

Plan of study (Gantt Chart)

Activities/ Months	March	April	May	June
1. Introduction	1 week (by 22nd March)			
2. Literature review	1 week (by 30th of March			
3. Tabulation of observations		4 weeks (by 30th April)		
4. Representation of results			3 weeks (by 10th May)	
5. Presenting outcomes				1.5 week (by 5th June)
6. Drafting conclusion and bibliography				2 days (7th June)

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