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Wildfire, dust, heat and adverse child health and birth outcomes: a global analysis across low-to-middle income countries

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Wildfire, dust, heat and adverse child health and birth outcomes: a global analysis across low-to-middle income countries

A dissertation submitted in partial satisfactory of the

requirements for the degree of Doctor of Philosophy

in

Public Health (Epidemiology)

by

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2021

The Dissertation of Sara Elizabeth McElroy is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Abstract of Dissertation

Wildfire, dust, heat and adverse child health and birth outcomes: a global analysis across low-to-middle income countries

by

Sara Elizabeth McElroy

Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2021
San Diego State University, 2021

Professor Tarik Benmarhnia, Chair

As the climate continues to change, there is a heightened public health concern about how extreme weather events can affect adverse health outcomes, especially in more vulnerable populations. Children and pregnant women living in low-to-middle-income countries (LMICs) are

considered highly vulnerable populations. Acute respiratory infections have become the number one cause of under-five mortality across the globe. Additionally, preterm birth, complications from preterm birth, and stillbirths are the number one cause of neonatal deaths worldwide. These adverse health outcomes are preventable. Thus, research needs to focus on preventable environmental determinants that can help reduce the number of childhood respiratory infections and adverse birth outcomes in LMICs.

Air pollution and extreme heat are preventable risk factors because exposure levels can be determined by individual behaviors and population-level policies and action plans. Wildland fire smoke and dust storms can release substantial amounts of particulate matter into the atmosphere. Prior evidence has tied these extreme weather events with adverse respiratory and cardiovascular outcomes and premature mortality in children. Additionally, exposure to extreme heat has been linked to higher risks of preterm birth and stillbirth in high-income countries. The proposed biological mechanisms of how particulate matter and extreme heat can cause these outcomes involve oxidative stress and inflammation. Previous evidence has mainly come from high-income countries, which may be because of challenges in exposure measurement.

The first chapter of this dissertation reviews the epidemiological evidence regarding the relationship of three extreme weather events (wildland fire smoke, dust, and extreme heat) and childhood respiratory outcomes and adverse birth outcomes in LMICs. The second chapter of this dissertation examines acute exposure to wildland and agricultural fire smoke affecting the risk of childhood respiratory outcomes in 14 LMICs. The third chapter is a case-study of acute exposure to heightened dust days and the risk of childhood cough in Benin. The fourth chapter studies the relationship between extreme heat and aims to identify specific susceptible windows of increased risk of preterm birth and stillbirth in a comprehensive set of LMICs. The latter three chapters expand on the limited evidence base of these exposure and outcome relationships in LMICs. The final chapter summarizes key findings, describes the implications and innovations of this research, and highlights future research objectives to build upon this dissertation research.

1. Introduction:

1.1 Overview of maternal and child health:

Respiratory infections kill more people than HIV, tuberculosis, and malaria combined[1]. Nearly two and a half million child deaths resulted from respiratory infections in 2016, making respiratory infections the number one cause of death among children younger than five years old[2]. Pneumonia accounts for about 15% of deaths in children less than five years of age. Lower respiratory infections are a significant contributor to child mortality in low-to-middle income countries (LMICs). Children across the globe experience three to six acute respiratory infections a year despite where they live or their socioeconomic status[3]. Nevertheless, the proportion of severe infection is higher in LMICs because of differing etiologies and risk factors, resulting in a higher case-fatality rate[3]. Although we have observed a substantial decrease of lower respiratory infection mortality since 2000, about 57%, most of the remaining deaths can be prevented and require more research in prevention and possible treatment interventions. Future research needs to focus on reducing these infections in children who live in LMICs due to their vulnerability and high mortality rates.

The welfare of mothers, infants, and children determines the next generation's health and can help predict future public health challenges and a country's productivity. An important indicator of maternal and child health is maternal and neonatal mortality rates. After the implementation of the Millennium Development Goals (MDGs), there was a significant decline in maternal and child mortality from 2000-2015. Sub-Saharan Africa and South Asia have the highest rates of neonatal and child deaths[4-7]. More specifically, two-thirds of the global burden of maternal and newborn deaths, including stillbirths, occurs in only ten countries, which are LMICs.[8] Stillbirths and complications from preterm birth are the leading factors in these neonatal deaths. Thus, it is imperative to focus research on means to prevent preterm birth and stillbirth rates, which will ultimately reduce neonatal deaths. Since LMICs have the highest rates of these negative birth outcomes, these populations suffer from a disproportionate health burden, lending an urgency to engage in preventive efforts that could reduce stillbirths and preterm births.

1.1.1 Childhood acute respiratory infections:

Acute respiratory infections are among the leading cause of childhood mortality across the globe and accounted for 10% of deaths in children younger than five years in 2017[9]. In 2016, there were about 2.4 million lower respiratory infections, making these infections the number one cause of mortality in children under five years of age[2]. The respiratory infection burden varies significantly across the globe, disproportionately affecting the young and poor[10]. People who have the highest risk of contracting or dying from respiratory infection come from rural households with low income and education.[11]. In addition, children who live in households with inadequate nutrition, unclean cooking fuels, no access to vaccines, and poor sanitation have an increased risk of respiratory infections[12]. In this context, children residing in LMICs are one of the most vulnerable populations to these infections.

Respiratory infections mortality in all ages is highest in sub-Saharan Africa, South Asia, and Southeast Asia. The Lancet's systematic analysis estimates of respiratory infection mortality for the Global Burden of Disease Study found that the highest rates of respiratory infection mortality were in Central Africa Republic, Chad, and Somalia[13]. Nearly a third of all respiratory infection mortality occurred in India and Nigeria. This figure shows the lower respiratory infection mortality rates per 100,000 people for children younger than five years[13].

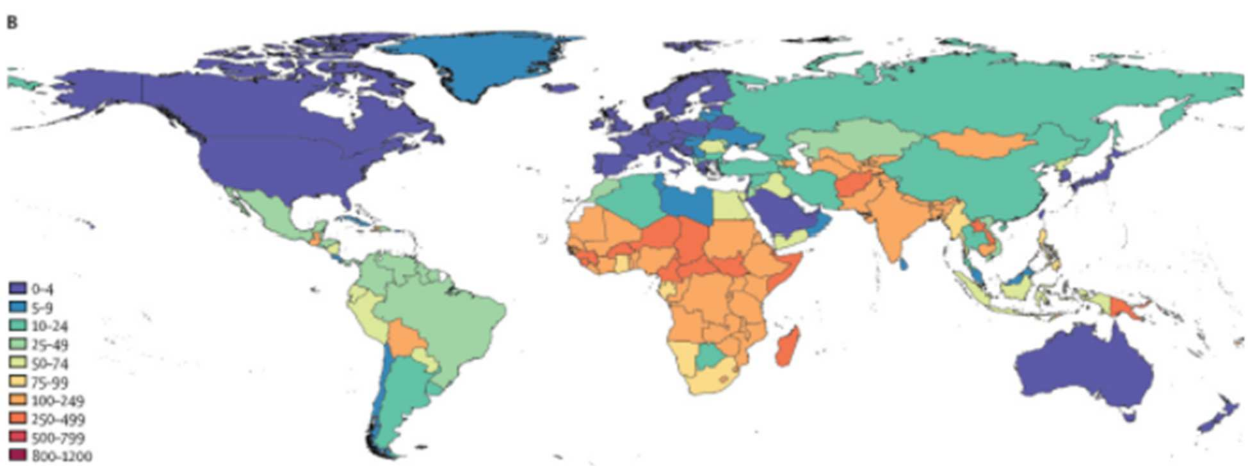


Figure 1. 1: Distribution of respiratory mortality rates per 100,000 children under five.

We can see that LMICs (especially in sub-Saharan Africa) have the highest rates of respiratory infection mortality across the globe. The two leading risk factors associated with increased risk of mortality from respiratory infections in children under five years of age included childhood wasting and exposure to indoor and ambient particulate matter[13]. Thus, research should focus on mitigation interventions to reduce children's exposure to particulate matter.

1.1.2 Stillbirth:

Stillbirths (as defined by the WHO as a fetal death that occurs at or after either 28 weeks of gestation or a minimum fetus weight of 1000-grams) were not included in conventional worldwide data-collection systems until very recently. It is noteworthy that stillbirths were not included in the Global Burden of Disease study[14] but were conveyed separately. The first published national stillbirth rates were published in 2006, and these reports described noticeably different country-specific rates.[8] These different rates were due to the absence and unreliability of data available in places where most stillbirths happen, such as sub-Saharan Africa and south Asia. An estimated 2.6 million stillbirths occurred annually in 2015, and 98% of these stillbirths took place in LMIC countries, especially among rural populations.[15,16] The Lancet Global Health map below depicts the top ten countries with the largest number and rates of stillbirths; almost all of these countries are LMICs[17]. The number of stillbirths that occur is similar to the number of deaths of children resulting from diarrhea and pneumonia. Nonetheless, the health burden of stillbirths is understudied and underreported in many countries. There has been little to no reduction of stillbirth rates in sub-Saharan Africa, despite progress there in the decline of children under-five deaths[8].

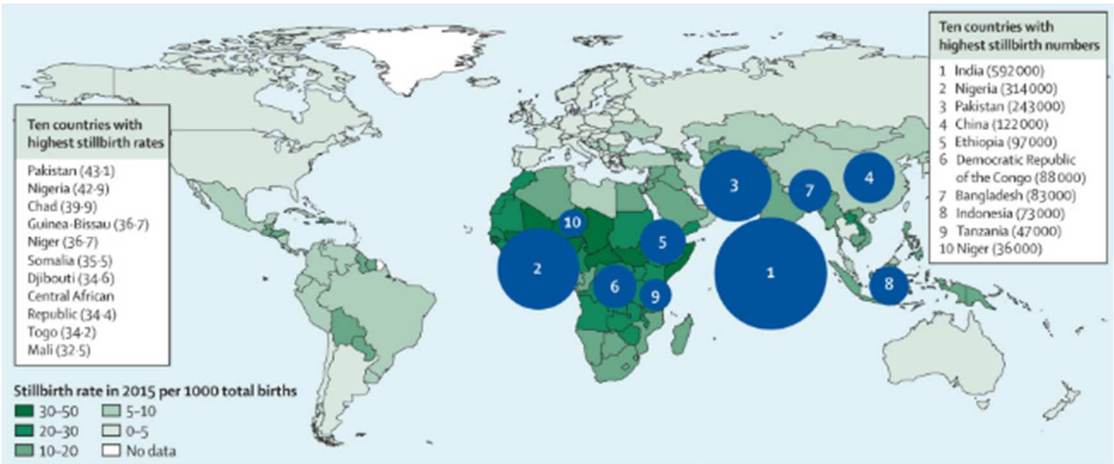


Figure 1. 2: Map of the countries with the highest stillbirth rates. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. The Lancet Global

1.1.3 Preterm Birth:

Preterm birth (PTB) has received more consideration than stillbirth in recent research because of its escalating rates across the globe. However, this research has been mainly focused on data from HICs. Each year, there are approximately 15 million preterm babies born. Preterm birth complications are the foremost cause of neonatal death and the second most frequent cause of death among children younger than five years of age, and this rate is increasing[18]. It has been estimated from available global data that approximately 10 million PTBs occur in sub-Saharan Africa and south Asia. More pointedly, India, China, and Nigeria account for about 6 million PTBs[19]. Of the ten countries with the highest rates of PTB, nine of them are LMICs. The disparity between survival rates of these premature babies in LMICs compared to high-income countries (HICs) is important. Half of babies born before 32 weeks gestation in LMICs die due to lack of feasible, cost-effective health care in LMICs. Furthermore, the infants that survive have been found to have higher rates of short- and long-term morbidities, such as neurologic and developmental disabilities[20].

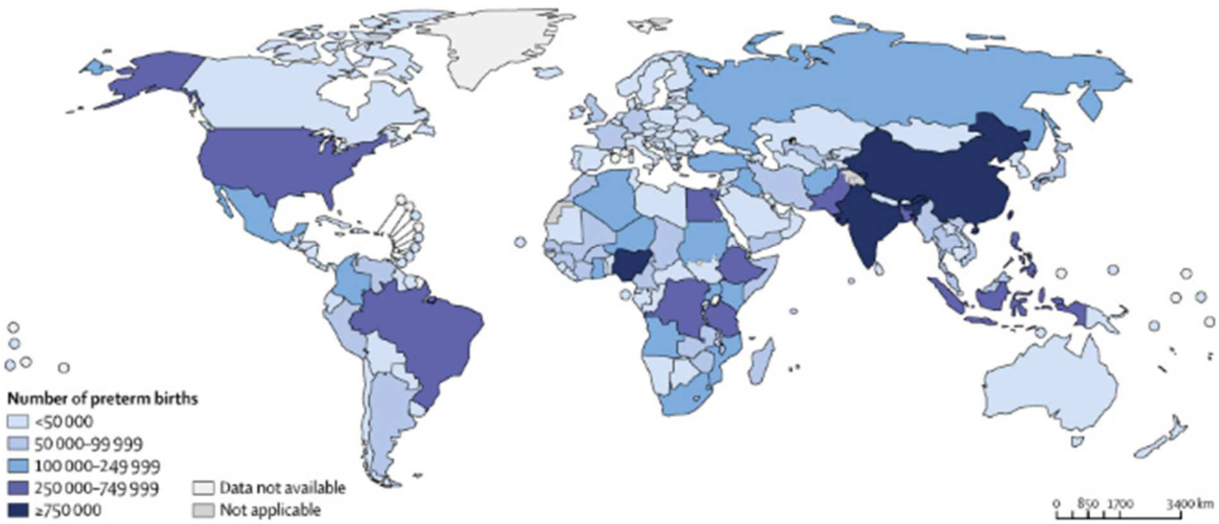


Figure 1. 3: Global distribution of the number of preterm births in 2017.

Although the majority of PTB complications occur in LMICs, there have been few studies on PTB prevention and on identifying particularly vulnerable female populations. Women residing in LMICs face fundamentally different exposures than women in HICs, for example, infectious diseases, poverty, pollutants, community stress, and gender inequality, all of which can predispose these women to adverse birth outcomes such as preterm birth and stillbirth.

Previous studies examining preterm birth and stillbirth have found many associated social and environmental determinants, some of these which include race/ethnicity[21-23], maternal age and education[24], urbanicity[25], maternal obesity[26], socioeconomic status[27,28], outdoor air pollution[29,30], extreme weather events[31,32], and other environmental exposures such as pesticides and polychlorinated biphenyls[33]. Of these determinants, exposure to environmental determinants (such as air pollution and extreme weather events) can be limited or prevented. There are large population-based interventions, such as early warning systems, that can reduce exposure to these factors or mitigate their consequences and thus mitigate risk of adverse birth outcomes. Therefore, research should be focused on how to reduce these exposures to environmental determinants in pregnant women to help reduce preterm birth and stillbirth.

1.1.4 Environmental determinants of birth outcomes and acute respiratory infections:

Environmental determinants such as air pollution and extreme heat have been tied to preterm birth and stillbirth in HICs[32,34-39]. Several studies have identified that a critical window of susceptibility for pregnant women is in the late stages of pregnancy[23,29,40-42]. More specifically, this research indicated that if women were exposed to extreme heat or particulate matter (PM) in the last weeks of pregnancy or the week of birth, they experienced a higher risk of adverse birth outcomes. A prospective study examining the effect of heat on preterm birth in Spain found a 2-day reduction in gestational age if women experienced a heatwave the day before birth[40]. In addition, a cohort study examining women from New Jersey reported an increased risk of preterm birth when a woman was exposed to heightened levels of PM2.5 in the two weeks prior to birth[23,43]. This dissertation will capitalize on this finding and examine this critical window of susceptibility in women in LMICs.

Subsequently, several previous studies performed in HICs have linked exposure to air pollution, specifically PM, to childhood respiratory outcomes such as asthma, bronchitis, pneumonia, and respiratory hospitalizations[44-49]. One study found that acute exposure to PM10 increased the risk of asthma hospitalizations and had a lagged effect of three days[49]. One systematic review that examined the association between ambient air pollution and childhood respiratory diseases in low-to-middle-income Asian countries found that short-term exposure to ambient air pollution was associated with increased childhood respiratory morbidity and mortality[50]. Moreover, acute exposure to PM10 and PM2.5 was associated with increased hospital admissions, emergency visits, and visits to pediatric clinics for acute upper and lower respiratory tract infections[50]. This dissertation will focus on acute exposure to PM and childhood respiratory outcomes.

LMICs suffer from a disproportionate percentage of the global cost of climate change, although most greenhouse emissions are produced by industrialized countries[51]. Furthermore, extreme heat and other related weather events exacerbated by climate change disproportionally impact people living in LMICs [52]. This disparity in climate change effects is due to 1.) the physical impacts—increases in the existing high temperatures that are likely to lead to large evaporation losses. Worsening this situation is the probability that in many developing countries, precipitation is not likely to increase as is expected in many high-latitude regions[53]. 2.) A large number of underprivileged people in these countries are generally more vulnerable and likely to feel the negative effects more than their HICs counterparts[54], and 3.) the economic and technological capacity to adapt to climate change is more limited in LMICs. Furthermore, LMICs often have extensive poverty, conflict areas, and fragile health care systems, making it harder for people residing in these areas to adapt and cope with such extreme weather phenomena[55]. Therefore, focusing research on environmental determinants is paramount to inform early warning systems that could mitigate the effect of these events in LMICs.

Consequently, we need to identify, with urgency, how such extreme weather events impact adverse birth outcomes and childhood health in LMICs to motivate and inform the implementation of preventive strategies. Concentrating research on acute exposure to these environmental determinants is imperative because they are, in fact, preventable. Large-scale interventions are possible to address these risks in pregnant women and children. Exposure to these dangerous conditions can be reduced or prevented through the implementation of early warning systems that, for example, recommend changes in behaviors, such as staying indoors, reducing physical activity, or leaving the area, or enhance health systems' responses. Research from HICs has shown that exposure to extreme heat and PM can increase the risk of adverse birth outcomes in HICs, and women residing in LMICs are more vulnerable than their HIC counterparts. Also, research from HICs and Asian LMICs has shown that exposure to PM can increase the risk of child cough, acute respiratory symptoms, and lower respiratory infections. Children are also considered a very vulnerable population, so it is critical that we identify time windows of the highest risk for childhood respiratory outcomes.

1.2. Overview of extreme weather events:

There is a plethora of evidence indicating that extreme weather events have increased in intensity, frequency, and duration in the last few decades. In particular, changes in temperature distributions and precipitation regimes have been linked to anthropologic climate change[56]. More explicitly, changes in precipitation patterns and rising global temperatures have increased the severity and duration of heat waves. Such changes also lead to immensely arid regions, which increases the likelihood of wildfires and dust storms. It is believed that climate change can alter weather patterns at a regional scale, and the impact of these events is more acute and traumatic. [57]. This study will concentrate on three environmental determinants: wildfire smoke PM2.5, dust PM10, and extreme heat. Exposure to each of these factors is manageable on a large scale, and therefore worthy of focused, comprehensive research.

The sections below detail how each of the three exposures (wildfire Pm2.5, dust PM10, and extreme heat) are distributed globally. Additionally, probable biological mechanisms for adverse birth outcomes and respiratory outcomes are discussed and how each of the three types of exposures can be measured and modeled. Finally, a literature review examines the relationships between wildfire PM2.5, dust PM10, and child respiratory outcomes as well as extreme heat, preterm, and stillbirth.

1.2.1 Wildfire and agricultural fires:

Large wildfires are a global phenomenon that poses a significant risk to property and life, partially due to changes in precipitation regime and immense development on fire-prone landscapes[58]. As temperatures rise and droughts increase in length and severity, severe wildfires increase in intensity and frequency globally. 2019 saw an unprecedented number of massive wildfires around the globe. Some of the more prominent wildfires were the fires in the Amazon, Indonesia, Alaska, California, Australia, Siberia, and the Arctic. The European Space Agency detected 79,000 wildfires (of different magnitudes) globally in August 2019 compared to only 16,000 fires during the same period in 2018. The Amazon has experienced more than 72,000 fires since January 2021, an 83% increase from the same period in 2018. NASA's Global Forest Watch Fires sent out 782,366 worldwide fire alerts within seven days from July 15th to July 22nd, 2019. The majority of these alerts went out to Russia (178,484), the Democratic Republic of the Congo (136,087), Zambia (52,801), and Angola (109,512).

Sub-Saharan Africa is one of the top fire-prone areas of the world, with a majority of burning occurring during the dry season[59]. Countries north of the equator experience the most burning from November to February and countries south of the equator from May through October. It is estimated that

51% of the African savanna burns every two years[60]. There can be several thousand fires burning in this region during the dry season in a single day.[61] Some studies estimated that global fires burn an area of about 350-422 million hectares and emit about 2.2 Metric Gigatons of carbon into the air, among which 67% of the burned area and 52% of the carbon emitted resulted from biomass burning in Africa alone[62-64]. Not all of these fires are wildfires. A majority are agricultural fires resulting from the slash-and-burn technique to clear forest and woody plants for agriculture. Trees and woody plants are cut down and allowed to dry and then are burned. These slash-and-burn fires can be exacerbated by climate change and are becoming harder to control.

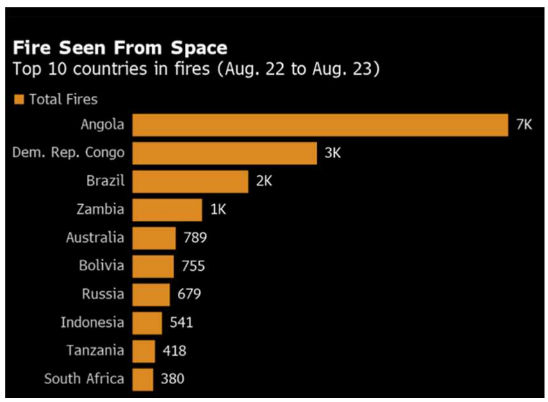


Figure 1. 4: Number of fires seen from space by NASA's MODIS instrument on the Terra satellite from August 22nd-August 23rd, 2019.

Moreover, the northern sub-Saharan African region accounts for 20-25% of the global carbon emissions from biomass burning or agricultural burning. One of the regions where the highest number of wildfires or agricultural fires took place was Angola, located in sub-Saharan Africa. NASA indicated that over 67,000 fires were reported in a one-week period in June 2018, as farmers employed slash and burn agriculture techniques to clear land for crops. Agricultural fires from Central and West Africa are the main component of biomass burning emissions across Africa, linked to 43,000 premature deaths per year[65].

1.2.2 Biological plausibility: fine particulate matter (PM2.5) and childhood respiratory outcomes:

Apart from the physical destruction from wildfires, their smoke contains large amounts of fine particulate matter (PM2.5)[66-68], tied to adverse health outcomes.[69] Exposure to PM2.5 in adults has been tied to adverse health outcomes,[69] including respiratory diseases[69], cardiovascular disease[70], reduced life expectancy, adverse birth outcomes, and death[71]. Children can be more severely affected by exposure to PM2.5 and smoke due to their reduced lung size, increased metabolic rates, higher respiratory rates, and their developing immune systems[72]. Studies that have examined acute exposure to PM in children have seen increases in respiratory symptoms, decreased lung function[73], increased airway inflammation[74], aggravated asthma, and chronic lung disease[75].

PM2.5 is small enough in diameter to penetrate the alveolus and enter the circulatory system. PM2.5 can then cause both physical and chemical damage to the respiratory system[76]. After inhalation of PM2.5, inhalation toxicity to the respiratory system can occur[77]. In addition, PM2.5 can cause oxidative stress, inflammation, and epigenetic changes in the respiratory system[78]. Oxidative stress is brought on when PM2.5 can generate reactive oxygen species and some oxidative metabolites, which can cause oxidative stress[79]. As a result of oxidation, reactive oxygen species react with other molecules, and when this occurs, an individual's antioxidant system cannot overcome the effect of excessively made reactive oxygen species[80]. This excess has been tied to cell function impairment and cell death. Oxidative stress can thus cause an inflammatory reaction. Finally, short-term exposure to PM2.5 is linked with demethylation of long interspersed nucleotide elements, an epigenetic change in the promoter region of the mitogen-activated protein kinase pathway[81]. All three, oxidative stress, inflammation, and epigenetic changes, are involved in the emergence and acceleration of respiratory diseases[82].

1.2.3 Methodological challenges in exposure PM2.5 measurement: remote sensing:

This study will use remote sensing data to overcome these methodological challenges in PM2.5 exposure measurement. Remote sensing data provide a valuable estimate of PM2.5 measurements in the absence of extensive local ground-based monitor networks, especially when the nearest monitor is greater than 100 km away. Just seven of the 54 countries in Africa have "real-time air pollution monitors", while only 6% of children across Africa live within 50km of a reliable air-quality monitor[83]. This monitor placement is in stark contrast to the 72% of children in North America and Europe[83]. Previously literature has relied on ground monitors to measure PM2.5, but air quality monitoring stations in sub-Saharan

Africa have been stalled or discontinued in recent years. Among the 47 countries that comprise sub-Saharan Africa, only six countries measure PM[84]. With the use of public platforms such as Google Earth Engine, daily and even hourly air pollution data are available for research. More recent studies have utilized data from the Moderate Resolution Imaging Spectroradiometer (MODIS) and Multiangle Imaging Spectroradiometer (MISR) instruments on NASA's Aqua and Terra satellites. These instruments have provided global observations of aerosol optical depth (AOD), a measure of light extinction by aerosol in the atmospheric column above the earth's surface. AOD is tied to PM2.5 by an empirical formula, which can be affected by the AOD vertical profile, humidity, temperature, and wind speed. We will utilize the MODIS Terra and Aqua combined Multi-angle Implementation of Atmospheric Correction (MAIAC) Land Aerosol Optical Depth Gridded Level 2 product produced daily at a one-kilometer pixel resolution.

A 2019 review article that summarized the methods, availability, and applications of PM2.5 exposure estimates found that many studies derived wildfire PM2.5 exposure from the utilization of ground measurements, satellites, and atmospheric models[85]. Dense aerosol plumes are easily observable and visualized, making it possible to monitor wildfire smoke PM2.5's transport and transformations over large geographic areas. Such products are just starting to be used to study the impact of wildfire smoke on child respiratory outcomes. In this dissertation, we will use methods from the most up-to-date studies examining wildfire PM2.5, combine remote sensing data (AOD) and visual inspection to estimate accurate exposure measures.

1.2.4 Review of literature: wildfire or agricultural fire PM2.5 and child respiratory outcomes:

There are blatant disparities between the areas where most of the wildfire or biomass burning smoke emissions occur (LMICs) and the number of epidemiological studies conducted. While numerous studies have examined the relationship between indoor biomass burning and child respiratory outcomes, only a few studies have studied how outdoor wildfire PM2.5 can affect children's respiratory outcomes. In addition, many previous studies done in LMICs have examined the effect of ambient PM2.5 and adverse respiratory outcomes in children. However, very few looked specifically at wildfire-attributable PM2.5, and these studies were not located in Africa. Four systematic reviews examining the health effects of wildfire and biomass smoke identified *zero* epidemiological studies that examined wildfire smoke and health outcomes in Africa[69,86-88].

Twelve total articles that examined wildfire PM2.5 and child respiratory outcomes. Nine studies were implemented in the United States[69,89-95], one from Indonesia[96], one from Singapore[97], and one from Brazil[98] (Table 1). Three out of the nine studies from the US were reviews. The dominant methodology was mixed-effects models (3 studies). Two studies utilized time-stratified case-crossover methodology, one a quasi-experimental approach of difference-in-differences, one multiple regression models, and one use a chi-squared test as their analysis method. Of the nine studies that performed analyses, three studies obtained exposure measurements from ground monitors, three studies utilized satellite remotely sensed data, one study used fire emission and dispersion models, and one study assessed exposure through a combination of ground monitors, chemical transport models, and remotely sensed data. The last study was not clear of how exposure measurement was ascertained.

Table 1. 1: Results from the literature review of wildfire smoke and respiratory outcomes in children.

Year	Authors	Exposure	Methods	Results
2021	Garica et al.	NA	Review	Fine particulate matter levels can reach extreme concentrations during wildfires, and are associated with acute decrements in peak expiratory flow
2021	Holm et al.	NA	Review	There is an established literature of health effects in children from components of ambient air pollution, which are also present in wildfire smoke, and an emerging literature on the effects of wildfire smoke, particularly for respiratory outcomes.
2021	Aguilera et al.	PM2.5	Mixed effect models	A 10-unit increase in PM2.5 (from nonsmoke sources) was estimated to increase the number of admissions by 3.7% (95% confidence interval: 1.2% to 6.1%). In contrast, the effect of PM2.5 attributable to wildfire was estimated to be a 30.0% (95% confidence interval: 26.6% to 33.4%) increase in visits.
2019	Lipner et al	PM2.5	Mixed effect models	Among older children aged 12–21 we found that wildfire PM2.5 was associated with lower FEV1 the next day but higher FEV1 the day after. We found no associations between wildfire PM2.5 and FEV1 in younger children or between wildfire PM2.5 and asthma control measured by the ACT/CACT in all ages.
2019	Stowell et al.	PM2.5	Time-stratified, case-crossover models were fit using conditional logistic regression	Children displayed significant associations between smoke exposure and asthma.
2019	Rosales-Rueda and M Triyana	daily aerosol index	difference-in-difference	Children exposed to the fires are shorter on average three years post-exposure and have lower lung capacity 10 years post-exposure, but only children who were exposed in utero continue to exhibit shorter stature at 10 and 17 years post-exposure.
2018	Hutchinson et al.	PM2.5	Time-stratified, case-crossover models were fit using conditional logistic regression	Young children had bigger increases in visits during the peak fire period than older age groups. Children aged 0–4 had a 136% increase in emergency department visits for asthma, and very young children aged 0–1 experienced a 243% increase.
2015	Tse et al.	zip code locations	McNemar and Chi-sqaured test	There was no observed increase in emergency department and/or hospitalization rates, oral corticosteroid dispensing frequency, or new asthma diagnoses after either wildfire.
2015	Liu et al.	NA	Review	Wildfire smoke consistently associated with increased risk of respiratory disease.
2014	da Silva Viana Jacobson et al.	PM2.5 and PM10	Mixed effect models	The analyses revealed reductions in peak expratory flow for PM10 and PM2.5 increases of 10 µg/m3
2008	Delfino et al	PM2.5	Generalized estimating equations for Poisson data	Wildfire-related PM2.5 led to increased respiratory hospital admissions, especially asthma. The The strongest wildfirerelated PM2.5 associations were for people ages 65–99 years (10.1% increase per 10 mg/m3 PM2.5, 95% CI 3.0% to 17.8%) and ages 0–4 years (8.3%, 95% CI 2.2% to 14.9%)
2006	Kunzli	PM10	Mixed effect models	All symptoms (nose, eyes, and throat irritations; cough; bronchitis; cold; wheezing; asthma attacks), medication usage, and physician visits were associated with individually reported exposure differences within communities
1995	Chew et al.	PM2.5	Multiple regression models	An increase in emergency room attendances for acute childhood asthma was observed in two large general hospitals in Singapore

There were some mixed findings; two studies (Lipner et al. and Tse et al.) found no relationship between wildfire or agricultural smoke and child respiratory outcomes. Conversely, the remaining ten studies did find a significantly increased risk for adverse respiratory outcomes in children and wildfire smoke. Specifically, that children under five years of age were the most susceptible.

1.2.5 Dust:

One of the most significant natural contributors to PM_{10} is mineral dust. The major sources of dust emanate from arid regions in Africa, Asia, and the Middle East. Dust storms and plumes in these areas are the most prominent and extensive aerosol features visible in satellite images[99]. It has been ascertained that there is a “dusty” season from October through April in the Sahara-Sahel region and May through August in the Middle East, in which there is an increase in the amount of dust emitted during such seasons[100]. Several hundred tera-grams of dust are emitted each year from the Sahara desert to regions all over the globe.[101] Dust storms result from strong winds that disperse large amounts of desert dust into the air, resulting in extensive particulate exposure over large areas. These storms impact air quality on local and global scales and can lead to both short- and long-term health effects. Particles in these dust storms can contain many different elements that include silicon dioxide (SiO2), aluminum oxide (Al2O3), iron (Fe2O3), large amounts of evaporated salt, organic content, pathogens, and anthropogenic pollutants (heavy metals, pesticides, sulfate, nitric acid, polycyclic aromatic carbons)[102]. Dust storms can generate high PM_{10} concentrations, which often exceed the World Health Organization (WHO) recommendations of safe levels (mean of 50 $\mu m/m^3$ within a 24-hour period)[103]. Prior research has linked exposure to PM10 to an increased risk of adverse health outcomes, including adverse respiratory outcomes in children.

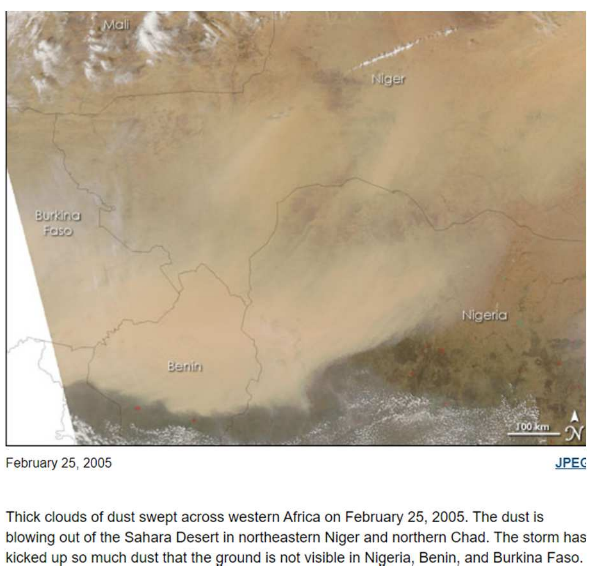


Figure 1. 5: MODIS image of a dust storm moving over Benin on February 25, 2005.

The “dust belt,” located in the Sahara-Sahel region in North Africa, contributes almost 50% of the world’s total dust emissions. Dust emissions from this region are transported to surrounding countries.

One such country is Benin, which has experienced several large dust storms from dust swept southwards from the Sahara-Sahel area. To the left is an image from NASA's MODIS satellite showing a massive dust storm over Benin in 2005. A study done by Tulet comparing satellite images of dust storms and simulated data found that the majority of dust emitted from the massive dust storm in March of 2006 was concentrated in Benin.[104] Other studies examining dust transport of West Africa found large amounts of dust in Benin in 2010 and that Benin was affected by another large dust storm in 2018. Benin is located in an area that frequently experiences significant dust events from the Sahara-Sahel region. This study will focus on Benin to examine the relationship between maternal exposure to dust PM10 and adverse birth outcomes.

1.2.6 Biological plausibility: coarse particulate matter (PM10) and child respiratory outcomes:

PM10 is defined as a suspended aerosol particle with a diameter less than 10µm. PM10 comprises a variety of dust from sea salt, mineral dust, construction and demolition dust, non-exhausted vehicle emissions, and industrial components[105]. A surfeit of evidence has tied short- and long-term exposure to particulate matter and adverse health outcomes, even if the vast majority of these studies did not focus on PM from dust. Studies have shown that short-term exposure to ambient particulate matter (from any source) can increase the risk of cardiovascular and respiratory morbidity and mortality[106-110]. More specifically, short-term exposure to PM10 has been tied to cough and more severe respiratory infections in adults and children[111-115]. There are several proposed pathways of how dust can affect health. African dust's main constituents include clay, minerals (mainly iron), and quartz, but African dust can also contain microoraganisms[116]. Aerosols rich in iron can cause pulmonary inflammation[117] , and the presence of microorganisms can provoke immune responses[118]. Children constitute a particularly vulnerable group because they are more sensitive to air pollutants than adults[119] due to children's immature detoxification mechanisms[120].

The respiratory system is the principal entrance for PM. It is inhaled, and because of the larger particle size, it is more likely to get deposited in the larger airways of the upper region of the lung. PM10 leads to physical damage, but not chemical damage, of the respiratory system, mainly in the larynx and alveolus[82]. Thus, PM10 has been tied to a greater pulmonary inflammatory response than PM2.5[121]. More specifically, these coarse particles are deposited in the bronchial passages and thus affect respiratory conditions such as asthma, chronic obstructive pulmonary disease, and pneumonia[122].

1.2.7. Methodological challenges in exposure PM10 measurement: Remote Sensing:

Disentangling dust particulate matter from all other ambient sources of PM10 has been a challenge and may explain the lack of research that has been done on desert dust. This dissertation will rely on remote sensing data to separate dust PM from ambient PM10 in areas with sparse numbers of ground monitors as in LMICs. Previous research has utilized ground monitor measurements of PM10 as a proxy for "dust' measurements, which could bias results because it is impossible to distinguish natural dust from anthropogenic concentrations within these measurements[123]. With the advancements in technology, determining the concentration of natural dust particles has become possible. The AOD measurement from the Moderate Resolution Imaging Spectroradiometer (MODIS) and Multiangle Imaging Spectroradiometer (MISR) instruments on NASA's Aqua and Terra satellites allows us to disentangle natural sources of dust from anthropologic ones. We will utilize the MODIS Terra and Aqua combined Multi-angle Implementation of Atmospheric Correction (MAIAC) Land Aerosol Optical Depth Gridded Level 2 product produced daily at a one-kilometer pixel resolution. This product can detect the presence of dust. I will use this product in tandem with a visual inspection of daily satellite images to ascertain dust exposure.

1.2.8 Review of the literature: African dust and child respiratory outcomes:

The majority of evidence examining how dust or PM10 attributable to dust affects respiratory symptoms in children has been from high-income countries or examines dust from other regions, mainly Asia[124,125] . Studies that examined the effect of African dust only looked at children in other geographical locations, which were HICs. A total of nine studies investigated the relationship between African dust and adverse respiratory outcomes in children. Only one of these studies took place in West Africa, and this study is a working paper. A recent systematic review, published in 2021, examining desert dust and global health mapped the location of these studies. They found that up until 2019, there were no studies conducted in Africa[126] (Figure 1.6).

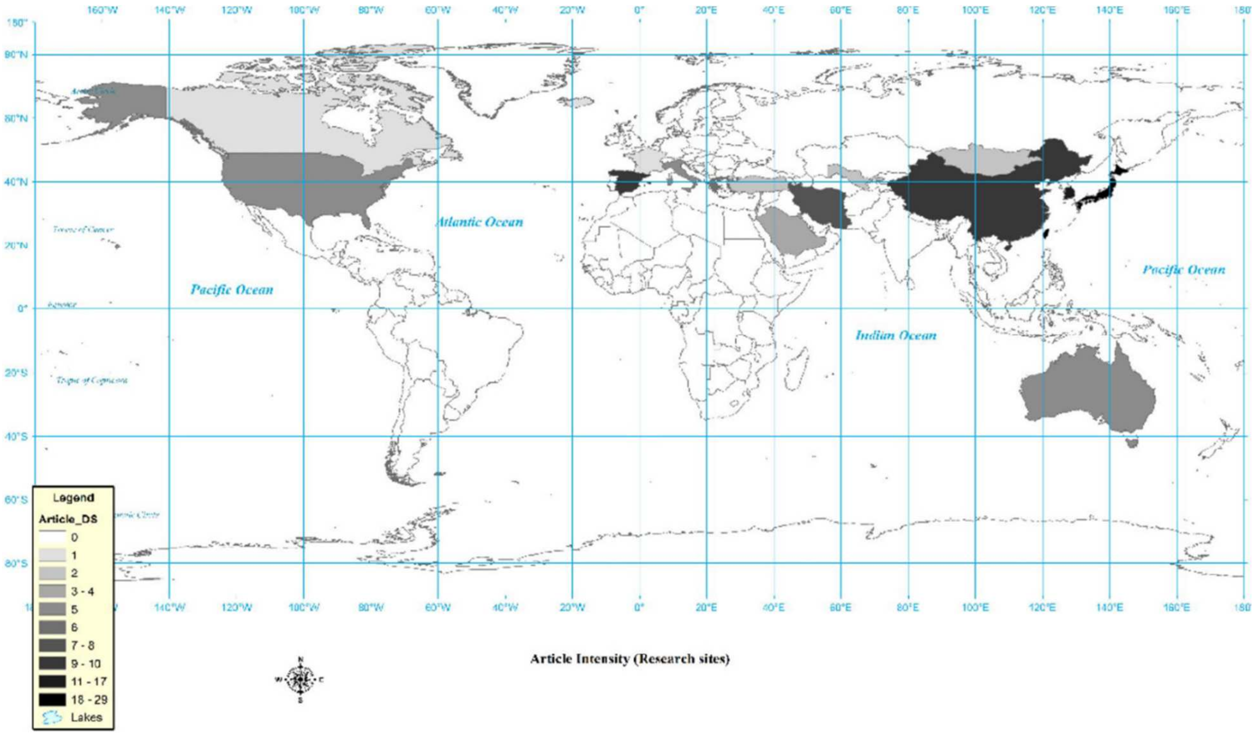


Figure 1. 6: Map of the distribution of studies done on desert dust and health outcomes from the 2021 systematic review.

The geological distribution of studies that examined African dust included: four from the Caribbean[116,127-129], three from Europe[101,130,131], one from Cyprus[132], and one from West Africa[133] (Table 2).

The primary methodology used in these analyses was Poisson regressions (6 studies). The other methodologies included two-stage least squares regression, time-stratified case-crossover, and a rank-sum test. Exposure ascertainment was primarily done using fixed ground monitors (5 studies). The other studies utilized reanalysis AOD from a satellite, a combination of satellite images, dust maps, and a back-trajectory model. Finally, one study used visual observation of dust days.

Table 1. 2: Results from the literature review of Saharan dust and adverse childhood respiratory outcomes

Year	Author	Exposure	Methods	Results
2018	Foreman, Timothy	AOD	Two-stage least squares regression	The occurrence of coughs and shortness of breath both increase, with a 1 standard deviation increase in AOD leading to a 1 percentage point increase in the probability of having a cough and a 3 percentage point increase in having experienced 12 shortness of breath
2016	Stafoggia et al.	PM10	Over dispersed Poisson models and random effect meat-analysis	%IR(85% CI) 2.47(0.22-4.77) No significant association between dust days and respiratory hospitalizations in children aged 0-14.
2014	Cadelis et al.	PM10 and PM2.5	Time-stratified case-crossover	The excess risk percentages (IR%) for visits related to asthma in children aged between 5 and 15 years on days with dust compared to days without dust were, for PM10, ((IR %: 9.1% (CI95%, 7.1%–11.1%) versus 1.1%(CI95%, −5.9%–4.6%))
2013	Reyes et al.	PM10 and PM2.5	Poisson regression models	While periods without Saharan dust intrusions were marked by a statistically significant association between daily mean PM2.5 concentrations and all- and circulatory-cause hospital admissions, periods with such intrusions saw a significant increase in respiratory-cause admissions associated with fractions corresponding to PM10 and PM10-2.5.
2011	Samoli et al.	PM10	Poisson regression models	A 10 µg m-3 increase in PM10 was associated with a 2.54 % increase (95%CI): 0.06 %, 5.08 %) in the number of paediatric asthma hospital admissions.
2008	Middleton et al.	PM10	Poisson regression models	+0.9 % all-causes and +1.2 % cardiovascular admissions per 10 µg m-3 PM10; +4.8 % all-causes and +10.4 % cardiovascular admissions on dust storm days
2009	Monteil et al.	PM10	Poisson regression models	Significant increase in the number of paediatric admissions for up to 7 days from the peak of dust cove
2008	Prospero et al.	PM10	Mann-Whitney rank-sum test, two-tailed	No association between dust and asthma but trending towards a realtionship
2005	Gyan et al.	Dust visability	Poisson regression models	Association between increased paediatric asthma admissions and increased Saharan dust cover. A deterioration of visibility due to Saharan dust cover increases a daily admission rate of 7.8 patients to 9.25

1.2.9. Extreme heat:

In the past few decades, significant trends of increasing global temperatures have been observed and tied to human influences[134-137]. Extreme heat events, or heat waves, can be characterized by stationary hot air masses or uninterrupted nights with unusually high minimum temperatures. In the US, heat waves are the number one cause of weather-related mortality, numbering more than all deaths attributed to hurricanes, lightening, tornados, floods, and earthquakes combined[138]. Given that all heat-related deaths are preventable, this large number of fatalities is troubling. For example, the 2003 European heat wave resulted in more than 70,000 deaths[139]. Similarly, there were massive extreme heat events in India in 2010 and 2015, including a 2010 heat wave that killed more than 1,300 people in one city alone[140]. Even though interest in extreme heat events and health has gained attention from these high-profile heat events in Europe and the US, there is a paucity of research examining these relationships in LMICs.

Previous studies have shown that prolonged exposure to extreme heat can cause heat-related illness, including heat cramps, heat exhaustion, heat stroke, and death in adults and the elderly. Fewer studies have examined exposure to high temperatures in pregnant women, another vulnerable population. Almost all of the research on extreme heat events and pregnancy outcomes comes from HICs. In general, these studies have found harmful effects of extreme heat on preterm birth and stillbirth. These studies have quantified the risk of negative birth outcomes utilizing various definitions of what is considered a heat wave.

There is no standard definition of a heat wave across the globe, making it difficult to compare effects of heat waves on health across different climate zones, cities, countries, or regions. Numerous studies have utilized different heat wave definitions regarding the temperature threshold (e.g., the 90th or 95th percentiles of temperature), temperature metric (e.g., maximum, minimum, mean, or diurnal temperatures), and duration of heat wave days (e.g., greater than 1 day, greater than 2 days, etc.). In addition, restricting analysis to only warm months or including the entire year of data hinders the comparison of heat effects across countries. The health impacts of heat waves are likely to vary temporally and spatially in their dose-response relationship. Studies that have compared health impacts using different heat wave definitions have found that a minor change in the heat wave definition resulted in differing estimated health effects[141]. The unique spatiotemporal health impacts indicate a need for local evidence-based studies of heat effects to inform early warning systems.

Adverse health effects from extreme heat are disproportionately affecting vulnerable populations, like pregnant women living in LMICs. Most of the evidence about extreme heat and negative birth outcomes has come from HICs. These findings cannot be extrapolated to LMICs because of the wide range of geographies, government structures, social issues, and cultural norms. Women residing in LMICs are more vulnerable to heat exposure due to lack of infrastructure (little to no air-conditioning), housing conditions, or less access to effective healthcare. Performing local evidence-based research creates an opportunity to inform heat-warning systems, action plans, and climate change adaptation strategies. This study will include a global analysis of 21 countries by exploiting each country's relative extreme heat events.

1.2.10 Biologic Plausibility: extreme heat and birth outcomes:

Physiological changes during pregnancy may impact the thermoregulation effectiveness of pregnant women. Throughout the pregnancy, the additional weight gained may decrease the ratio of body surface area to body mass, which in turn may limit a women's capacity to retain heat[35]. In addition, heat production could increase due to fetal growth and metabolism[142]. Thus, the ability for pregnant women to cope with heat stress may be limited due to the increase in internal heat production and the decrease in capacity for heat stress, which could trigger spontaneous labor. Furthermore, other studies have proposed that extreme heat might lead to a heightening in hormones of the hypothalamic-pituitary-adrenal axis, such as cortisol. This is one of the primary pathways which has been linked with activation of uterine contractions, which could potentially lead to preterm birth. Heat can also lead to dehydration, which in turn increases the viscosity of the blood, elevating cholesterol levels, and shifting blood flow from the developing fetus to the skin's surface to lower the bodies internal temperature. These processes of physiologic changes may decrease uterine oxygen and induce labor[40,143].

There have been very few studies that have examined how exposure to extreme heat influences risk of stillbirth. One of the postulated mechanisms is that heat exposure may cause damage to cells, the placenta, and vascular systems, resulting in insufficient fetal nutrition[144]. In addition, heat has been linked to birth defects such as congenital cataracts or heart defects, which could lead to unviability of the fetus[145].

1.2.11. Methodological challenges in exposure extreme heat: remote sensing:

With the lack of weather stations across most LMICs, obtaining reliable daily temperature measurements across many countries would be difficult. The available temperature data that is collected from the sparse number of ground monitors is mainly at the national-level, and these datasets differ greatly between countries. Multiple temperature datasets would need to be accessed and merged to create a large daily dataset, which would be extremely difficult. To overcome this challenge in available temperature data, this dissertation will use remote sensing data in the form of globally gridded daily temperature dataset. There are several globally gridded temperature datasets that are available to the public, but most of them are not on the daily scale. The publicly available Global Daily Temperature from the Princeton Meteorological Forcing Dataset, which was created by Sheffield, Wood and Roderick, will be utilized in these analyses. This weather data is at a 0.25°x 0.25° spatial resolution and at 24-hour temporal resolution and entails a combination of reanalysis data from the NCEP-NCAR and observational data from the Climatic Research Unit. The reanalysis datasets combine observational data with physics and climate-based models to improve the data in observationally sparse regions. The final product is a mixture of observational data, modeling, and resampling. This data has been utilized in other studies as a valid source of temperature and humidity data[146], and I will capitalize on this finished product in this study. Utilizing a global remote sensing dataset ensures that these analyses have a homogeneous exposure measurement that can be measured and compared across countries.

1.2.12. Review of literature: extreme heat and preterm birth and stillbirth in LMICs:

Numerous studies have been implemented on exposure to extreme heat and adverse birth outcomes. A systematic review of temperature exposure during pregnancy and birth outcomes conducted by Zhang et.al. in 2017 identified 36 epidemiologic studies[147]. Most of these studies were conducted in HICs and published recently (after 2010). Sixteen studies were done in Europe, ten in North America, five in Asia (Israel, China, and Japan), three from Australia, one from Africa, and one worldwide. Study designs included ecological time series, case-crossover, and retrospective cohorts. Twenty-four out of the 36 studies examined preterm birth and temperature, 14 studies assessed the effect of temperature on birth weight, and only four studies examined the relationship between temperature and stillbirth.

Different temperature indicators have been used throughout the studies. The majority utilized direct temperature metrics, e.g. mean, minimum, or maximum temperature. Two studies used apparent temperature, and one study used satellite-based and model-predicted temperatures. Many studies focused their research on the entire gestational period or by trimester. Only one of the studies examined the acute effect of extreme heat on adverse birth outcomes (within the month of birth). Overall, there were mixed findings from the studies that examined extreme heat episodes and preterm birth. Nineteen studies found an association between maternal exposure to high temperatures and preterm birth, and four studies found null results. All four studies examining stillbirth found an association between maternal exposure to extreme heat and stillbirth.

Since 2017, there have been many more studies conducted on temperature and birth outcomes. Again, most of these studies were located in HICs like the US, Canada, and Australia. Several studies have been conducted in Asia (Iran, South Korea, Taiwan, and China). Only one study was conducted in Africa (Ghana) since 2017[148]. A majority of these studies are now using global-gridded temperature datasets that are derived from remote sensing data, climate models, and interpolation. Statistical methods ranged from logistic regression to distributed lag nonlinear models to estimate the effects of extreme heat on adverse birth outcomes. Results were much more consistent between these studies, with a majority finding an associated between heat and preterm birth and still birth. One study examined the effect of acute exposure to heat 1 week prior to birth and found an association with increased risk of preterm birth[149].

Overall, previous studies generally lacked usage of contemporary remote sensing techniques to ascertain exposure levels. Numerous studies still relied on measurements from fixed ground monitors, which LMICs lack. In addition, only two studies examined the acute effect of extreme heat on adverse birth outcomes, and these studies found this acute exposure period before birth to be a high window of susceptibility for pregnant women. This study capitalizes on these findings and examines how these acute exposures affect pregnant women in LMICs.

1.3 Early warning systems:

As a result of climate change, extreme weather events are likely to increase in frequency and intensity over the coming decades. These extreme weather events cannot be prevented, but their human and financial costs can be mitigated by taking advantage of advances in meteorological forecasting that promote the development and implementation of early warning systems that target vulnerable populations. In order to implement these early warning systems, there needs to be valid epidemiological evidence that has elucidated patterns of highest risk in specific regions or populations. Once this first step is completed, policy makers will have the knowledge to develop these systems and target them to vulnerable regions and people.

Early warning systems aim to provide meteorological and climate-predication-based data on the probability of future extreme weather events that may affect human health. These data are used to alert decision-makers and the general public about possible dangerous conditions brought on by extreme weather events and to guide implementation of an action plan designed to mitigate such negative health effects of the environmental event. In general, several elements go into developing early warning systems. These include 1.) Weather forecasts of the event, 2.) A method for assessing how future extreme weather events patterns may evolve and how they could affect health outcomes, 3.) The threshold that the early warning system is going to utilize for action, and 4.) A system of alerts and actions for communication to specific targeted groups or the general public about the approaching period of dangerous conditions and to government agencies about the possible severity of health impacts. Early warning systems are often part of a larger action plan. These action plans encompass the early warning system itself, but also the following criteria: 1.) Education for the general public on the extreme weather events, 2.) Training in preparedness for responders, 3.) Guidelines for actions to mitigate risk, 4.) Guidance for the implementation of strategies and maintenance of infrastructure to reduce risk, 5.) An evaluation program of the action plan, 6.) Health surveillance in real-time, 7.) Long term strategies for the area to reduce risk, and 8.) Monitoring and evaluation of interventions that are in place[150].

Since extreme weather events vary per their spatial-temporal patterns, it is important for early warning systems to utilize real-time or close to real-time data on a local scale. For example, there is no universal heat value that defines a heat wave. Thus, heat waves are relative to a location's climate. The same meteorological conditions could qualify as a heat wave in one region but not in another. In addition to meteorological factors, demographic and socioeconomic factors play a critical role in the susceptibility of an individual's risk to extreme weather phenomena. People who are exposed to multiple risk factors are at a higher risk for adverse health outcomes from extreme weather events and should be classified as a vulnerable person and targeted by the early warning system. Research is needed to support and maintain these early warning systems, particularly the systematic collection of epidemiologic data on all health risks associated with extreme weather events. Local epidemiologic data can also help inform decision-makers about the effectiveness of future interventions.

There are numerous heat-health action plans and early warning systems that have already been implemented across the globe. Most of these heat-health action plans are located in Europe, the US, and Australia, but there also are some LMICs that have recently implemented these plans. India, Bangladesh, Bhutan, Sri Lanka, and the Maldives all have plans in place for heat-health preparedness. While many countries have implemented fire danger rating systems, there is at least an equal number that have no system in place. A Global Fire Early Warning System supported by the United Nations International Strategy for Disaster Reduction was formed to develop a globally consistent suite of fire danger and early warning systems to mitigate wildfire disasters, but this program is still in development. Finally, Australia seems to be the only country that has a dust-health action plan implemented.

The Lancet Countdown on health and climate change has outlined the steps for countries to take for adaption, planning, and resilience for health in the context of climate change. Six indicators of resilience and adaption were identified and included: 1.) National adaptation plans for health, 2.) City-level climate change risk assessments, 3.) Detection and early warning of preparedness for, and response

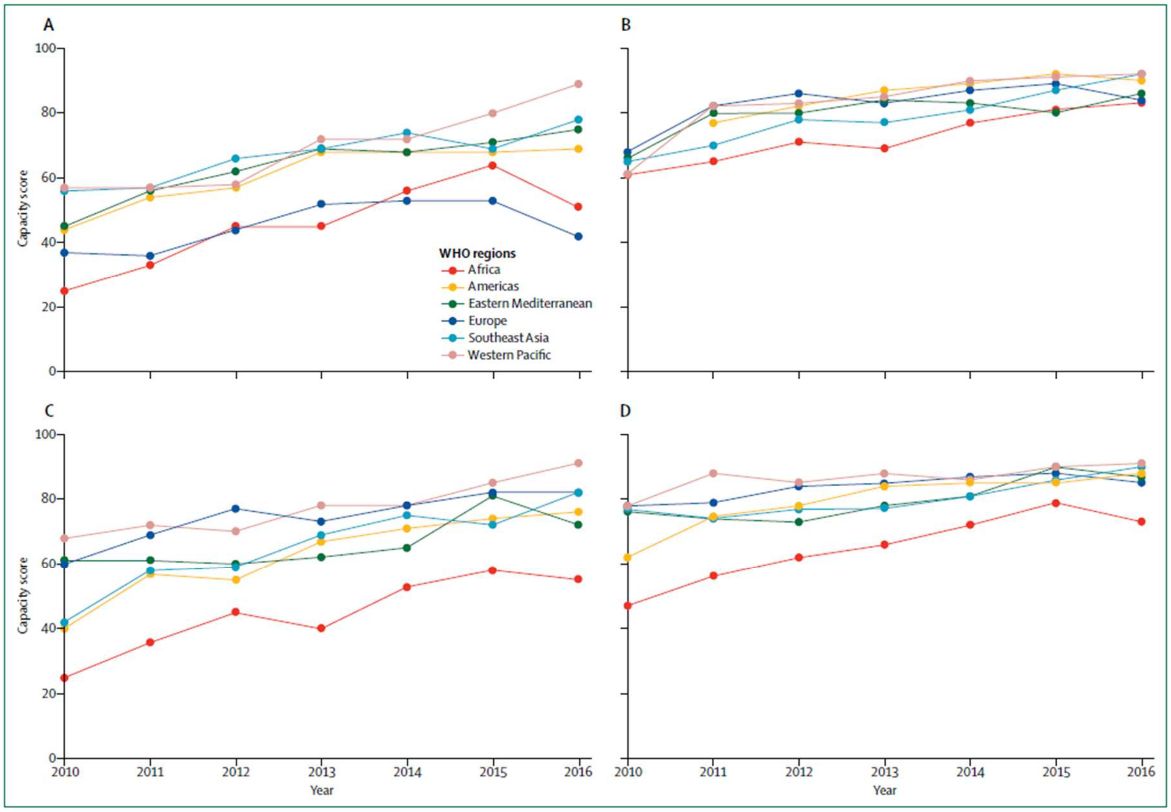


Figure 13: **International Health Regulations capacity scores by WHO regions**
(A) Human resources capacity score. (B) Surveillance capacity score. (C) Preparedness capacity score. (D) Response capacity score.

Figure 1. 7: International Health and capacity scores by WHO region A) Human resources capacity score. B) Surveillance capacity score. C) Preparedness capacity score. D) Response capacity scores as seen in the Lancet 2019 Countdown[151].

to climate-related health emergencies, 4.) Climate information services for health, 5.) National assessments for climate change impacts, vulnerability, and adaption for health, and 6.) Climate-resilient health infrastructure. They found that LMICs, especially LMICs in Africa, were lacking in all six indicators. In addition, the Lancet article also addressed multiple populations of vulnerable people. Pregnant women and children were not among them. Pregnant women and children who reside on LMICs are especially vulnerable and will become more vulnerable as climate change exacerbates exposures to extreme weather phenomena. This dissertation thus aims to provide local epidemiologic evidence to inform future early warning systems in LMICs.

1.4 Study population: Demographic Health Survey:

The Demographic Health Survey (DHS) Program was established by the United States Agency for International Development (USAID) in 1984. The main objective of the DHS Program is to improve the collection, analysis, and dissemination of population, health, and nutrition data and to facilitate use of these data for planning, policymaking, and program management. More than 300 DHS surveys in over 990 countries have been conducted since the program's inception. Several countries that are non-USAID supported have participated through funding from other donors such as UNICEF, UNFPA, the World Bank, and national governments. The DHS Program has made their data available to all researchers, which enables this dissertation to utilize a standardized household survey that specifically focuses on child and maternal health across multiple LMICs. Thus, standardized adverse birth and respiratory outcomes assessments are provided for these analyses from one data source. DHS surveys are nationally representative and focus on fertility behavior, health, and wellbeing of women of reproductive age and their children. Women ages 15-49 responded to questionnaires about the complete birth histories of their children, which included health information about their children.

Phase 7 of the DHS survey was implemented in 2013 and was continued through 2018. Countries could participate in this phase anytime within this time period. In Phase 7 of the DHS survey, the birth history section of the questionnaire introduced, for the first time, the dates of birth of children. This addition of day of birth also allows us to determine the day of death of stillbirths by combining this information with an "age at death" indicator. Adding the day of birth enhances the ability to study effects of acute events such as extreme heat and health outcomes. Without this new addition of data, entire exposure events that could influence adverse birth outcome risk would be missed because birth outcomes could only be ascertained at a monthly scale. Furthermore, previous literature has indicated that the week before birth is a crucial window of susceptibility for increased risk of adverse birth outcomes. Using data on a monthly level would not allow this research to investigate this important time frame in a woman's pregnancy. Additionally, the DHS survey collected birth outcome data at a small spatial scale (a city block for urban areas and a village for rural areas), which permits this research to capture the variation of adverse birth outcome risk at a very acute spatial scale across and within countries. The DHS survey phase 7 provides this research with a unique opportunity by giving us access to standardized maternal and child health data across multiple countries, along with the ability to link exposure to extreme environmental events at an acute temporal scale with these health outcomes. This makes it possible to investigate how these acute exposures to heat within a known high-risk period in a woman's pregnancy affect adverse birth outcomes.

1.5 Specific aims:

In 2016, there were about 2.4 million lower respiratory infections, making these infections the number one cause of mortality in children under five years of age[2]. The respiratory infection burden varies significantly across the globe, disproportionately affecting the young and poor[10]. Lower respiratory infections are a significant contributor to child mortality in low-to-middle income countries (LMICs). Children across the globe experience three to six acute respiratory infections a year despite where they live or their socioeconomic status[3]. Nevertheless, the proportion of severe infection is higher in LMICs because of differing etiologies and risk factors, resulting in a higher case-fatality rate[3].

Complications from preterm birth (defined as a live birth before 37 weeks gestation) are known for being the leading direct cause of neonatal mortality. Neonates that are preterm and survive have a higher risk of short-term and long-term morbidities, which place a substantial burden on health care systems and families. LMICs are experiencing the highest rates of preterm births, accounting for more than 60% of these births. Even more devastating than preterm births are stillbirths (defined as a fetal death that occurs after 28 weeks of gestation), the vast majority of which take place in LMICs. Ninety-eight percent of the 2.6 million annual stillbirths that occur globally are in LMICs, with South Asia and sub-Saharan Africa accounting for three-quarters of this total.

Research suggests several environmental determinants, such as extreme weather events, that can increase the risk of adverse birth and respiratory outcomes. Wildfires and dust storms are acute events that typically contribute massive amounts of exposure to particulate matter (PM). There has been a plethora of evidence that ties PM exposure to adverse respiratory outcomes in children. Depending on the diameter of the PM, two different biological mechanisms have been hypothesized both involve inflammation and oxidation stress. Numerous studies have found that pregnant women exposed to heat have an increased risk of negative birth outcomes, especially in the last week of gestation. Acute exposure to extreme heat in late pregnancy has also been associated with preterm birth and stillbirth. In this regard, two potential pathways have been suggested: (1) heat stress, which can cause preeclampsia, oligohydramnios, and uterine contractions, and (2) dehydration, which could cause decreases in uterine blood flow and an increase in pituitary secretion, which can induce labor. Concentrating research on large-scale, preventable environmental exposures in LMICs is critical for reducing the burden of adverse birth and respiratory outcomes.

In the context of climate change, we have witnessed unprecedented extreme weather phenomena attributed to changes in precipitation regimes and increasing temperatures globally. Such weather patterns have contributed to the increasing severity and frequency of wildfires, dust storms, and heat waves. Rising global temperatures have made landscapes more vulnerable to massive wildfires and emittance of dust due to the amplified dryness. Adverse effects of wildfire, dust, and extreme heat events disproportionately impact people residing in LMICs, who lack the resources, information, and infrastructure to cope with these events.

Most studies tying exposure to extreme heat, dust PM, wildfire PM, and adverse birth and respiratory outcomes have been conducted in high-income countries (HICs). Many studies have examined desert dust and child respiratory outcomes, but these have been conducted in Asia or HICs. There has been no study to date that has explored the relationship between Saharan dust and child respiratory outcomes in African countries. However, previous evidence does indicate an immediate to lagged effect of exposure to smoke and dust on respiratory outcomes in children. Studies from HICs that have studied adverse birth outcomes have indicated that acute exposure during the days before birth seems to be a critical factor regarding susceptibility to extreme heat. Examining this acute exposure window is imperative, as this is when most preterm births and stillbirths are triggered. Preventive measures targeting pregnant women in their late pregnancy could mitigate the impact of such extreme events on adverse birth outcomes. Evidence from HICs indicates the importance of understanding heterogeneity in thresholds at which heat could influence birth outcomes, highlighting the need to document such patterns locally. It is essential to study these exposures in LMICs to identify specific seasonality or spatial-temporal patterns and target women in late pregnancy to inform early warning systems. Evidence-based early warning systems are effective in developed countries for extreme weather events such as heat waves and wildfire smoke.

Previous studies have mainly been focused on HICs because measuring exposure to wildfire PM2.5, dust PM10, and extreme heat in LMICs has been challenging. Notwithstanding, a lack of accessible vital records and health data makes it difficult to study such topics. LMICs rarely engage in routine air pollution and meteorological data collection, which poses problems in assessing acute exposure levels to these environmental events. Few studies have examined these environmental exposures and adverse birth and respiratory outcomes in LMICs, but these studies generally rely on monthly or annual averages of exposure. In this dissertation, I will be relying on modern techniques such as remote sensing data and climate statistical and dynamical modeling to overcome this challenge in measuring exposures. Additionally, I will use robust epidemiological methods to deal with unmeasured confounding and obtain valid causal estimates.

In this study, I propose to link remote sensing air pollution and meteorological data with Demographic Health Surveys (DHS) data on adverse birth and respiratory outcomes. With the release of the newest phase of the survey came a unique opportunity to capitalize on the fact that this version added the day of birth (or death) for each child, not just the birth month. This change in the survey allows for the performance of analyses on a more acute and specific level, i.e., daily measurements that have shown to be relevant for considering critical windows of susceptibility.

This dissertation will ascertain the effect of three extreme environmental events: wildfire/agricultural fire smoke PM2.5, dust PM10, and heat on adverse birth and respiratory outcomes in various LMICs. More specifically, the following aims are going to be addressed:

Aim 1: Identify the effect of acute exposure of wildland and agricultural fire PM2.5 and childhood respiratory outcomes in 14 LMICs.

Aim 2: Identify the effect of acute exposure to dust PM10 and child cough in Benin

Aim 3: Perform a global analysis and identify the effect of acute exposure to extreme heat, one week before birth, and preterm birth and stillbirth in 21 LMICs.

2. Wildland and agricultural fire smoke and childhood respiratory outcomes in sub-Saharan countries:

2.1 Abstract:

This study is the first study that has examined the relationship between wildland and agricultural fire smoke exposure and risk of child respiratory outcomes in a comprehensive set of low-to-middle-income countries in West and Sub-Saharan Africa. Sub-Saharan Africa is one of the top fire-prone areas of the world, with a majority of burning occurring during the dry season. As our climate changes, we are seeing an unprecedented number of wildfires across the globe. Epidemiological evidence from LMICs examining wildfire and acute agricultural smoke exposure and adverse respiratory outcomes in children is scarce. Children can be more severely affected by exposure smoke due to their reduced lung size and higher respiratory rates. We aim to examine the relationship of acute exposure to smoke and child respiratory outcomes (cough and rapid breathing) by linking finely resolved remotely sensed satellite data with the Demographic Health Survey for 14 LMICs in Africa (n=343,946 children). We conducted mixed effect Poisson (with robust variance) models that incorporated survey weights and accounted for respiratory outcomes clustering. We found an increased risk of cough and rapid breathing in children within two weeks of exposure to smoke, and this effect attenuated by four-weeks period. The countries that saw the strongest effects of smoke on child cough and rapid breathing were Malawi and Uganda. Additionally, we identified that countries whose climate consisted mostly of arid and dry conditions had a higher risk of cough when children were exposed to wildfire or agricultural fire smoke.

2.2 Introduction:

Large wildfires are a global phenomenon that pose significant risk to property and life, partially due to changes in precipitation regime, as well as immense development on fire-prone landscapes[58]. As temperatures rise and droughts increase in length and severity, severe wildfires are increasing in intensity and frequency globally[152,153]. There have been three climatic factors that drive the inter-annual variability of fires across Africa, and these are the amount rainfall, the seasonality of rainfall, and the occurrence of weather conditions, such as lightning strikes, with high fire danger[154]. 2019-2020 saw an unprecedented number of massive wildfires around the globe[155]. The European Space Agency detected 79,000 wildfires (of different magnitudes) across the globe in August 2019 compared to only 16,000 fires during the same period in 2018[156]. NASA's Global Forest Watch sent out 782,366 worldwide fire alerts within a 7-day period from July 15th to July 22nd, 2019. The majority of these alerts went out to the Democratic Republic of the Congo (136,087), Zambia (52, 801) and Angola (109, 512)[157].

Sub-Saharan Africa is one of the top fire-prone areas of the world, with a majority of burning occurring during the dry season[59]. Countries north of the equator experience the most amount of burning from November to February and countries south of the equator from May through October[64,158]. It is estimated that 51% of the African savanna burns every two years[60]. Some studies estimated that global fires burn an area of about 350-422 million hectares and emit about 2.2 Metric Gigatons of carbon into the air, among which 67% of the burned area and 52% of the carbon emitted, resulted from biomass burning in Africa alone[62-64]. Not all of these fires are wildfires. Many are agricultural fires, resulting from the slash-and-burn technique to clear forest and woody plants for agriculture. Other reasons for agricultural fires include burning for fertilization, land management, and pest control[65]. These slash-and-burn fires can be exacerbated by climate change and are becoming harder to control. Agricultural fires from Central and West Africa are the main component of biomass burning emissions across Africa. In a previous health impact assessment study (not using observed health data but using published dose-response relationships), such fires which have been linked to 43,000 premature deaths per year[65].

Apart from the physical destruction from wildfires, their smoke contains large amounts of fine particulate matter (PM2.5)[66-68], which has been tied to adverse health outcomes[69]. Some of these health problems include respiratory diseases[69], cardiovascular disease[70], reduced life expectancy, adverse birth outcomes, and death[71]. PM2.5 is tied to this broad range of adverse health outcomes because of the particle's small size. PM2.5 are inhaled, bypassing the upper respiratory tract, where the particles can travel into the deepest part of the lungs, the alveoli[110]. From the alveoli**,** PM2.5 can cross into the bloodstream, adversely impacting the vascular system, the lungs, and other vital organs[159]. Additionally, because of PM2.5's small size, the particles can stay suspended in the air for weeks and can travel long distances, which increases the opportunities for adverse health impacts.

Epidemiological evidence from Low-to-middle-income countries (LMICs) examining wildfire smoke and health effects is scarce. There are blatant disparities between the areas where most of wildfire or biomass burning smoke emissions take place (LMICs) and the number of epidemiological studies that have been conducted. Four recent systematic reviews examining the health effects of biomass smoke identified *zero* epidemiological studies that examined wildfire smoke and health outcomes in Africa[69,86-88]. The lack of studies conducted in LMICs could be attributable to challenges in exposure measurement and paucity of available health data. Previous literature has relied on ground monitors to measure PM2.5 but air quality monitoring stations in sub-Saharan Africa have been stalled or discontinued in recent years. Among the 47 countries that comprise sub-Saharan Africa, only six countries measure PM[84]. Given that LMICs face many additional hardships compared to their high-income country counterparts, it would be wrong to assume the dose-response mechanisms and effect size relationships between biomass smoke and health are homogeneous. Thus, conducting local epidemiological studies relying on observed health outcomes within LMICs is crucial.

It is also particularly important to study such impacts among vulnerable populations within LMICs. Children can be more severely affected by exposure to PM2.5 and smoke due to their reduced lung size, increased metabolic rates, higher respiratory rates, and their developing immune systems[72]. Acute respiratory infections are among the leading cause of childhood mortality globally and accounted for 10% of deaths in children younger than five years in 2017[9]. The respiratory infection burden varies significantly across the globe, disproportionately affecting children and low-income communities[10]. People who have the highest risk of contracting or dying from respiratory infection come from rural households with low levels on income and lower education levels.[11]. In this context, children residing in LMICs constitute one of the most vulnerable populations to these infections. This study fills an important gap in the literature by capitalizing on state-of-the-art remotely sensed data to overcome the challenge of exposure classification coupled with acute child respiratory outcomes at a fine spatial scale using the most recent data from Demographic and Health Surveys (DHS) in sub-Saharan Africa.

This study aims to examine the relationship between wildfire and agricultural smoke and child respiratory outcomes within 14 LMICs located in western and sub-Saharan Africa by implementing mixed effect Poisson models with survey weights. Furthermore, we will investigate how smoke can affect adverse respiratory outcomes by climate zone.

2.3 Methods:

2.3.1 Health data:

Data for children aged under five years are obtained from the DHS database (ICF, n.d.). DHS surveys are nationally representative and focus on fertility behavior, health, and wellbeing of women of reproductive age and their children. Women ages 15-49 responded to questionnaires about the complete birth histories of their children, which included health information about their children. In addition, individual- and household-level data, such as household wealth, education level, prenatal care, and health insurance status, are recorded. DHS also provides global positioning system (GPS) data for each primary sampling unit (PSU). A PSU is defined as a city block in an urban area and a village in a rural area. Surveyors used global positioning system devices to collect geospatial information to identify the central point of the populated area of each PSU[160]. The DHS survey randomly displaced GPS coordinates to ensure respondent confidentiality. The displacement is carried out so that urban PSUs contain a minimum of 0 and a maximum of 2 kilometers of error, and rural PSUs contain a minimum of 0 and a maximum of

5 kilometers of positional error with a further 1% of the rural clusters displaced a minimum of 9 and a maximum of 10 kilometers[161].

2.3.2 Exposure data and classification:

A MODIS Terra and Aqua combined Multi-angle Implementation of Atmosphere Correction (MAIAC) Land Aerosol Optical Depth (AOD) data product was utilized to determine if there was a presence of smoke in the air on a given PSU-day. This product is a gridded Level 2 with a spatial resolution of 1 KM and a temporal resolution of 1 day (MCD19A2.006). The Optical_Depth_047 band was downloaded using Google Earth Engine (GEE). The daily optical depth was obtained from July 2015 to February 2020, for each 1 KM pixel within every country included in the study. In addition to the AOD measurements, there is a band called AOD_QA, which is a 16-bit unsigned integer. A unique 16-digit number indicates the presence of smoke in the air to which DHS participants may be exposed to. The binary exposure of having smoke present or not on a given PSU-day was downloaded for each of the PSUs across the 14 countries and the entire study period.

For our main exposure of interest, a binary indicator was created by defining a child as exposed if he or she experienced at least one smoke day within the two weeks prior to the interview date. In addition, we created other indicators to examine a potential dose-response relationship. If a child was exposed to one day within the two weeks prior to the survey, a dummy exposure variable was made that indicated one. The dummy variables also indicated exposed to two days and exposed to three or more days within the two-week period prior to the interview. We repeated these exposures for a four-week time frame to also examine lagged effects.

2.3.3 Outcome classification:

Each mother was asked if their child experienced cough symptoms within the last two weeks before the interview date. Furthermore, if the child did have a cough within the previous two weeks, the mother was asked if the child experienced rapid breathing and or has a problem in the chest or a blocked or running nose. A child was considered to have a cough if the mother answered “yes” if the child had a cough in the past two weeks. A child was considered to have rapid breathing if the mother answered "yes" to the rapid breathing question.

2.3.4 Statistical analyses:

We used a series of mixed effects Poisson (with robust variance) regression models to investigate the relationship between acute exposure to smoke and cough and rapid breathing. The models take the following form:

$$y_{i,k} = \beta_0 + \beta_1\, Smoke_k + \beta_n Z_n + u_k + \epsilon_{i,k}$$

where $y_{i,k}$ is a binary indicator for cough, or rapid breathing for child *i* in PSU *k*; $smoke_k$is the smoke variable of interest; Z_n is a vector of maternal and household-level a priori identified confounders. These include type of residence (rural or urban), highest achieved maternal education and household's wealth. u_k is a DHS cluster random effect term, which accounts for the nesting of children within DHS clusters; $\epsilon_{i,k}$ is an error term. Population weights were included in the models using DHS sampling weights to account for complex survey design.[42] We ran these models for each of the two time periods (two and four-weeks) and each of the smoke exposure definitions (binary, 1 day, 2 day, and 3 or more days) in each country.

We also perform stratified analyses to investigate the association between smoke, cough, and rapid breathing by climate type. These climate types were determined by using the Köppen-Geiger (KG) classification system.

2.4 Results:

2.4.1 Main results:

Our sample size consisted of 343,946 children, with 66,588 cough cases and 27,502 rapid breathing cases (Table 1). There was a total of 41,573 smoke days within the study period. Benin and Mali experienced the most amount of smoke days, and Uganda and Burundi experienced the lowest number of smoke days (Figure 1). Uganda had the largest proportion of cough cases (38%), and Mali had the least amount of cough cases (8%). Children living in Burundi experienced the highest number of rapid breathing incidents (15%), and children living in Zambia experienced the lowest (3%).

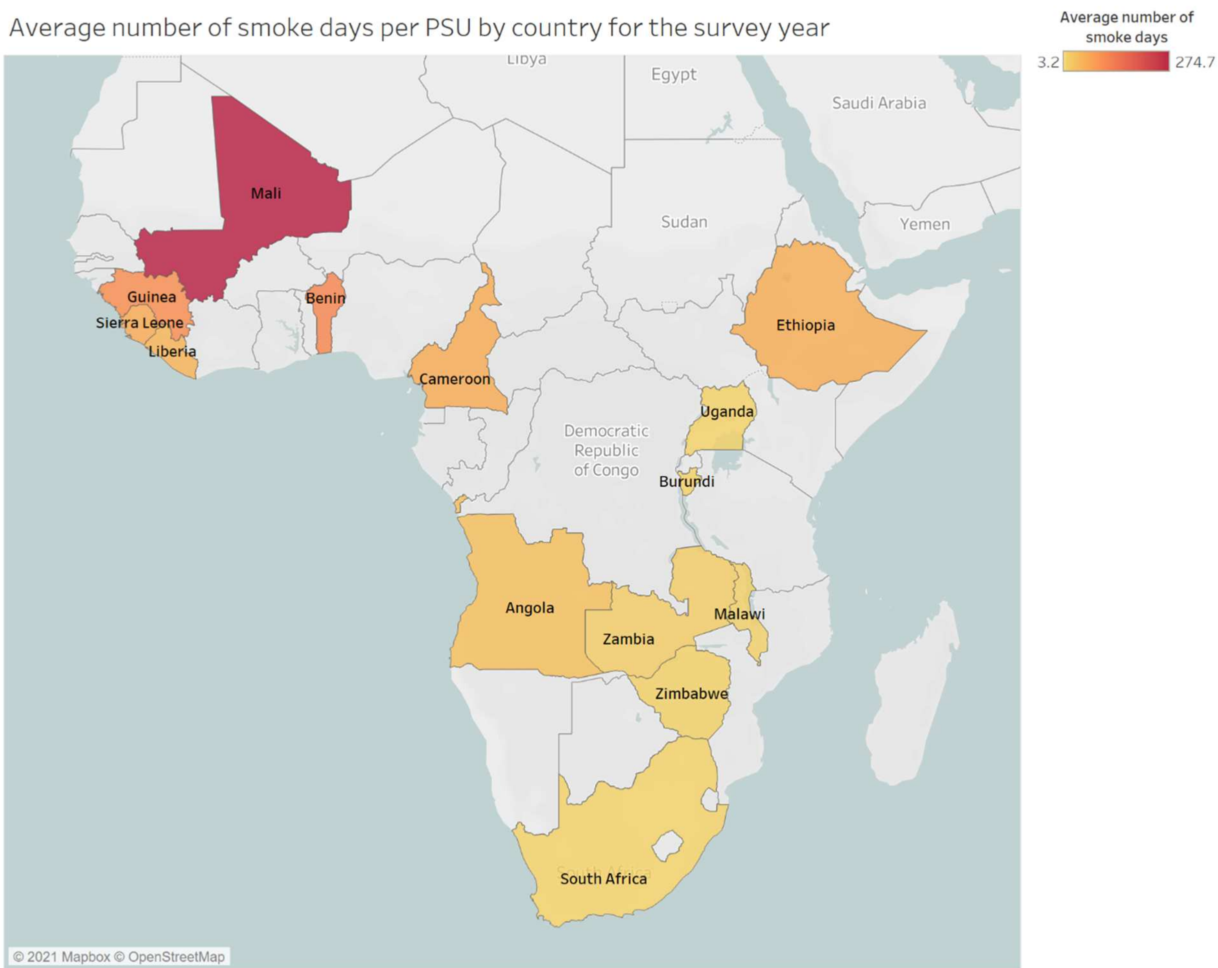
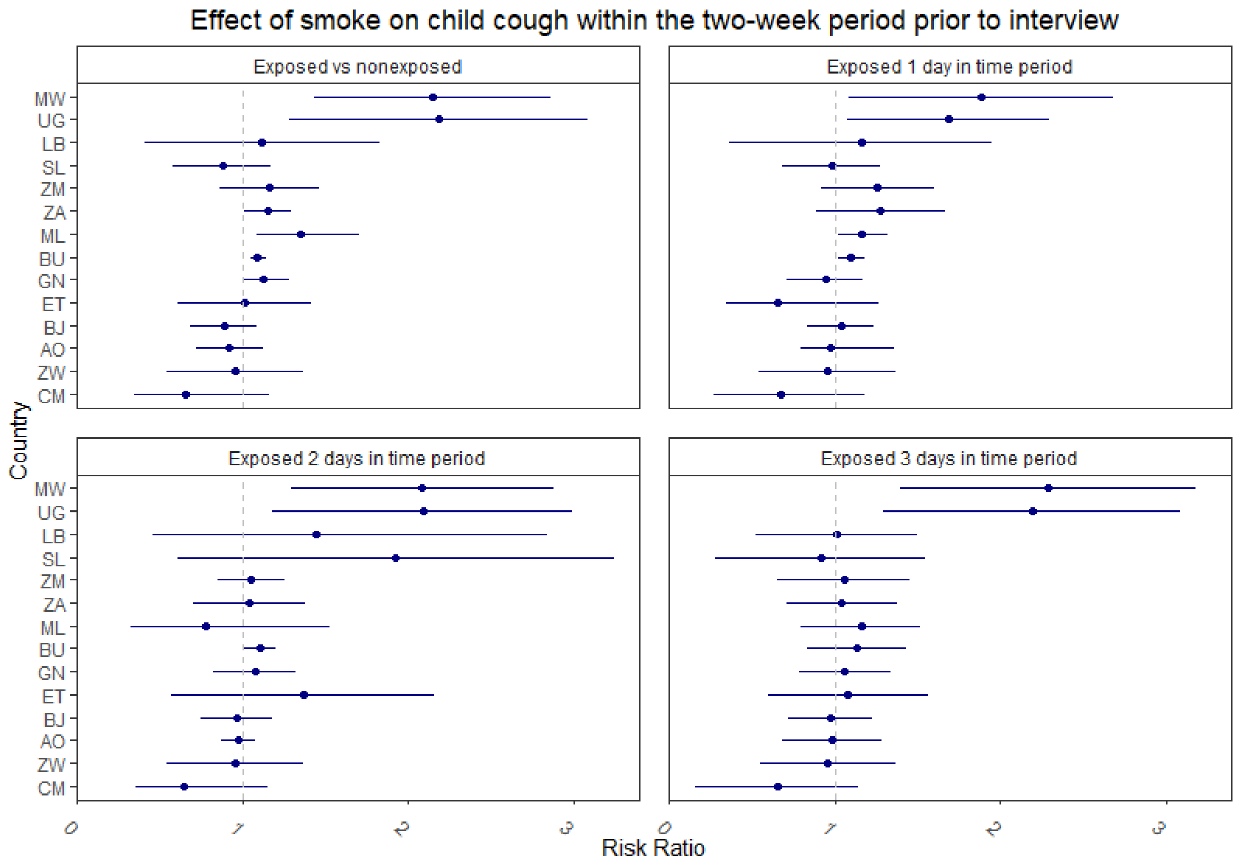


Figure 2. 1: Average number of exposed PSU-days through the year of the study period, by country.

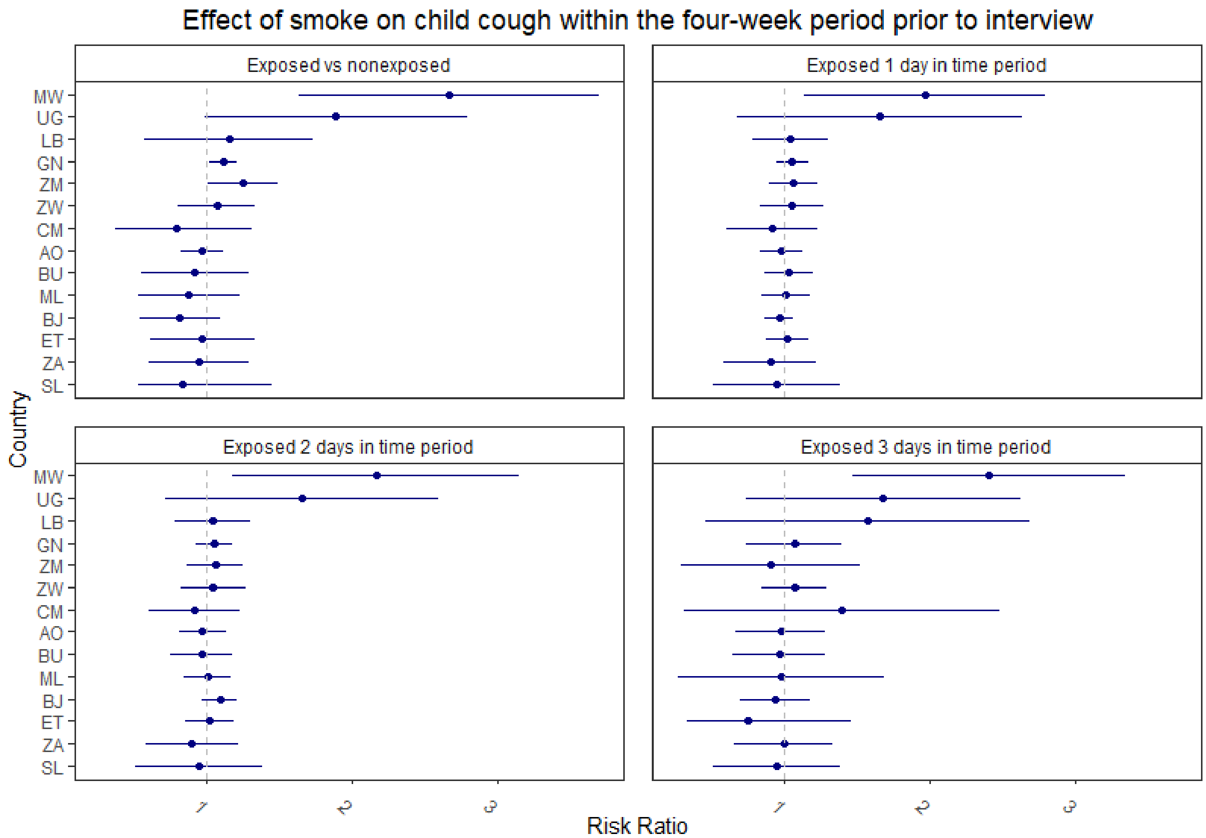
We found that the acute effect of smoke exposure was stronger within the two-week period before the interview date and dissipated during the four-week time period (Figure 2 and Figure 3). Uganda and Malawi experienced the largest overall effect of smoke and childhood cough with risk ratios (RR) and 95% CI of 2.18 (1.29-3.09) and 2.15 (1.43-2.86), respectively. These effects got slightly larger when looking at the dose-response relationship (Figure 2). South Africa, Burundi, Guinea, and Mali all saw strong effects of wildfire or agricultural fire smoke on childhood cough. We did not detect any effects in other countries.



MW=Malawi, UG=Uganda, LB=Liberia, SL=Sierra Leone, ZM=Zambia, ML=Mali, BU=Burundi, GN=Guinea, ET=Ethiopia, BJ=Benin, AO=Angola, ZW=Zimbabwe, CM=Cameroon

Figure 2. 2: Risk ratios and 95% CIs from multi-level Poisson regressions for exposure to smoke within the two weeks prior to interview date for each country.

The results from the four-week time period show that most of the acute effects observed in the two-week period have attenuated (Figure 2.3). The only country that continued to show any lagged effects of smoke exposure was Malawi with a RR and a 95% CI of 2.66 (1.63-3.69). When examining the binary exposure definition, Liberia and Zambia show imprecise effects of exposure to smoke and increased risk of child cough. As the dose-response days increase, the precision of our estimates decreased, leading to imprecise estimates for exposure to smoke for three or more days within the four-week period before the survey date. Rapid breathing results were similar to the cough outcomes and are not displayed here.



MW=Malawi, LB=Liberia, GN=Guinea, ZM=Zambia, ZW=Zimbabwe, CM=Cameroon, AO=Angola, BU=Burundi, ML=Mali, BJ=Benin, ET=Ethiopia, ZA= South Africa, SL=Sierra Leone

Figure 2. 3: Risk ratios and 95% CIs from multi-level Poisson regressions for exposure to smoke within the four weeks prior to interview date for each country**.**

<u>2.4.2 Climate type:</u>

There were three main climate types, including tropical wet, tropical savanna, and dry, within the countries included in this study. We found that the countries included in the dry climate type experienced the largest risk of childhood cough when children were exposed to wildfire smoke or agricultural smoke within the two-week period before the survey date (Figure 2.4). The countries that were included in the dry climate type were South Africa, Mali, and Zimbabwe. The countries included in the tropical savanna climate type also saw effects of acute exposure to smoke and increased risk to child cough. These countries were Ethiopia, Benin, Burundi, Cameroon, Guinea, and Uganda. Finally, countries that were classified as being tropical wet climate type did not see any effect of acute exposure to smoke and childhood cough risk. These countries were Sierra-Leon, Malawi, and Zambia.

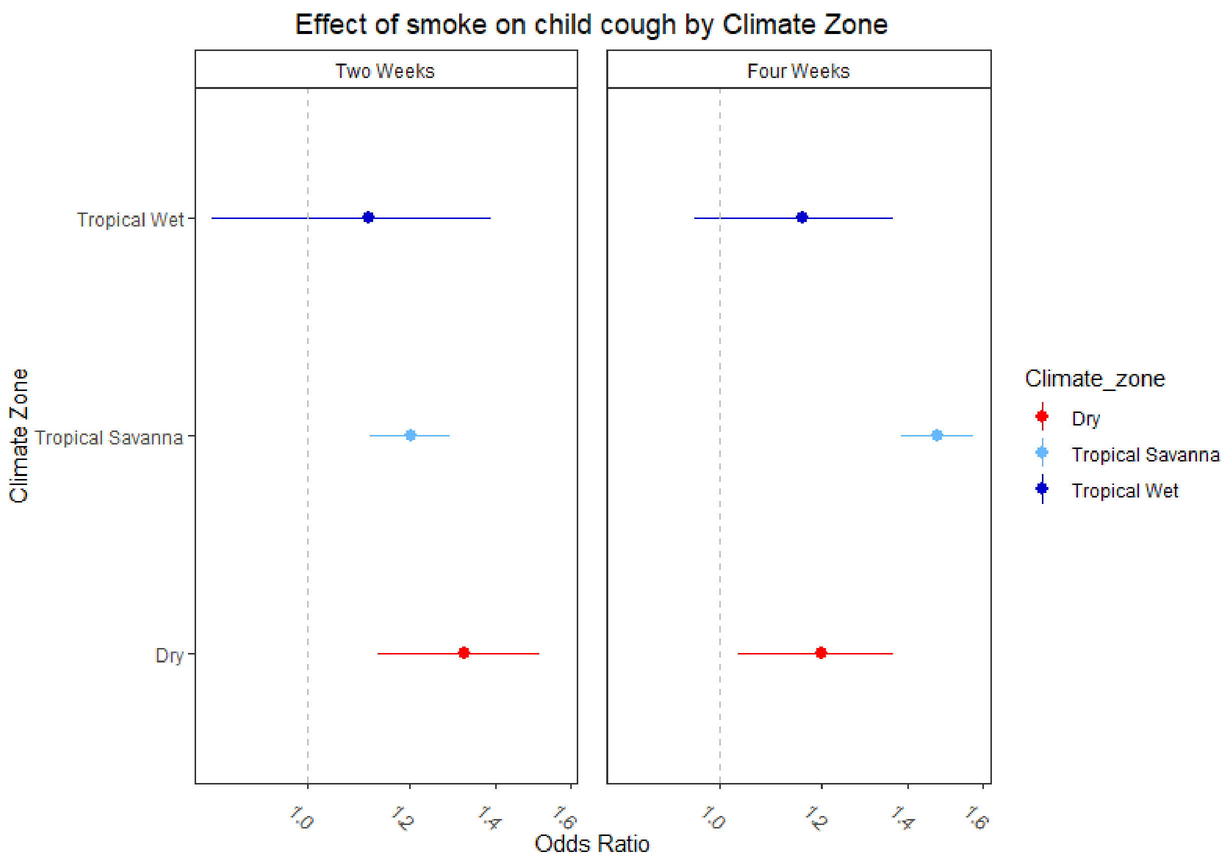


Figure 2. 4: Odds ratios and 95% CIs from stratified logistic regression analyses for each climate type.

<u>2.5 Discussion:</u>

In this paper, we brought new evidence about the association between exposure to wildland and agricultural fire smoke and adverse respiratory outcomes in children respiratory health across many African countries, where such epidemiological evidence has been lacking. This was made possible by linking remotely sensed data with a standardized health survey to overcome previous methodological challenges in assessing smoke exposure and the paucity of health data in LMICs. NASA's MAIAC aerosol product was used to ascertain smoke days throughout Africa. Overall, we observed acute effects of smoke exposure and adverse respiratory outcomes in children across several countries. Our results identified that the observed effect of increased risk for child cough and rapid breathing attenuates two-weeks after exposure. The countries where children were most affected by smoke exposure were Malawi, Uganda, Mali, South Africa, and Guinea. We also examined the relationship between smoke exposure and child cough by the country's climate type and found that countries that were mostly dry had children that experienced the highest risk of cough from wildland or agricultural fire smoke exposure.

Our study, to the best of our knowledge, is the first study that examined the relationship between smoke exposure and risk of child respiratory outcomes in a comprehensive set of LMICs in West and sub-Saharan Africa. These results are crucial to understanding how wildland or agricultural fires affect the surrounding populations, and more importantly, how they affect children, a vulnerable subset of the population. Respiratory infections are the leading cause of mortality in children under five years of age, and thus, studies examining these respiratory outcomes in LMICs, where these rates are the highest, are critical. Our findings can help identify areas of highest risk where adaptions strategies can be implemented. For instance, incorporating such country-specific epidemiological evidence into early warning systems can be beneficial. Early warning systems aim at reducing the individuals' exposure to smoke by recommending collective or individual behavioral changes. Such actions include, for example, the reduction of outdoor activities or school closures. Individual behavioral changes can also be promoted such as using individual protections (N95 masks or respirators that filter particles), recommendations to stay indoors or limiting physical activity as well as reducing activities that impact other sources of air pollution, such as smoking or wood burning. Furthermore, for such early warnings systems to be fully operational, it is also important that fire detection programs are developed.

Traditionally, wildfires were detected through manual observation, but with advances in technologies, efforts have been made to mitigate fires using early detection and fire risk mapping[162,163]. Development of technologies such as computer visions, machine learning, and remote sensing techniques have provided new tools for fire warning systems, which can be extended to LMICs. Some of these new fire detection methods come from satellites that cover Africa. One such example is the Meteostat second generation-spinning enhanced visible and infrared imager (MSG-SEVIRI), which is located on a geostationary satellite[164]. This instrument has a 1 km spatial resolution, which allows for the identification of smaller agricultural fires. Combining information from health studies and these remotes sensed data could help governments develop early fire detection programs.

There have been mixed results reported from studies that have previously examined wildfire or agricultural smoke PM2.5 and child respiratory outcomes, which our findings agree with. Almost all of the literature was conducted in HICs, and effects were observed in some countries but not others. Lipner et al. found reduced peak expiratory flow when older children aged 12 to 21 were exposed to wildfire smoke, but no association in younger children[165]. Tse et al. found no association between wildfire smoke and emergency department visits, hospitalizations, or new asthma diagnoses[94]. Conversely, several studies found associations between exposure to wildfire smoke and increase in asthma or respiratory outcomes in children[92,93,95,97]. The effect sizes ranged from an 8% increase in asthma cases to a 136% increase in emergency department visits for asthma when children were exposed to wildfire smoke. A recent study found that there was suggestion of lagged results, with the highest risk at four days after exposure to wildland smoke and under-five child mortality, which agree with our findings[166].

It may seem reasonable to initially assume that fine particles from wildfire smoke have similar toxicological mechanisms and impacts on human health, but results from recent animal studies have suggested that there may be a difference in the toxicity of wildfire specific PM2.5 than ambient PM2.5 from other sources[167-170]. *In vivo* animal studies of wildfire-derived PM2.5 exposure have demonstrated increased oxidative stress and cell death in mice[169], lower counts of lung macrophages, higher levels of inflammatory cells and cytokines, and greater antioxidant depletion. These results were derived from a study of smoke from California wildfire in a mouse model[167,168]. The study concluded that the lungs of mice who were exposed to wildfire PM2.5 showed significant damage compared to mice exposed to 10-fold higher doses of normal ambient PM2.5 from the same area. A recent human study done in California found evidence that supports the finding previously demonstrated in the mice studies[171]. They found up to a 10% increase in respiratory hospitalizations when individuals were exposed to wildfire smoke PM2.5 as compared to ambient PM2.5. In addition, the amount of wildfire smoke PM2.5 released during a large wildfire event are enormous, more than the typically ambient levels of PM2.5[171].

One reason for such mixed results is related to the difficulty in ascertaining accurate population exposure to wildfire smoke measures. Previous studies have mainly relied on ground monitor data and assigned the same exposure to all individuals in proximity to one monitor[172], or from an average of multiple monitors in the proximate area[173]. Smoke plumes are very dynamic in nature and may vary on a spatial scale smaller than what monitors can capture. Thus, if individuals are assigned only one value of the exposure, this will likely lead to bias toward the null and increased variance. Another reason why there is inconsistency in wildfire and health studies is that there is no gold standard for isolating wildfire specific PM2.5**.** Previous studies that have examined the health impacts from wildfires have used a variety of methods to estimate PM2.5 attributable to wildfires, which include chemical transport models, machines learning, remote sensing data, ground monitors, meteorological data, or a combination of these[87,92,174,175]. Estimates of wildfire PM2.5 can vary drastically**,** depending on the methodology utilized in the study[176]. These differences could be attributed to misclassification of wildfire smoke exposure. Many of the previous studies have only relied on fixed ground monitors, but these monitors are sparsely located in LMICs where wildfires are more likely to be located[84].

Our study is not without its limitations. One limitation that we acknowledge involves the selective survival of children. For children to report a cough, they need to have survived to the time of the interview, which increases the probability that the children who were included in the DHS survey were healthier than children that did not survive to the time at the interview. This would most likely attenuate effect sizes in our study. Also, agricultural fires, mainly from slash and burn farming, are seasonal in nature, and if this seasonality did not occur at the same time as the DHS interview, we are likely to have missed most of the fire's effects on children. An additional limitation is exposure misclassification. When using satellite images, the presence of dust, clouds, or other phenomenon could be misclassified as smoke, but using the smoke model within the MAIAC product can make this process more automated, thus reducing error. Finally, we could not distinguish between the type of fire smoke (wildfire or agricultural). The chemical toxicity could be different depending on the type of fuel the fire is burning as highlighted above, and future studies could further investigate such potential differential toxicity according to the type of fire on children's health.

Agricultural fires from Central and West Africa are the main component of biomass burning emissions across Africa, which have been linked to 43,000 premature deaths per year[65]. There is a stark contrast in the evidence from these areas and the number of fires that occur in Africa. Future research needs to examine health effects from wildland and agricultural fires in these underrepresented countries. As the climate changes, these fires are predicted to become for intense and increase in frequency. Not only are these countries where the majority of fires take place, children residing in LMICs lack infrastructure, access to healthcare services, and differ culturally, all of which can make them more vulnerable to smoke exposure compared to their HICs counterparts.

Chapter 2, in part, is currently being prepared for submission for the publication of the material. McElroy, Sara; Dimitrova, Anna; Aguilera, Rosanna; Gershunov Alexander; Benmarhnia, Tarik. The dissertation author was the primary investigator and author of this paper.

3. Saharan dust and childhood cough: a case-study in Benin:

3.1 Abstract:

Mineral dust is one of the largest natural constituents of coarse particulate matter (PM_{10}). Most of these dust emissions originate from northern Africa and several hundred tera-grams of dust are emitted annually from this region. Dust storms can generate high PM_{10} concentrations, which often exceed the World Health Organization (WHO) recommendations of safe levels (mean of 50 µm/m^3 within a 24-hour period). Previous evidence has linked dust PM_{10} to adverse respiratory outcomes in children, but the majority of these studies have been from high-income countries (HICs) or examined dust from other regions of the world, mainly Asia. Evidence from low-to-middle-income countries (LMICs) in Africa is scarce. Respiratory infections are one of the leading causes of under-five mortality across the globe, yet

there is a poignant disparity of studies examining these outcomes in children in the region where most of the dust is emitted. Thus, it is paramount that we illuminate new evidence about the association between acute exposure to dust PM_{10} and adverse respiratory outcomes in children in Africa. This study aims to accomplish this by linking remotely sensed satellite data to a nationally representative survey (the Demographic Health Survey) and implement a time-stratified case-crossover analysis. We identified acute effects of exposure to dust and increase risk of cough in children under-five. The effect of increased risk is strongest within two-weeks of exposure and dissipates by four weeks. Children living in rural areas and in households with lower income had a greater risk of adverse respiratory outcomes when exposed to dust. We were able to elucidate the specific time-period and conditions of increased risk for respiratory problems in children living in Africa.

3.2. Introduction:

One of the largest natural contributors to particulate matter with a diameter less than10 µm or less than 2.5µm in length (PM_{10} and $PM_{2.5}$, respectively) is mineral dust. The major sources of dust emanate from arid regions in Africa, Asia, and the Middle East[177] Dust storms from these areas are the most prominent and extensive aerosol features visible in satellite images[99]. Several hundred teragrams of dust are emitted each year from the Sahara desert to regions all over the globe.[101] Dust storms result from strong winds that disperse large amounts of desert dust into the air, resulting in extensive particulate exposure over large areas. These storms impact air quality on local and global scales and can lead to short- and long-term health effects[122,178,179]. Dust storms can generate high acute PM_{10} concentrations, which often exceed the World Health Organization (WHO) recommendations of safe levels (mean of 50 $\mu m/m^3$ within a 24-hour period)[103].

In the context of climate change, we have witnessed unprecedented extreme weather phenomena attributed to changes in precipitation regimes and increasing temperatures globally. Such weather patterns have contributed to differing patterns in wind directions and changes in drought locations resulting in an overall decline of African dust[180,181]. However, other factors such as future changes in land use and increasing water demands could affect future dust emissions, especially at more regional scales[182].

Despite the observed reduction of North African dust, the future of North African dust remains unclear, as shown by disagreements in climate models of future precipitation projections in the region[183]. Major dust storms prevail today and affect large geographical areas across Africa, North Atlantic, and North America[184]. Currently, one of the largest source of dust emissions is the Bodélé Depression in Chad, which gets dispersed over Northwest Africa[181,185] in countries like Benin. In addition to dust from the Bodélé region, dust from Saharan region is also a major contributor to dust emissions[181,186]. Saharan dust is usually transported to the southwest and Benin is located downstream of this transportation pathway[187].

A plethora of evidence ties short- and long-term exposure to particulate matter and adverse health outcomes even if the vast majority of these studies did not focus on PM from dust. Studies have shown that short-term exposure to ambient particulate matter (from any source) can increase the risk of cardiovascular and respiratory morbidity and mortality.[106-110] More specifically, short-term exposure to PM10 has been tied to cough and more severe respiratory infections in adults and children[111-115]. There are several proposed pathways of how dust can affect health. African dust's main constituents include clay, minerals (mainly iron), and quartz, but African dust can also contain microoraganisms[116]. Aerosols rich in iron can cause pulmonary inflammation[117] and the presence of microorganisms can provoke immune responses[118]. Children constitute a particularly vulnerable group because they are more sensitive to air pollutants than adults[119].

Acute respiratory infections are among the leading cause of childhood mortality across the globe and accounted for 10% of deaths in children younger than five years in 2017[9]. The respiratory infection burden varies significantly across the globe, disproportionately affecting the young and poor[10]. People who have the highest risk of contracting or dying from respiratory infection come from rural households with low levels of income and lower education levels.[11]. In this context, children residing in low-to-middle-income countries (LMICs) are one of the most vulnerable to these infections.

The majority of evidence examining how dust or PM10 attributable to dust affects respiratory symptoms in children has been from high-income countries or examines dust from other regions, mainly

Asia[124,125]. A recent systematic review, which examined health effects from Asian dust, identified 12 out of 89 studies that focused primarily on child health effects[118]. There are far less studies that examine health effects of African dust on children in Sub-Saharan and west Africa[133]. We must provide evidence to address respiratory health in children in LMICs to inform and implement actionable policies. An example of how targeted warnings can work is how Korea tries to reduce exposure to Yellow Dust. The government has developed a warning system with behavioral guidelines when PM10 levels exceed a certain threshold. These advisories have been linked to better health in children and higher birth weight of newborns[188].

This lack of evidence might be tied to methodological challenges in conducting studies in LMICs. Investigators must overcome two main challenges when trying to estimate local health burdens and exposure to dust related PM directly. The first challenge is measuring the exposure and outcomes accurately, and the second challenge is separating PM10 attributable to dust from other correlated variables that might also influence children's health. This study will overcome these challenges by utilizing remote sensing measurements from the Moderate Resolution Imaging Spectroradiometer (MODIS) instruments flying onboard NASA's Aqua and Terra satellites and linking these data with the Demographic Health Survey, a georeferenced household survey.

We will implement a case study in Benin examining the acute exposure of dust and childhood cough. We chose Benin for our case study because dust emissions from the Bodélé Depression and the Saharan region have been shown to disperse over Benin. A study done by Tulet comparing satellite images of dust storms and simulated data found that the majority of dust emitted from the massive dust storm in March of 2006 was concentrated in Benin.[104] One study examined the composition of atmospheric aerosols in Benin and found that dust made up 26%-59% of the total aerosols[189]. Benin is located in an area that frequently experiences large dust events from the Sahara region and thus is an adequate location for this case-study.

3.3. Methods:

3.3.1. Health Data:

Data for children aged under five years are obtained from the DHS database (ICF, n.d.). DHS surveys are nationally representative and focus on fertility behavior, health, and wellbeing of women of reproductive age and their children. Women ages 15-49 responded to questionnaires about the complete birth histories of their children, which included health information about their children. In addition, individual- and household-level data, such as household wealth, education level, prenatal care, and health insurance status, are recorded. DHS also provides global positioning system (GPS) data for each primary sampling unit (PSU). A PSU is defined as a city block in an urban area and a village in a rural area. Surveyors used global positioning system devices to collect geospatial information to identify the central point of the populated area of each PSU[160]. The DHS survey randomly displaced GPS coordinates to ensure respondent confidentiality. The displacement is carried out so that urban PSUs contain a minimum of 0 and a maximum of 2 kilometers of error, and rural PSUs contain a minimum of 0 and a maximum of 5 kilometers of positional error with a further 1% of the rural clusters displaced a minimum of 9 and a maximum of 10 kilometers. [161]

3.3.2. Exposure data and classification:

A MODIS Terra and Aqua combined Multi-angle Implementation of Atmosphere Correction (MAIAC) Land Aerosol Optical Depth (AOD) data product was utilized to determine if there was a presence of dust in the air. This product is a gridded Level 2 with a spatial resolution of 1 km and a temporal resolution of 1 day (MCD19A2.006). AOD at the 0.47 μm wavelength was downloaded using Google Earth Engine (GEE). Daily AOD was obtained from January 1, 2017, to December 31, 2018 for each 1 km pixel within Benin. Also available from the MAIAC data collection are flags identifying the presence of either dust or smoke aerosols[190]. The dust model is identified by a unique 16-digit integer and was downloaded for each PSU located in Benin.

For each of the 73 days we considered, the presence of dust was visually inspected for Benin. True-color images (red, green, and blue bands) were evaluated using the MODIS Surface Reflectance product for the presence of dust. For each day within the study period, the MODIS satellite image was visually inspected, and exposure ascertainment was determined. When dust was identified, a polygon was drawn around the dust plume. Any PSUs within this polygon were considered exposed, and any PSUs located outside the polygon were classified as unexposed (Figure 2). If the presence of dust could not to be visually ascertained because of cloud cover or unclear images, the measure of the AOD_QA band was used to classify exposure status. In addition, this measure was also used as a validation measure to validate the visual classifications. The exposure data and health data were linked through the PSU ID resulting in a binary exposure classification for each day per PSU.

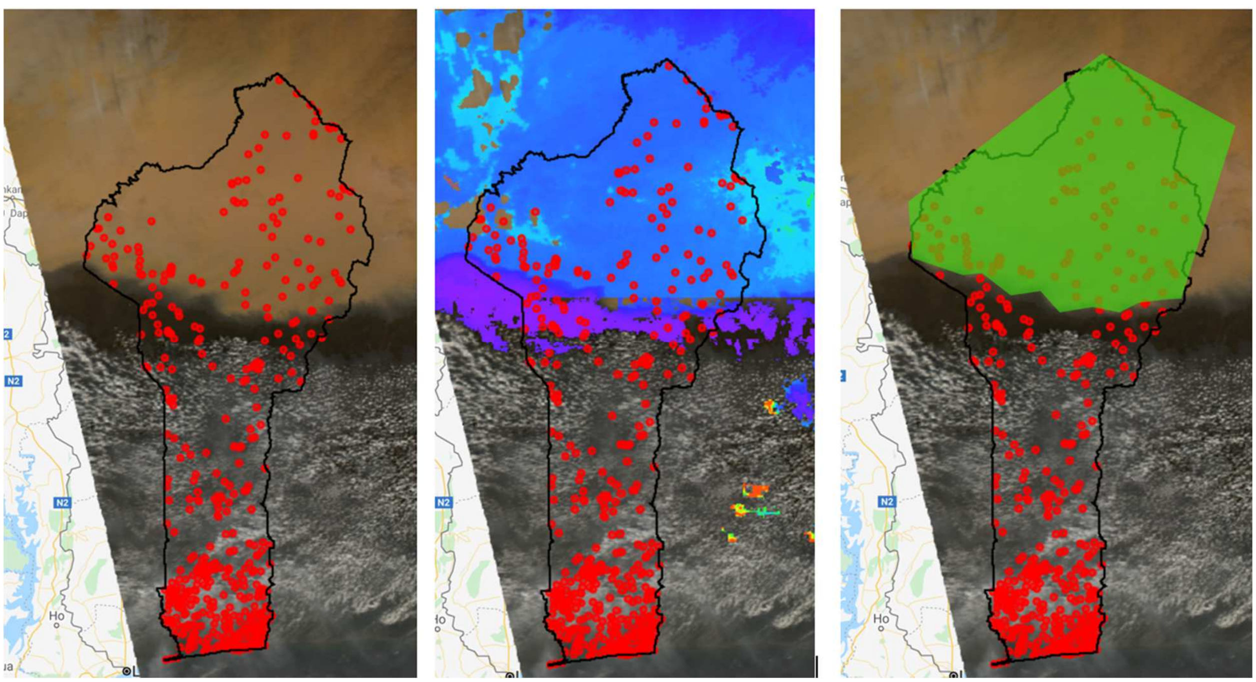


Figure 3. 1: Satellite image of Benin with locations of each PSU. A) True-color image of a dust storm in Benin using the Aqua Surface Reflectance Daily Global 1km and 500km resolution product. B) The same image with the Terra and Aqua MAIAC Land Aerosol Optical Depth 1km added as a layer. C) The same image with a polygon drawn around the dust cloud and exposed PSUs.

3.3.3. Outcome classification:

Each mother was asked if their child experienced cough symptoms within the last two weeks before the interview date. Furthermore, if the child did have a cough within the previous two weeks, the mother was asked if the child experiences rapid breathing and has a problem in the chest or a blocked or running nose. A child was considered to have a cough if the mother answered yes to any of the above three questions.

3.3.4. Statistical analyses:

A time-stratified case-crossover analysis was implemented to examine the acute effects of dust exposure on childhood cough. This approach has been well established in the literature to estimate acute health effects of environmental exposure. It has been widely applied to estimate associations between short-term exposure to air pollution and health outcomes[191-195]. The outcome of cough is the unit of observation or case day, and dust data on the date of the outcome event is compared with three control days. These analyses match case days to a control day of the same day of the week, in the same month and year as the case day. Matching on day of the week controls for potential week-varying confounders such as the week/weekend difference in environmental factors. Matching by month and year controls for potential confounding by seasonality and long-term trends.[196]

We conducted two analyses that examined acute effects at different time periods. The first analysis entailed the case date to be defined as the day two-weeks prior to the interview date. Control days were then matched to this case date. An additional analysis was implemented, with the case date being defined as the date four weeks prior to the interview date. We chose this timeframe to gain insights into any lagged effects. Conditional logistic regression models were run for each of these two time periods. Time-variant confounders such as meteorological data were controlled for in the analyses.

3.3.5. Effect measure modification:

We explored the role of effect measure modifiers by stratifying the regression models by urban or rural residence, level of maternal education, and household wealth. The DHS survey generates a wealth index, and it is a composite measure of a household's cumulative living standard. Variables included in calculating the wealth index include household assets, building material, and types of water and sanitation facilities[197]. Maternal education is a continuous measure of the number of years of total education the mother had. A binary variable was created from this continuous measure to indicate if the mother received more education or zero to little education. To determine if there were differences between the stratified groups, a Cochran's Q test of heterogeneity was performed.

3.4 Results:

Benin's DHS phase 7 survey recorded information on 13,589 children. There was a total of 2,018 cases of cough reported from November 23rd, 2017 to February 4th, 2018. The majority of households in Benin lived in rural areas, had the lowest household wealth index measure, and the mean years of maternal education were about three years (Table 1). There was dust found in about 10% of the case dates (two weeks prior to the interview date). When examining the time period of four weeks prior to the interview, about 8% of case-days were classified as exposed to dust. Figure 3.2 illustrates the total number of days (between November 23rd, 2017 and February 4th, 2018) where dust was detected for each PSU location. The areas with the highest number of dust days were in northern and central Benin. Southern Benin experienced the lowest number of dust days throughout the study period.

Table 3. 1: Descriptive statistics of the study population of households of children under 5 in Benin.

	Overall (N=13589)
Outcome Status	
Cough	2018 (14.9%)
No cough	10520 (77.4%)
Missing	1051 (7.7%)
Exposure Status	
Dust present	1314 (9.7%)
Dust not present	12132 (89.3%)
Missing	143 (1.1%)
Household Wealth	
1-Low wealth	3020 (22.2%)
2	2776 (20.4%)
3	2670 (19.6%)
4	2639 (19.4%)
5-High wealth	2484 (18.3%)
Maternal Education (years)	
Mean (SD)	2.18 (3.65)
Median [Min, Max]	0 [0, 17.0]
Place of Residence	
Urban	5401 (39.7%)
Rural	8188 (60.3%)

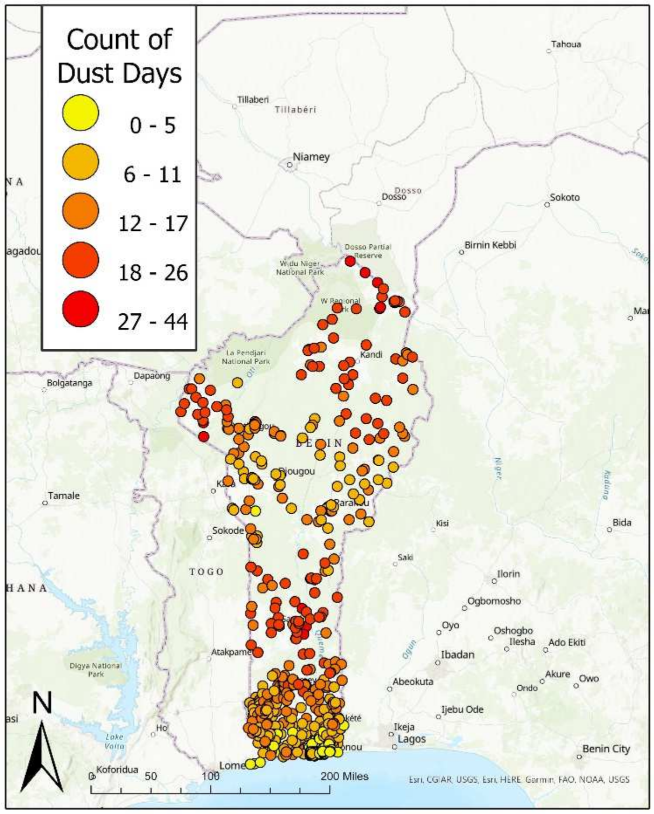


Figure 3. 2: Total number of exposed days to dust per PSU in Benin from November 23rd, 2017 to February 4th, 2018.

Figure 3.3 depicts the odds ratios for both the two- and four-week time periods. There was an observed effect of increased risk of cough within the two weeks prior to the interview when a child was exposed to dust. The Cochran Q heterogeneity found no significant differences in the effect modifiers (Appendix B) but there seems to be a general pattern of effect differences. Children who lived in rural areas were more affected by this increase in the risk of cough than children who lived in urban locations. Poorer households saw an increased risk of cough when their children were exposed to dust than more affluent households. There seemed to be a risk of increased risk of cough in children no matter their mother's level of education. We did not observe any lagged effects (up to 4 weeks) of exposure to dust, which is portrayed in the effect estimates using the case-date as four weeks prior to the interview.

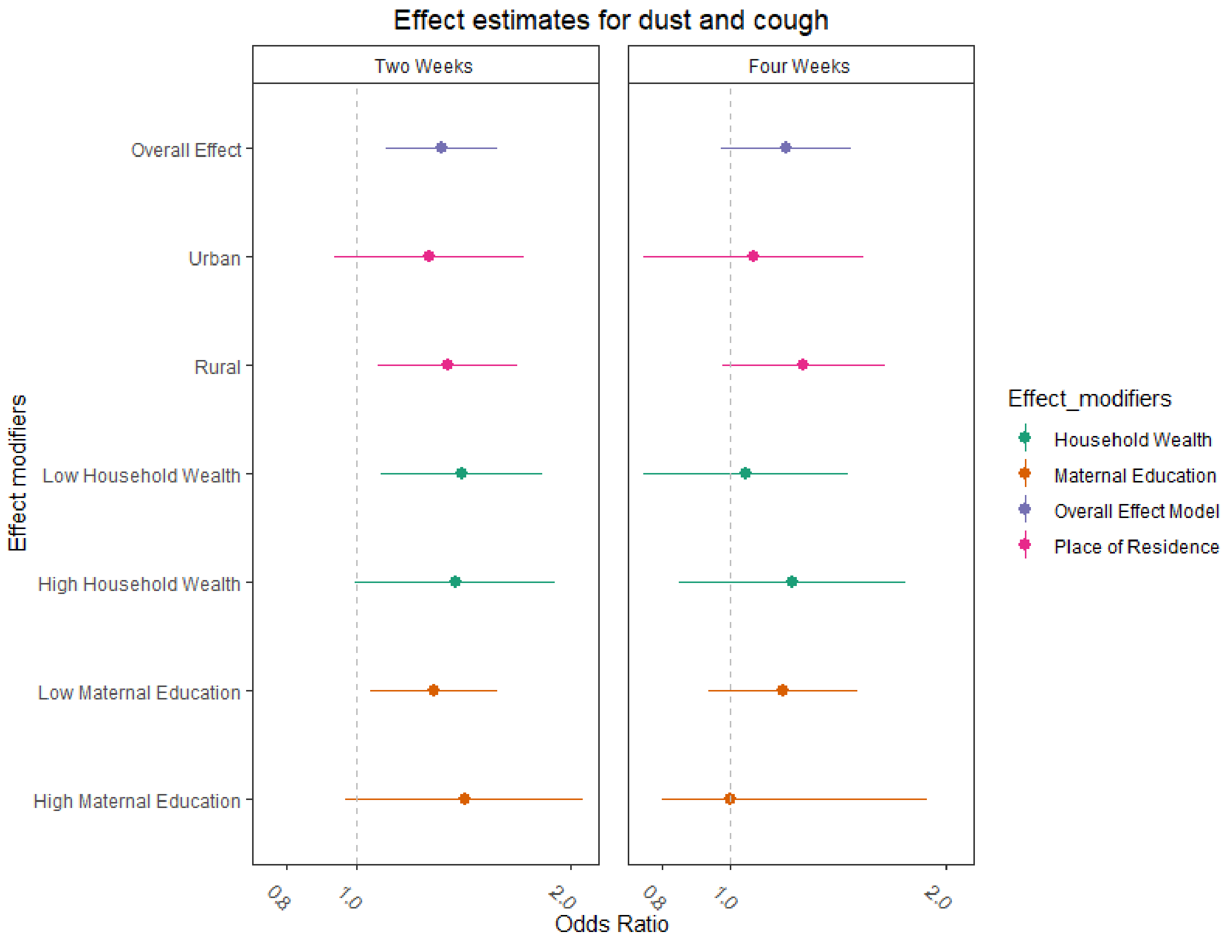


Figure 3. 3: Odd ratios of overall effect model and models examining effect measure modification for both two- and four-weeks prior to the interview date. Each color represents a different effect modifier.

<u>3.5 Discussion:</u>

This is one of a few studies that have examined how acute exposure to African dust can affect children's health in a LMIC located in Africa. Our analyses identified acute effects of increased risk of cough in children under five who lived in Benin when exposed to dust. In addition, there were disparities in risk of cough depending on the family's wealth and type of place of residence (rural or urban). Children living in poorer, rural conditions are especially vulnerable to risk of cough compared to children living in urban and more wealthy areas.

The majority of evidence examining how dust or PM10 attributable to dust affects respiratory symptoms in children has been from high-income countries or examines dust from other regions, mainly Asia[124,125] Studies that examined the effect of African dust only looked at children in other geographical locations, which were HICs[124,130,131]. Only one of these studies took place in West Africa, and this study is a working paper[133]. A recent systematic review, published in 2021, examining desert dust and global health mapped the location of these studies. They found that up until 2019, there were no studies that were conducted in Africa[126] Since 2019, there has been an additional study that examined Saharan dust effects on infant mortality in African children[123].

Our study explored the acute effects of dust on child health by utilizing remote sensing data to classify dust exposure. Previous evidence has mainly relied on ground monitors, which can be unreliable when measuring dust. Weather stations measure visibility and if there is visible dust in the air, but these measures are inadequate and not always reported[133]. These stations are also geographically sparse across Benin, which calls for the application of satellite-based dust observations. By utilizing NASA's daily MAIC aerosol optical depth and land surfacer reflectance products, we were able to study the acute effects of dust on childhood cough. This product has been validated in previous epidemiological studies[198-200]. Many of the previous literature examined dust and respiratory effects on a monthly or annual scale. These time scales are not adequate to capture the acute effects of dust in children. Our results show that the effect dissipated after two weeks of symptoms. This study also examined the spatiotemporal distribution of dust events that can influence childhood cough across Benin. By linking these remotely sensed data with the DHS survey PSU locations, we were able to identify specific areas of highest risk, which could be helpful for actionable policy in implementing early warning systems.

Identifying the effects of dust on child health presents a complex set of challenges. One primary concern is that high levels of dust can be correlated with drought and soil conditions that may influence a child's health through other mechanisms than exposure to PM. Drought and dry soil conditions can influence agriculture and economic activities, which can affect children's health through malnutrition[123]. To account for these correlations, Benin was chosen as a case study due to the fact that the majority of the dust over Benin is from the Saharan Desert and is therefore transported over long distances[181,185]. Thus, drought and soil conditions that create the right environment for significant dust emission episodes are far from the source of the health data. The study design inherently controls for these conditions at the local level, and the time-varying confounder land surface temperature was included in the regression models. Another limitation of this study is possible exposure misclassification. By visually examining satellite images for the presence of dust, there can be human error. Clouds, smoke, and dust may appear similar on satellite images. However, with the addition of the AOD dust model, the classification accuracy was greatly improved. Moreover, we still identified an effect, and such misclassification may contribute to lead our estimated towards the null (so our results can be considered as conservative). An additional limitation that we acknowledge involves the selective survival of children. For children to report a cough, they need to have survived to the time of the interview, which increases the probability that the children who were included in the DHS survey were healthier than children that did not survive to the time at the interview. This would most likely attenuate effect sizes in our study.

Even though dust emitted from the Sahara region is predicted to decrease in the context of climate change, other areas of dust emissions are predicted to increase, mainly in southern Africa[201,202]. These new patterns in dust emissions will create new areas of increased vulnerability to dust. Thus, we need to gain insight into how dust transport and emissions can adversely affect children's health today.

Chapter 3, in full, has been submitted for publication of the material as it may appear in the Journal "Environmental Research". McElroy, Sara; Dimitrova, Anna; Evan, Amato; Benmarhnia, Tarik. The dissertation author was the primary investigator and author of this paper.

4. Extreme heat, preterm birth, and stillbirth: a global analysis across 14 low-middle-income countries

4.1 Abstract:

Stillbirths and complications from preterm birth (PTB) are two of the leading causes of neonatal deaths across the globe. Low-to-middle-income countries (LMICs) are experiencing some of the highest rates of these adverse birth outcomes. Research has suggested that environmental determinants, such as extreme heat, can increase the risk of PTB and stillbirth. Under climate change, extreme heat events have

become more severe and frequent and are occurring in differential seasonal patterns. Little is known about how extreme heat affects risks of PTB and stillbirth in LMICs. Thus, it is imperative to examine how exposure to extreme heat affects adverse birth outcomes in regions with some of the highest rates of preterm and still births. Most of the evidence linking extreme heat and adverse birth outcomes has been generated from high-income countries (HICs) notably because measuring temperature in LMICs has proven challenging due to the scarcity of ground monitors. The paucity of health data has been an additional obstacle to study this relationship in LMICs. In this study, globally gridded meteorological data was linked with spatially and temporally resolved Demographic Health Surveys (DHS) data on adverse birth outcomes. A global analysis of 14 LMICs was conducted per a pooled time-stratified case-crossover design with distributed-lag nonlinear models to ascertain the relationship between acute exposure to extreme heat and PTB and stillbirths. We notably found that experiencing higher maximum temperatures and smaller diurnal temperature range during the last week before birth increased the risk of preterm birth and stillbirth. This study is the first global assessment of extreme heat events and adverse birth outcomes and builds the evidence base for LMICs.

4.2 Introduction:

Adverse pregnancy outcomes, including preterm birth and still birth, annually affect nearly 19 million women worldwide. The World Health Organization (WHO) states that these outcomes are increasing every year[203]. Preterm birth (defined as a live birth before 37 weeks gestation) increases the risk of several adverse health outcomes later in life, including respiratory diseases, neurodevelopment and growth impairments, and other morbidities, which places a substantial burden on health care systems[204,205]. Stillbirth is defined as fetal death after 28 weeks gestation or at least 1000-grams at birth, and there are an estimated 2.6 million stillbirths each year, one every 16 seconds[206]. Low-to-middle-income countries (LMICs) experience the highest rates of these adverse birth outcomes. Of the ten countries with the highest rates of preterm birth, nine are LMICs[17]. Furthermore, 98% of the global number of stillbirths take place in LMICs[15,16] .The large proportion of adverse birth outcomes occurring in LMICs may be due to deficiency in access to health care and lack of education and resources dedicated to pregnancy health[207]. Environmental determinants constitute one set of modifiable risk factors than can be intervened on at the population-level. A proportion of adverse birth outcomes can be prevented by reducing exposure to environmental determinants. One study found around 0.2% of preterm births can be attributable to extreme heat[35]. These adverse birth outcomes can be avoided given that heat impacts are preventable with better warning systems, heat advisories, and action plans that inform the public of measures that can be taken to mitigate exposure, such as staying hydrated, staying in the shade, and not exerting oneself. In addition, the provision of designated cooling centers, reinforcement of health-care system preparedness during such extreme events and education about heat illnesses. Thus, identifying modifiable risk factors will help prevent neonatal deaths and preterm births as well as improve maternal and child health by informing targeted interventions.

Previous studies examining preterm birth and stillbirth have identified the role of environmental risk factors such as outdoor air pollution[29,30] , ambient temperature[31,32], rainfall variability[208], wildfires[209], and ice storms[31]. In the context of climate change, we have seen an increase in severity and duration of extreme weather events such as heat waves[138,210]. In this study, we focus on exposure to heat conditions toward the end of the gestational period to capture acute effects of heat. Pregnant women are particularly vulnerable to extreme heat and are at the highest risk of heat related health conditions, including heat stroke, respiratory conditions, and adverse birth outcomes[211,212]. Previous literature suggests extreme heat may trigger preterm birth or stillbirth through the following biological mechanisms: 1) decrease in the ratio of body surface area to body mass[35] , 2) dehydration [40,143], and 3) birth defects such as heart conditions.[145]

Several studies have identified the last week of pregnancy as a critical window of susceptibility to extreme heat[23,29,40-42,213]. More specifically, experiencing an extreme heat event toward the end of gestational period can trigger the mother to give birth that week. Previous literature also highlights the heterogeneity in heat conditions and contextual factors that could influence birth outcomes, which motivates the need to expand this work to lesser studied regions, where evidence is lacking[214,215].

Moreover, most studies have been conducted in high income countries in North America, Europe, and Asia[35,36,216,217]. A recent systematic review by Cherish et. al published in 2020 examining the associations between high temperatures and adverse birth outcomes found 48 studies that investigated the relationship between heat and preterm birth and only eight papers that examined heat and stillbirth[218]. The stigma attached to pregnancy loss could explain the discrepancy in the number of studies examining stillbirth. All these studies were conducted in upper-middle- and high-income countries. Drawing inferences from these studies and extrapolating them to women in LMICs could be invalid because of the vastly different social, demographic, and meteorological environments.

The lack of studies in LMICs that have examined the relationship between extreme heat and adverse birth outcomes could be attributed to methodological challenges in measuring exposure levels[219]. Previous studies in HICs have mainly relied on ground monitor meteorological station networks, which most LMICs lack the resources and infrastructure to build and maintain[220]. As a result, LMICs rarely engage in routine and comprehensive meteorological data collection, which poses problems in assessing acute exposure levels of heat. Furthermore, the few studies[221-223] conducted in LMICs relied on national monthly or annual averages of exposure, which hampers examination of acute exposure periods with fine geographic resolution. In this study, we addressed these limitations and methodological challenges by using globally gridded meteorological product to measure acute exposure to heat with fine spatiotemporal resolution. Data on adverse birth outcomes was obtained from the Demographic Health Surveys (DHS) and linked with the meteorological data. With the release of the newest phase of the DHS survey came a unique opportunity to capitalize on the fact that this version includes day of birth (or death) for each child, which was not available in earlier surveys. This allows us to perform more detailed analyses, i.e., using daily measurements that can reveal critical windows of susceptibility.

A majority of the world's population live in LMICs, which are the most vulnerable to the impacts of climate change; it is thus crucial that we examine the effects of temperature on risk of preterm birth and stillbirth in LMICs as conclusions from studies conducted in developed countries are not generalizable. This study aims to be the first to quantify acute heat effects on risk of preterm birth and stillbirth in 14 LMICs.

4.3 Materials and Methods:

4.3.1 Description of study population:

Fourteen LMICs (Angola, Benin, Burundi, Ethiopia, Haiti, Malawi, Nepal, Nigeria, Philippines, South Africa, Tajikistan, Timor-Leste, Uganda, and Zimbabwe) spanning various climate zones were included in these analyses. These countries were selected because they participated in the most recent survey (phase 7), which was completed between 2014-2018 of the Demographic Health Surveys (DHS) program data for at least one of the outcomes of interest (preterm birth or stillbirth). These surveys are nationally representative and provide detailed maternal and child health information which is standardized across countries. Women ages 15-49 responded to questionnaires about the complete birth histories of their children, which included information about birth weight, duration of pregnancy, date of birth (day, month, year) and infant mortality. In addition, individual- and household-level data, such as household wealth, education level, prenatal care, and health insurance status, are recorded. DHS also provides global positioning system (GPS) data for each primary sampling unit (PSU). A PSU is defined as a city block in an urban area and a village in a rural area. Surveyors used global positioning system devices to collect geospatial information to identify the central point of the populated area of each PSU[160]. To ensure respondent confidentiality, GPS coordinates were randomly displaced by the DHS survey. The displacement is carried out so that urban PSUs contain a minimum of 0 and maximum of 2 kilometers of error and rural PSUs contain a minimum of 0 and a maximum of 5 kilometers of positional error with a further 1% of the rural clusters displaced a minimum of 9 and a maximum of 10 kilometers[161].

All women aged 15 to 49 in these countries were considered for the analysis if they answered questions about their birth histories, household demographics, and health practices. Women who were interviewed across the 14 countries had birth history data, which ranged from 2009 to 2018.

4.3.2 Linking of health Data and meteorological data:

For this study, we linked two data sources: The DHS and a global gridded temperature. The latitude and longitude for each PSU within the DHS surveys was used as the spatial linking component. Even though these surveys are cross-sectional in nature, the retrospective information on previous births allows us to observe multiple birth outcomes over time within each village. Moreover, the newest phase of the DHS surveys included birth date at the daily-level compared to previous surveys which only recorded month and year of birth, thus allowing us to determine a 7-day period prior to birth as our exposure window.

We matched the DHS data with geographically gridded weather data that included maximum and minimum temperature from the Climate Prediction Center's (CPC) Global Daily Temperature data provided by NOAA/OAR/ESRL Physical Science Laboratory in Boulder Colorado (https://psl.noaa.gov/)[41].This temperature data is globally gridded at a 0.5°x 0.5° (~55x55 km) spatial resolution and at 24-hour temporal resolution and utilizes the Sheppard Algorithm. Previous epidemiological studies have utilized the CPC Global Daily Temperature and found it a valid measure of temperature[42].

4.3.3 Temperature data:

We considered three measurements of temperature in our analyses: daily maximum (Tmax), minimum (Tmin), and diurnal temperature range (Tmax - Tmin), specific to each PSU. These three metrics were selected to examine how extreme heat effects birth outcomes. Diurnal temperature range (a proxy for humidity) was selected to assess how humidity plays a role in risk of adverse birth outcomes. Each daily temperature value measure was linked with daily individual cases of preterm births and stillbirths using information about the geographic coordinates of survey participants and timing of birth.

4.3.4 Exposure and outcome classification:

Preterm birth status was obtained via the "duration of pregnancy" question in the birth history questionnaire. Duration of pregnancy is reported in months and any birth that was recorded as less than 9 months of gestation is considered preterm; about 6% of all births in our sample classified as preterm. Stillbirths were obtained per the questions "Is the child alive or dead at time of interview?" and "Age at death" within the birth history questionnaire. If the child was not alive at the time of interview and age of death indicated that the child died at birth, then this child was considered stillborn.

4.3.5 Time-stratified case-crossover with distributed nonlinear lag design:

A time-stratified case-crossover design was utilized to estimate the acute risk of extreme heat and preterm birth and stillbirth. This approach has been well established in the literature to estimate acute health effects of environmental exposure and has been widely applied to estimate associations between short term exposure to extreme heat and health outcomes[191-194,224]. This design allows for the control of any time-fixed confounders such as maternal age, nutrition, access to health care, wealth, education, etc. Individual adverse birth outcome events are the unit of observation, or case day, and environmental data on the date of the adverse birth outcome event is compared with three control days. These analyses match case days to a control day of the same day of the week, in the same month and year as the adverse birth outcome. Matching on day of the week controls for potential week-varying confounders such as the week/weekend difference in temperature and rates of adverse birth outcomes. Matching by month and year controls for potential confounding by seasonality and long term trends[196]. We applied distributed-lag nonlinear models (DLNM) with the case-crossover logistic model to assess the nonlinear and lagged associations between temperature and adverse birth outcomes up to 7 days before the birth date. The nonlinear and lagged temperature and adverse birth outcome associations were modeled using spline functions. A spline function incorporates multiple polynomial segments joined by knots to make a continuous curve. The number of knots can be adjusted to increase or decrease smoothness of the curve. We chose knot placement using quantiles of the temperature distributions (see Appendix A). Our final model of nonlinear temperature-adverse birth outcome relationship used b-splines with one knot at the 40th quantile of the temperature distribution. Different knot placement was assessed for the temperature-preterm birth and temperature-stillbirth associations. The model with the lowest Akaike Information Criterion (AIC) was chosen for the analysis (See Appendix A). The lagged-adverse birth outcome relationship was modeled using natural cubic splines and could lag up to 7 days. This 7-day window of high susceptibility was identified in previous literature[22-24,50]. Since the study design controls for time-invariant confounders the only covariates that need to be controlled for in the model are time-varying meteorological variables (humidity and wind speed). A pooled case-crossover analysis with random effects across all PSUs and countries was performed for both preterm birth and stillbirth.

4.4 Results:

In total, 103,535 births were included in this study across the 14 countries. There were 5,882 preterm birth cases and 1,210 stillbirth cases. The distribution of preterm birth and stillbirth cases by country are depicted in Table 1. The highest rate of preterm births was in Malawi (10.4%), while the lowest rate occurred in Nigeria (1%). The highest proportion of stillbirths were recorded in Ethiopia (3.5%) and the lowest in Tajikistan (0.6%). These percentages are the proportion of adverse outcomes within the total number of births of women who participated in the DHS survey. Temperature distributions for each country can be seen in Table 1. Figure 1 depicts the distribution of temperature thresholds for the 95th percentile for all countries included in the study.

Table 4. 1: Outcome and exposure summary statistics for each country included in the study.

Country	Total number of births	Number of preterm births	Number of stillbirths	Average >= 95th threshold °C
Angola	7447	146	69	32.34
Benin	7956	763	75	37.43
Burundi	7856	231	57	28.22
Ethiopia	1113	123	39	32.08
Haiti	6530	522	49	34.35
Malawi	9380	970	82	31.39
Nigeria	33924	356	542	36.96
Nepal	3553	74	30	32.89
Philippines	2130	222	25	33.35
South Africa	3548	457	49	33.32
Tajikistan	3786	137	22	32.68
Timor-Leste	4353	446	52	33.81
Uganda	8825	1343	92	31.78
Zimbabwe	3134	92	27	32.89

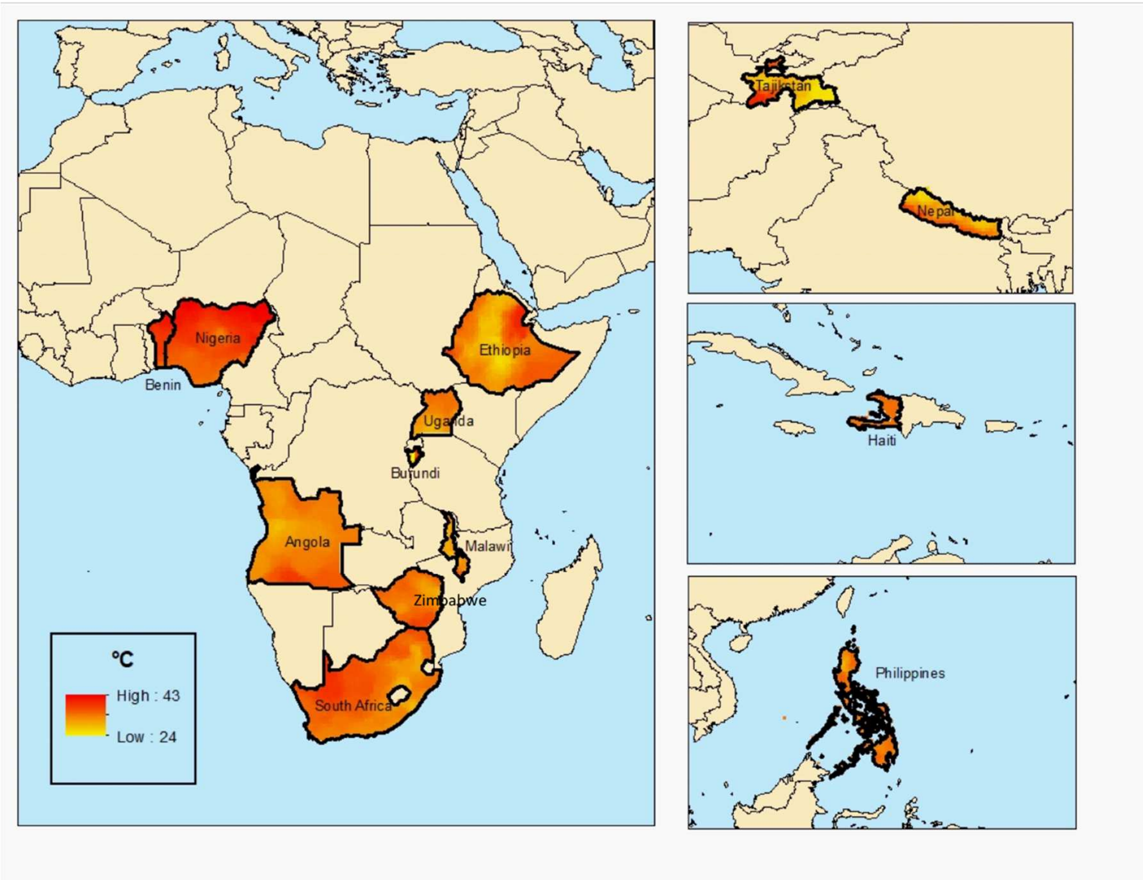


Figure 4. 1: Map of countries that participated in Phase 7 of the DHS survey included in this study and spatial distribution of temperature thresholds (daily maximum temperature>95th percentile at the 30km level).

Overall, we find an increased risk of preterm birth among women who were exposed to extreme heat within the seven days before giving birth (Figure 2). The distributed lag nonlinear model identified a range of temperatures that increased the risk of preterm birth. When pooling estimates from all countries, the rate of preterm birth increased when women were exposed to temperatures higher than 20°C, and the same risk decreased at temperatures below 20°C, which was the point of overall minimum effect. We also explored potential lagged effects in the seven days before birth. Supplementary Figure 1 depicts the estimated risk ratio by temperature unit at specific lags (1, 3, 5, and 7 days) and by varied temperatures (13.3, 22.1, 32.7, and 35.2), corresponding to the 1st, 5th, 95th, and 99th percentiles of the temperature distribution, using 20°C as the reference temperature. The results suggest that hotter temperatures have a more immediate effect on preterm birth than lagged effects. For example, lagging the exposure by 5 or 7 days (Figure S1 (C) shows minimal effect on preterm birth compared to the risk of exposure with zero to one day of lag (Figure S1 (A). Similarly, the graphs showing risk by distribution of temperature confirm an immediate increased risk of preterm birth at hotter temperature 32.7-35.2°C (Figure S1 (G, H)). However, at moderate temperatures there was no observed lagged effect.

An elevated risk of preterm birth was also identified among pregnant women who experienced diurnal temperature ranges of (i.e., difference between maximum and minimum temperatures) less than 16°C (Figure 2). There was no lagged effect observed for the diurnal-preterm relationship (see Supplementary Figure 2). We did not identify any effects of temperature on preterm births when using minimum temperature to define extreme heat. (See Appendix B).

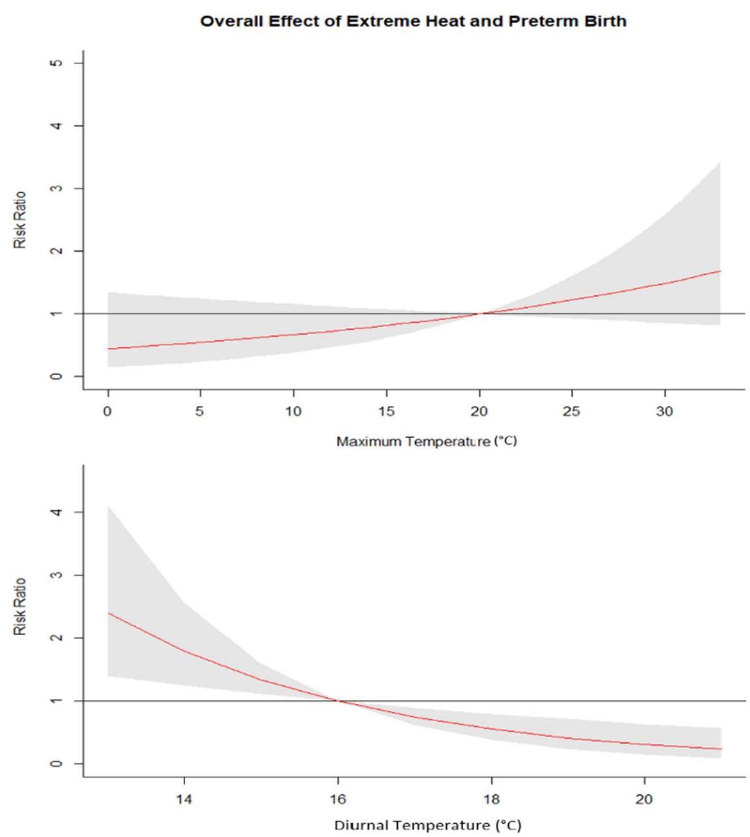


Figure 4. 2: Overall effect of distributed lag nonlinear case-crossover curve with reference at 20°C for maximum and diurnal temperature and preterm birth.

As for stillbirth, our results indicate an increased risk among pregnant women who experienced hot temperatures within the seven days prior to giving birth. The hot temperature-stillbirth nonlinear association showed a window of temperatures, 20°C to 30°C, where a pregnant woman is more susceptible to increased risk of stillbirths when compared to the risk of stillbirth at the identified reference temperature of 20°C. A decreased risk of stillbirths was observed for temperatures less than the reference temperature (Figure 3). Supplementary Figure 3 depicts the estimated risk ratios (RR) by temperature at specific lags (1, 3, 5, and 7 days) and by lag at specific temperatures (13.3, 22.1, 32.7, and 39), corresponding to the 1st, 5th, 95th, and 99th percentiles of the temperature distribution, using 20°C as the reference. These graphs present the lagged effect of extreme heat on stillbirth. As temperatures increase, there is a lagged effect of 3 and 5 days (Figure S3 (B, C)). This pattern is further highlighted on days with temperatures at the top percentile; we see an increase in still birth risk at the lags three to five days (Figure S3 (H)). As temperature decreases, this lagged effect is attenuated until there is no lagged effect at colder temperatures (see Figure S3 (E, F, G)).

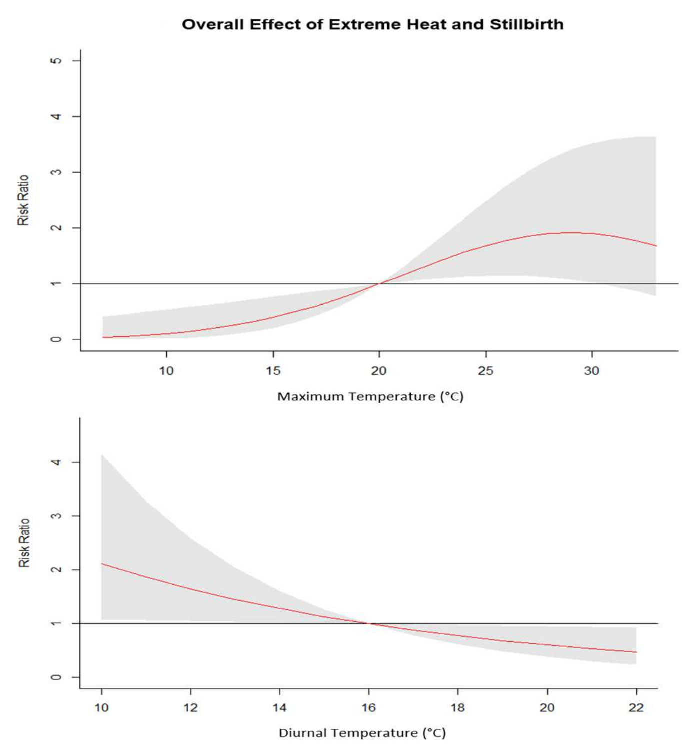


Figure 4. 3: Overall effect of distributed lag nonlinear case-crossover curve with reference at 20°C for maximum and diurnal temperature and stillbirth.

A slight increase in stillbirth was observed for pregnant women who experienced a day within the week prior to giving birth with smaller diurnal temperature ranges (RR= 2.1, 95% CI 1.01, 4.02). The window of elevated risk was found to be for diurnal temperature range less than 14 degrees Celsius (Figure 3). The lagged structure of the stillbirth-temperature relationship can be seen in Supplementary Figure 4. There was an immediate effect of small diurnal temperature ranges on risk of stillbirth as seen in Figure S4 (E). For days with recorded 10°C diurnal temperature range, there was an increased risk of stillbirth throughout the 7-day lag period. As the diurnal temperature range increased, there was no observed lagged risk. Similarly, we did not identify any effect on stillbirth when using minimum temperature metrics to define extreme heat (see Appendix B).

4.5 Discussion:

We brought to attention new evidence on the relationship between extreme heat and adverse birth outcomes in countries where the evidence has been scarce. This is the first study examining the effect of acute exposure to extreme heat on preterm and stillbirths in multiple LMICs, drawing data from the DHS. We overcame the sparse vital records available in LMICs by utilizing the DHS surveys and found amplified risk of both preterm birth and stillbirth in the investigated countries.

Overall, we found a consistent and positive association between extreme heat beyond specific thresholds and risk of preterm birth and stillbirth in LMICs. Similar patterns of increased risk of preterm birth and stillbirth were observed, when using multiple metrics to examine ambient temperature (maximum temperature and diurnal temperature range). Our findings indicate that pregnant women start experiencing increased risks of adverse birth outcomes when they experience temperatures greater than 20°C. As temperatures rise, this elevated risk grows culminating with the highest risk of adverse birth outcomes occurring at greater 30°C.

Our findings from the lagged analyses suggest there are different critical windows of vulnerability to extreme heat for preterm birth and stillbirth. An immediate effect of high temperatures is observed for preterm birth. In contrast, increased risk of stillbirth is observed three to five days after the extreme temperature. These observed differences in effect time could be explained by differing biological mechanisms for each adverse birth outcome. Future research is needed to determine the biological mechanisms into these different critical windows of risk for preterm birth and stillbirth, but previous studies have proposed several hypotheses of how extreme heat might cause these outcomes.

Physiological changes during pregnancy may impact the thermoregulation effectiveness of pregnant women. Throughout the pregnancy, the additional weight gained may decrease the ratio of body surface area to body mass, which in turn may limit a woman's capacity to retain heat[35]. In addition, heat production could increase due to fetal growth and metabolism[222]. Thus, the ability of pregnant women to cope with heat stress may be limited due to the increase in internal heat production and the decrease in capacity for heat stress, which could trigger spontaneous labor. Furthermore, other studies have proposed that extreme heat might lead to a heightening in hormones of the hypothalamic-pituitary-adrenal axis, such as cortisol[225,226]. This is one of the primary pathways which has been linked with activation of uterine contractions, which could potentially lead to preterm birth[227]. Heat can also lead to dehydration, which in turn increases the viscosity of the blood, elevating cholesterol levels, and shifting blood flow from the developing fetus to the skin's surface to lower the body's internal temperature. These processes of physiologic changes may decrease uterine oxygen and induce labor[40,143].

There are very few studies that have examined how exposure to extreme heat influences risk of stillbirth[148,228,229]. One of the postulated mechanisms is that heat exposure may cause damage to cells, the placenta, and vascular systems, resulting in insufficient fetal nutrition[144]. In addition, heat has been linked to birth defects such as congenital cataracts and heart defects, which could lead to unviability of the fetus[145].

We also identified that humid days play a role in risk of preterm birth. Days with smaller differences between maximum and minimum temperatures (i.e. diurnal temperature range, a proxy for humidity[230]) were found to have an impact on estimated preterm birth risk. In our changing climate, diurnal temperature ranges have been gradually decreasing and it is predicted this pattern will continue in the future[231] This finding elucidates that women are at risk of adverse birth outcomes not only from experiencing high temperatures but also when they experience hot days followed by warm nights.

Almost all the previous evidence about extreme heat and its effect on adverse birth outcome risk has come from HICs. Two systematic reviews of temperature exposure during pregnancy and birth outcomes conducted by Zhang et.al. in 2017 and Bekkar, et al. in 2020 identified 36 epidemiologic studies[147,228]. The reviewed literature included thirty-six studies examining adverse birth outcomes in Europe, North America, Asia (Israel, China, and Japan), and Australia, and one from Africa (Ghana) (See Appendix Table 1). Twenty-four out of the 36 studies examined preterm birth and temperature, 14 studies assessed the effect of temperature on birth weight, and only eight studies examined the relationship between temperature and stillbirth. Overall, we found about the same or slightly higher effect sizes for preterm birth and stillbirth compared to the studies conducted in HICs.

This study is one of the first studies that examined risk factors for preterm birth and stillbirth in a comprehensive set of LMICs. We found that acute exposure to extreme heat is a critical risk factor for both adverse birth outcomes. Previous studies examining the effect of temperature on adverse birth outcomes in LMICs have relied on coarse temporal exposure data. This study incorporated distributed lag nonlinear models in tandem with the classic case-crossover design to capture these nonlinear and lagged acute relationships of temperature and adverse birth outcomes. Since extreme heat events display distinct spatial and temporal patterns, it is important for early warning systems to utilize real-time or close to real-time temperature data on a local scale. Besides utilizing remote sensing data, the use of low-cost sensors has been suggested to obtain more accurate exposure data in LMICs[232]. The advancement of meteorological sensing technologies and increasing access to mobile phones and the internet provides numerous opportunities for research in LMICs.

In addition to meteorological factors, demographic and socioeconomic factors play a critical role in the susceptibility of individuals to adverse birth outcomes[233]. Pregnant women who are exposed to multiple risk factors are particularly susceptible during extreme heat events and should be classified as vulnerable people[234]. Such women should be targeted by early warning systems through dedicated actions. For example, in areas where women mainly work outside for their livelihoods, a simple recommendation to stay indoors (if they have access to air conditioning) or remain in the shade on extreme heat days can reduce exposure. Another example, the Conditional Cash Transfer (CCT) has recently been suggested as a viable strategy to deal with the effects of extreme weather events[235]. In addition, training, and skill development for additional sources of income in places where heat waves occur frequently could be implemented.

Additional research is needed to support and maintain the proposed early warning systems, particularly the systematic collection of epidemiologic data on health risks associated with extreme heat events. An example of how incorporating local epidemiologic evidence into heat action plans improved an early warning system can be seen in New York City (NYC). NYC traditionally relied on National Weather Service (NWS) heat alert criteria to activate their local heat emergency plan, such criteria used were not derived from local epidemiologic analysis of heat-dependent health effects, and instead were based on national criteria. In a study done by Weinberger that examined the NWS heat alerts and how well it prevented mortality across 20 cities found no changes in mortality attributable to the NWS heat alerts in NYC from 2001-2006[236]. In 2008, NYC changed their local heat emergency plan by lowering the threshold for triggering heat advisories based on local epidemiological studies. One study found that this alteration in the heat plan resulted in 0.80 fewer heat-related illnesses per day, which corresponds to a total of about 50 prevented heat-related illnesses during the summers of 2009 and 2010[237]. We know that incorporating local evidence into early warning systems works in reducing adverse health outcomes. This study provides local epidemiologic data that has elucidated spatial and temporal aspects of extreme heat exposure and associated risks across14 LMICs. Our results can help inform decision-makers about the temperature thresholds at which risks for pregnant women become elevated.

We acknowledge some limitations concerning the analyses that were implemented in this study. First, all exposures were assigned per globally gridded meteorological data that were previously validated. Our measurements are only as good as the data available, which could lead to potential exposure misclassification. Yet, using remote sensing information may reduce the risk of exposure misclassification compared to the previously standard use of ground monitors. LMICs have a very small number of ground monitors and extrapolating from these very few measurements is likely to produce less accurate exposure data then the CPC Global Daily Temperature gridded measurements. However, these data are independent from the outcome of interest and any exposure misclassification is non-differential. Second, we did not examine the impact of co-occurring extreme weather events such as drought and dust storms. Additional research needs to examine how these co-occurring events may contribute to the risk of preterm birth and stillbirth. Third, this study relied on a selective sample of mothers who were willing to participate in the DHS survey and survived to the time of interview. Given that LMICs have high rates of maternal mortality, future studies need to better account for selective survival. All outcomes were based on self-reports of survey participants. Women were asked to report on their birth histories over the previous five years, which can introduce recall bias especially for preterm births which may explain the surprisingly low rates in some countries. Finally, we acknowledge how imprecise a monthly assessment of preterm birth is, which most likely introduced outcome misclassification into our study. This outcome misclassification most likely attributed to our imprecise effect estimates. We felt this measurement was a necessary trade-off for the ability to examine preterm birth and stillbirth risk across geographical regions on a daily scale.

4.6 Conclusion:

Our study is one of the first to examine acute exposure to heat in LMICs and the risk of preterm birth and stillbirth. Due to climate change, extreme heat events have become more frequent, intense, and longer-lasting in recent decades — a trend projected to accelerate in the future. LMICs lack the infrastructure to deal with extreme heat and so it is especially important to study how heat affects pregnancy outcomes, as these women are more vulnerable. Our results indicated elevated risks of adverse birth outcomes across LMICs. Continued research into the mechanisms that are driving this disparity is crucial to ultimately reduce the number of neonatal deaths worldwide.

4.7 Supplemental Material:

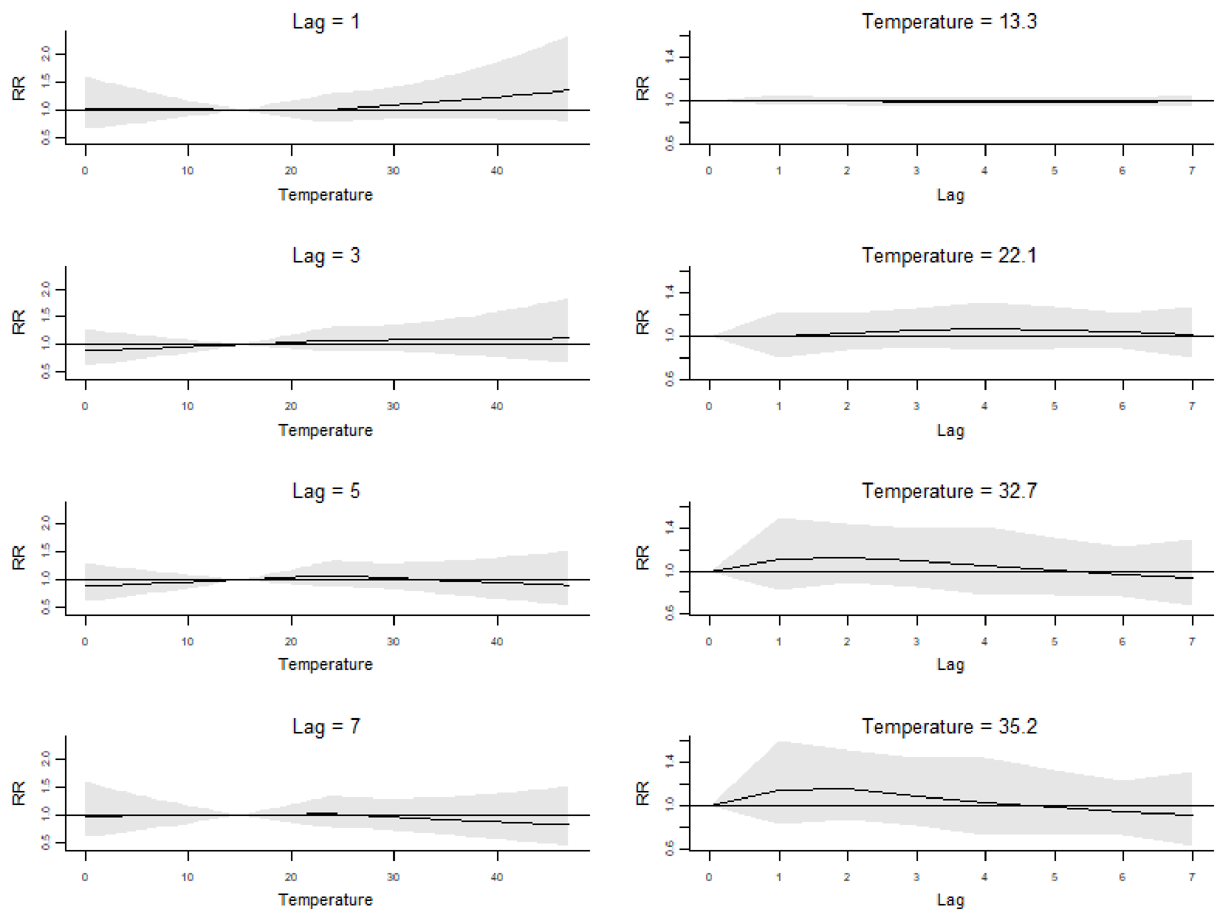


Figure 4.S. 1: Plot of RR for preterm birth by maximum temperature at specific lags (left) and RR by lag at the 1st, 5th, 95th, and 99th percentiles of temperature distribution (right), with respect to reference temperature 20°C.

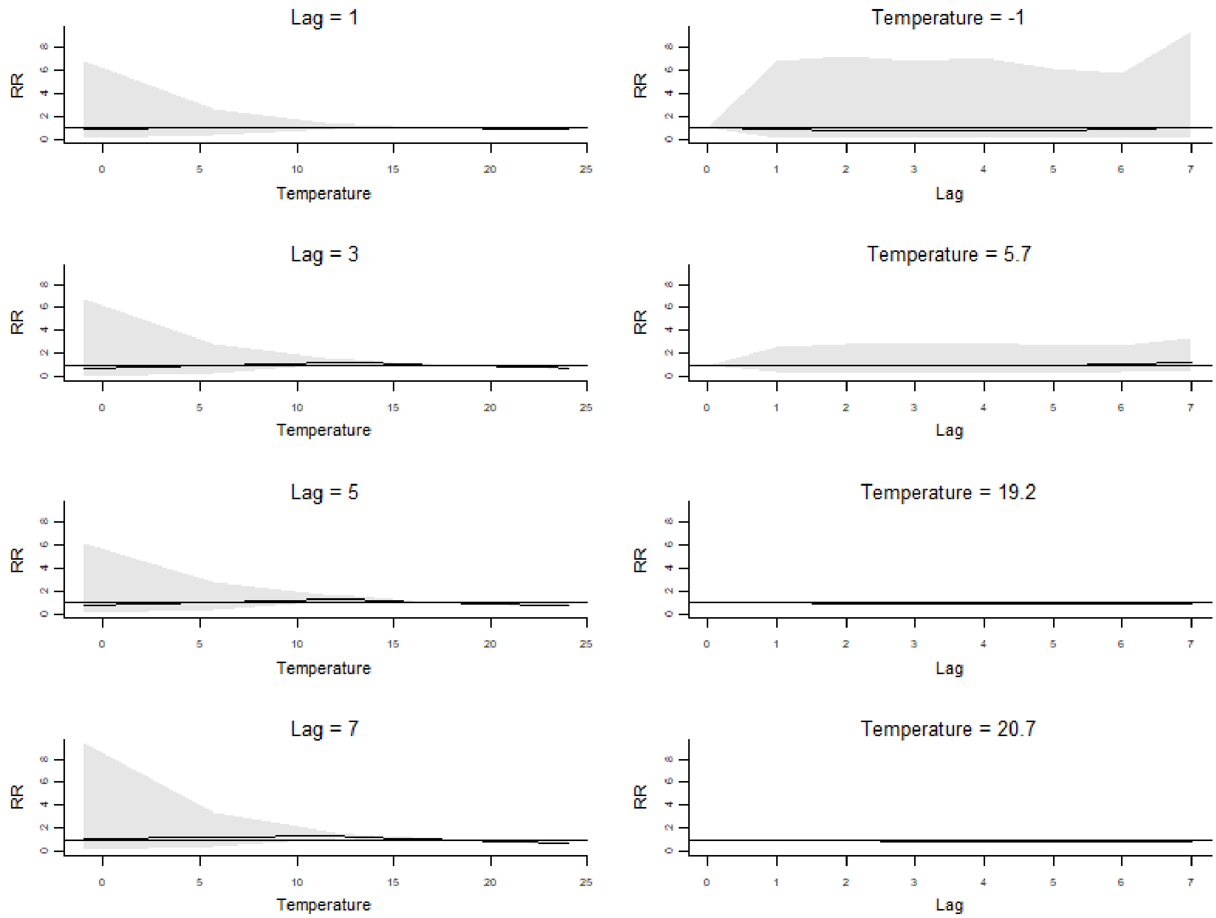


Figure 4.S. 2: Plot of RR for preterm birth by diurnal temperature at specific lags (left) and RR by lag at the 1st, 5th, 95th, and 99th percentiles of temperature distribution (right), with respect to reference temperature 16°C.

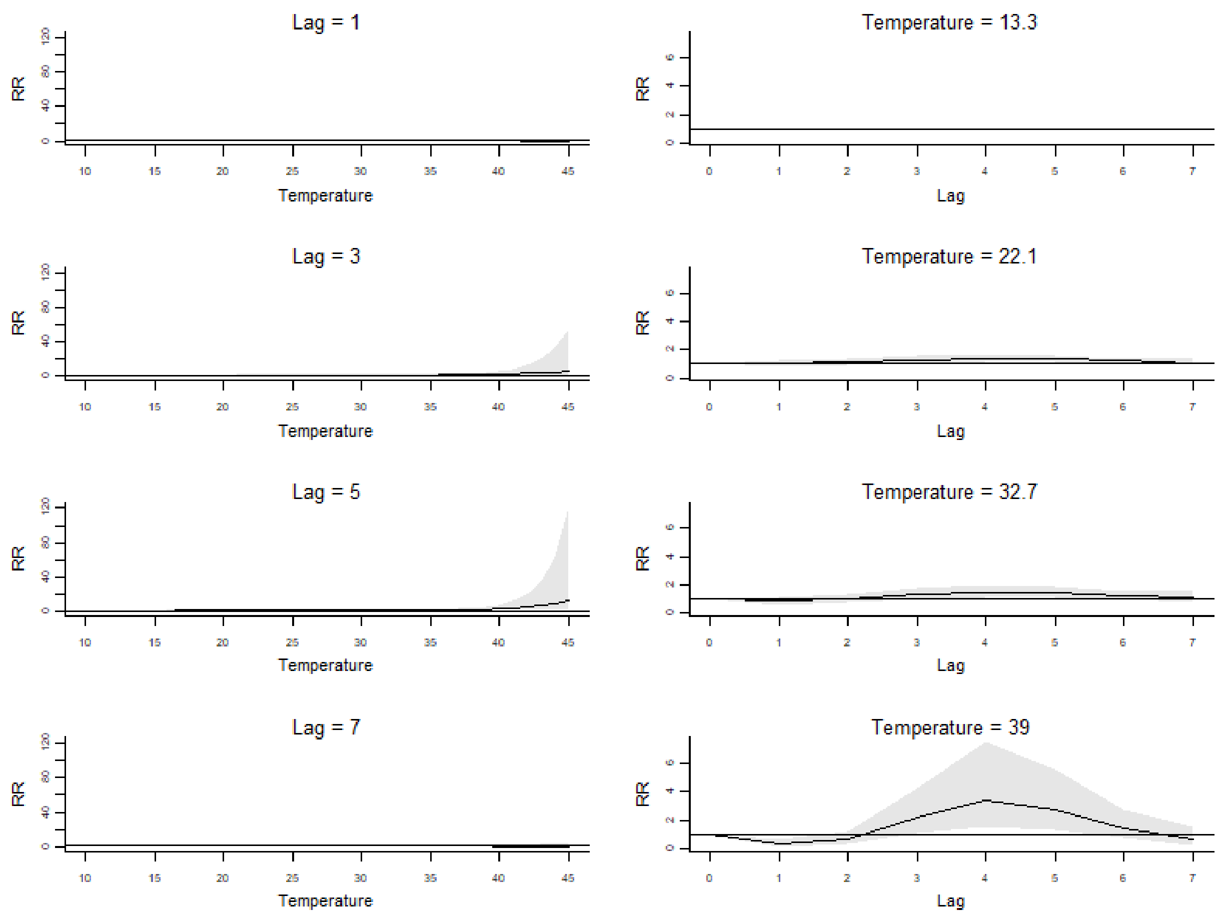


Figure 4.S. 3: Plot of RR for stillbirth by maximum temperature at specific lags (left) and RR by lag at the 1st, 5th, 95th, and 99th percentiles of temperature distribution (right), with respect to reference temperature 20°C.

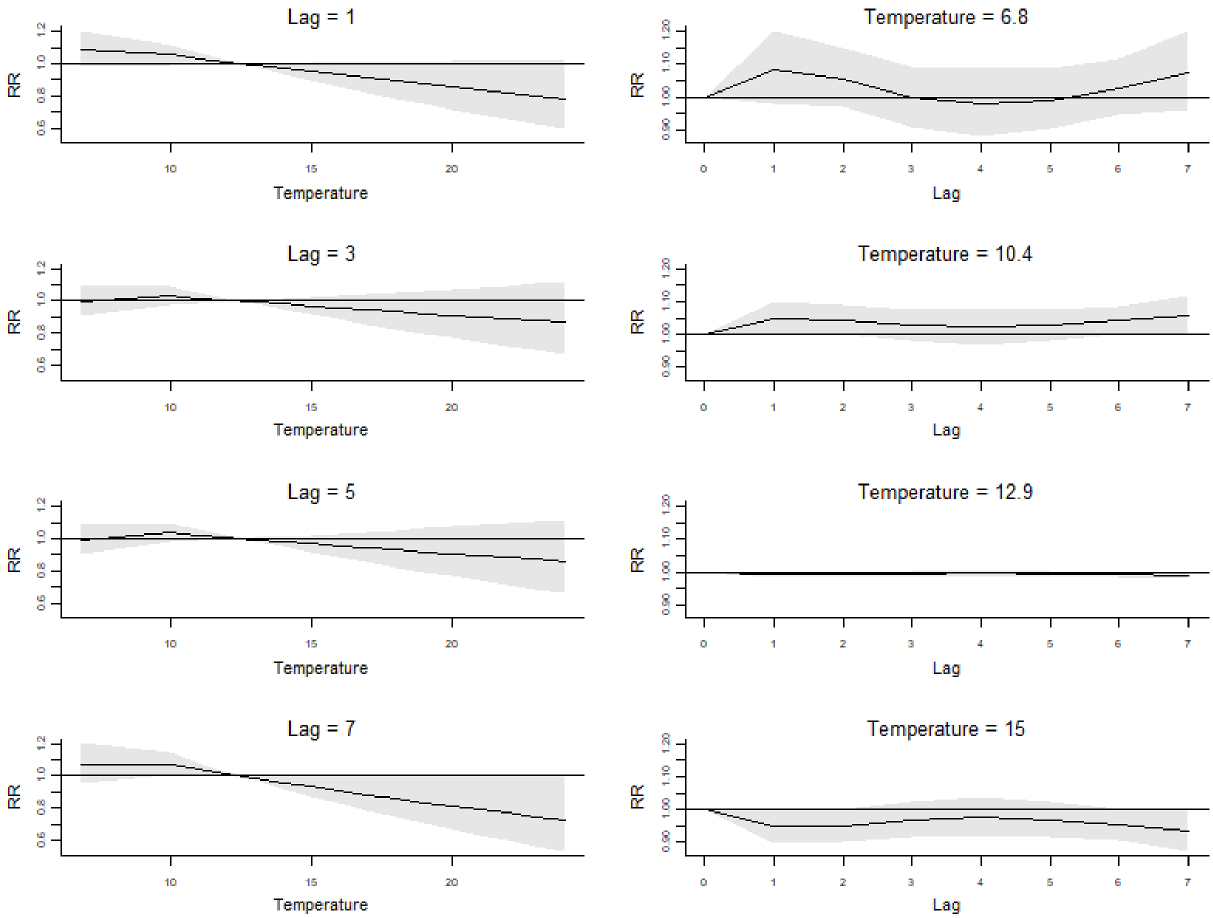


Figure 4.S. 4: Plot of RR for stillbirth by diurnal temperature at specific lags (left) and RR by lag at the 1st, 5th, 95th, and 99th percentiles of temperature distribution (right), with respect to reference temperature 16°C.

Chapter 4, in full, has been submitted for publication of the material as it may appear in the Journal “Environmental International”. McElroy, Sara; Ilango, Sindana; Dimitrova, Anna; Gershunov, Alexander; Benmarhnia, Tarik. The dissertation author was the primary investigator and author of this paper.

5. Discussion:

5.1 Summary of dissertation research:

As our climate changes and the patterns of the increasing number of extreme weather events continue across the globe, it is imperative that we understand how these events affect child health. Most of the available evidence examining these relationships between wildland fire smoke, dust, extreme heat, and adverse child health outcomes are conducted in HICs. Due to methodological challenges in both exposure classification and outcome ascertainment, evidence from developing countries is limited. This lack of evidence is problematic because LMICs are more disadvantaged because of insufficient infrastructures, difficulties accessing health care, ongoing conflicts and wars, and inadequate education. Children living in LMICs are projected to be impacted by climate change the most, and thus, we must address the gap of insufficient evidence of smoke, dust, heat, and adverse health outcomes in children in LMICs[238]. Addressing this paucity of evidence can help us understand the etiological mechanisms of extreme weather events and adverse birth and childhood respiratory outcomes in LMICs, informing early warning systems and action plans.

The purpose of this dissertation was to examine three separate extreme weather events and adverse health outcomes across a comprehensive set of LMICs. This research expands the current literature from LMICs by overcoming previous methodological challenges in exposure classification and paucity of health data by linking remotely sensed data with a nationally representative health survey. The first aim examined the relationship between wildland and agricultural fire smoke and child respiratory outcomes in multiple LMICs. We observed mixed results across countries and identified differences in the observed effect depending on the timing of exposure. The highest period of risk for respiratory outcomes in children under five was within two weeks of exposure to smoke. We observed the highest risk for child cough was found in Malawi and Uganda. Additionally, countries classified as arid were most affected by smoke exposure. Countries classified as having a tropical wet climate saw the least effect of smoke on child respiratory outcomes.

The second aim studied how acute exposure to dust events can affect child cough in Benin by utilizing a time-stratified case-crossover approach, which inherently accounts for time-invariant confounding. This study addressed the current literature gap by addressing the relationship between acute dust exposure in a vulnerable population within LMICs. Previous studies have examined the association between Asian dust and childhood respiratory outcomes or Saharan dust and respiratory outcomes in HICs. However, no studies assessed how Saharan dust affected child cough in Africa. We found that the highest risk period was observed within two weeks after exposure to dust, and this effect dissipated and was no longer observed after the two-week period. Additionally, we identified some suggested patterns of effect modification of living in rural and lower income households. Maternal education did not modify the relationship between acute dust exposure and child cough risk.

The final aim of this dissertation focused on extreme heat and the risk of adverse birth outcomes (preterm birth and stillbirth) within 14 LMICs. We sought to identify a window of heightened risk within the gestational timeline. Based on previous literature, which suggested the week before birth is a high-risk period, we studied the acute exposure to extreme heat and adverse birth outcomes by implementing a time-stratified case-crossover analysis with a distributed non-linear lag model. We observed an increased risk of preterm birth and stillbirth when pregnant women were exposed to a heatwave. Our findings from the distributed lagged analyses suggest different critical windows of vulnerability for women exposed to extreme heat for preterm birth and stillbirth. An immediate effect of high temperatures is observed for preterm birth. In contrast, an increased risk of stillbirth is observed three to five days after exposure to extreme temperature.

This dissertation addresses several of the important indicators to measure climate change and health presented in the 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. Section one of this report aimed to track quantitative data about population vulnerability, exposure, and health outcomes that are indictive of the effects of climate change on human health. This dissertation covers several of these indicators such as assessing exposure to wildfires, studying how prolonged drought, which can cause increases in dust storms, affects children, and measuring how vulnerable populations are influenced by extreme heat. Overall, this dissertation can be a great starting point in building the evidence base in these important indicators for the effects of climate change of child health.

This dissertation advances our knowledge about extreme weather events and adverse birth and respiratory outcomes in LMICs. This dissertation utilized modern exposure assessment techniques and the Demographic Health Survey to overcome previous methodological issues. The assessment of acute exposure to wildfire smoke presented in chapter 2 will help inform future fire detection and air quality action plans. This research focuses on a particularly vulnerable population, children, where there has been almost no evidence coming from LMICs. The case study presented in chapter 3 elucidated the highest risk of child cough and became the first study that examined Saharan dust in children living in Africa. Finally, the comprehensive study of extreme heat and adverse birth outcomes in many LMICs presented in chapter 4 will add to the existing evidence about the proposed hypothesis for the biological mechanism. Also, this study employed robust epidemiological methodology to account for time-invariant confounders and the non-linear relationship of temperature.

5.2 The implications of extreme weather events and adverse health outcomes in LMICs:

5.2.1 Etiological mechanisms:

As extreme weather events are predicted to increase with frequency and severity, we need to prioritize evidence about the etiological mechanisms that drive the relationship between extreme weather events and adverse health outcomes, especially in LMICs. Although the actual biological mechanism of how acute exposure to wildland fire smoke and dust cause respiratory outcomes in children or how extreme heat can cause preterm birth and stillbirth are still only hypothesized, this research has added to the evidence base about these mechanisms.

This dissertation illuminated the window of susceptibility for risk of adverse respiratory outcomes in children for wildland fire smoke and dust exposure. These findings suggested an observed heightening of cough and rapid breathing risk up to two weeks after exposure to smoke or dust. We saw that effects dissipated after the initial two-week period. Thus, action plans and warning systems should take this critical window of susceptibility for higher risk of adverse respiratory symptoms into account. We also identified subpopulations of children that were more vulnerable to adverse respiratory outcomes when exposed to dust, which include children living in rural lower-income homes. These data can be incorporated into air quality warnings that focus on child populations.

This dissertation identified the specific temperature threshold where an increase in the risk of adverse birth outcomes was observed. Additionally, we elucidated the different lag structures of the effects of extreme heat on preterm birth and stillbirth. Information like this is crucial to incorporate into heat-action plans that are specifically targeted towards pregnant women. The heat-action plan can describe how exposure to heat waves can have an immediate effect on the risk of preterm birth, and thus, pregnant women should act instantly. Subsequently, the risk of stillbirth is highest days after exposure, so it is essential for pregnant women to be cautious until several days after experiencing a heatwave.

5.2.2 Policy Implications

The first step for LMICs to start implementing early warning systems, heat-action plans, or air quality action plans is adaption planning and risk management. Countries need this national strategy to guide subnational and local implementation. There is a substantial lack of funding available for LMICs to implement risk management efforts. The WHO Health and Climate Change Survey results indicated that only 9% of countries that participated had enough funds to implement adaptation plans[238]. The 2020 Lancet Countdown on health and climate change found that African countries spend the least amount of money on health adaptation plans to climate change than all other regions of the world[238].

Epidemiological studies examining extreme weather events and adverse health outcomes are critical to helping develop these adaptation plans. This dissertation should be built upon to keep the evidence base of climate and health growing within these vulnerable countries. More specifically, governments in LMICs need to prioritize developing and implementing early-warning systems or action-plans at the local level. Epidemiological studies can help identify countries with the highest risk, and thus, resources can be allocated to those countries where adaption plans are needed the most. We determined that several countries had an elevated risk of child cough when smoke was present (Malawi, Uganda, South Africa, Mali, and Burundi).

While epidemiological evidence regarding extreme weather events' health and economic impacts is growing, few efforts have been dedicated to developing robust early warning systems that consider both local meteorological systems and the population's characteristics and vulnerabilities[214,239].
To improve and develop early warning plans, governments need to incorporate modern techniques such as dynamic climate models, short-term meteorological forecasts, land-use models, and satellite observations[239]. An efficient early warning system involves the systematic collection and analysis of relevant information coming from areas of imminent risk by integrating data from many disciplines. With the advancement of publicly available meteorological data at more acute spatial and temporal scales, and the accessibility of premade satellite products such as the Normalized Difference Vegetation Index (NDVI) and land use information, governments can harness these resources to advance their early warning systems. Also, remote sensing-based retrieval of satellite data of air pollutants can be used for regional- scale monitoring and to evaluate the impact of transport of air pollution. Moreover, it provides a regional- level pollution profile that can be incorporated into local warning systems. One study examining air pollution monitoring in LMICs found in that none of the LMICs utilized remote sensing as part of the national regulatory networks[240].

One of the most critical aspects of an early warning system is developing and disseminating forecasting data. Existing early warning systems typically predict the occurrence of extreme weather events at a lead-time up to a week. Nevertheless, recent approaches have been developed for long-range seasonal outlooks, such as subseasonal-to-seasonal forecasts (S2S). This method bridges the gap between daily or weekly weather forecasts and monthly seasonal outlook patterns[241]. S2S is effective in predicting a cyclone with a lead time of 28 days[242]. The additional time this approach will give local governments to enact action plans could be crucial. Indeed, while recent developments in S2S forecasting show particular promise, they have not been applied to improving prevention efforts of public health impacts and developing proactive preparedness actions plans. Developing phased early warning systems at different time scales can save lives and help LMIC's healthcare systems anticipate and prepare for respiratory and gestational health impacts from weather extremes. While short-range early warning systems (i.e., 1-3 days) help trigger preventive actions such as staying in the shade, long-range early warning systems (e.g., >30 days) help to plan for health care utilization and adopt appropriate resources among communities that are expected to be particularly impacted.

Another solution to implementing accurate meteorological and air quality data in early warning systems is the use of low-cost sensors. Because LMICs lack ground monitor stations, this can be an eloquent alternative for data collection. Low-cost sensors can produce hourly measurements throughout the day. Also, with low-cost sensors, there can be a differentiation between urban, peri-urban, and rural areas. There can also be a distinction made between emission sources, which can provide insights into the overall air pollution burden of a city[243]. The advancement of meteorological sensing technologies and increasing access to mobile phones and the internet provide numerous opportunities for research in LMICs.

The apparent and concerning lack of evidence, notably the lack of epidemiological studies and measured quantitative data, poses major challenges for evidence-based decision-making for early warning systems and adaptation strategies. We believe that this dissertation is a good starting point, but more data at smaller spatial scales is needed to incorporate into early warning systems of LMICs.

5.3 Innovation of this dissertation research:

5.3.1 Exposure assessment:

A paucity of studies explores the relationship between extreme weather events, such as heat waves, wildland fires, agricultural fire smoke, and dust storms in LMICs. This lack of evidence could be attributed to the challenge in obtaining reliable exposure ascertainment. Previous literature investigating these weather phenomena has mainly relied upon meteorological stations and ground monitors for exposure measurement. However, there are very few weather stations and ground monitors located in

LMICs. The area with the least amount of ground monitors is sub-Saharan Africa, with only five manual ground sensors in Ghana, Nigeria, and Kenya[240].

This dissertation aimed to overcome these previous challenges in exposure classification by retrieving remotely sensed satellite data of wildland smoke and dust storms. Accessing these data was free, and the Google Earth Engine platform is user-friendly. The MAIAC AOD product that was used in this dissertation is a reliable tool to measure exposure when ground measurements are not possible. One study in Central China found that the MAIAC AOD product exhibited good spatiotemporal consistency and was mostly in agreement with AOD values from AERONET (gold standard of ground monitors) measures[200]. Although, there are some limitations, which will be discussed in a later section. With the advancement in technologies, many aerosol satellite products are available to the public, which allowed us to be able to classify the presence of smoke and dust. In addition, a globally gridded climate data set was used to estimate extreme heat across Africa. These products have been previously validated and can be utilized in future research.

5.3.2 Performed analyses for LMICs:

Evidence about climate and health severely lacks in LMICs, where most people are affected by poor air quality and extreme heat[244], especially in sub-Saharan Africa. Figure 5.1 depicts the mean annual PM10 concentrations for several cities across sub-Saharan Africa. All but two cities surpass the WHO-recommended air quality guidelines for safe levels of PM10. Some cities have a mean annual PM10 concentration of eight times what is recommended as acceptable air quality levels. People living in sub-Saharan Africa are also experiencing extreme heat records. Since these areas are experiencing the greatest effects of poor air quality and extreme heat, we must learn how exposures to these extreme weather events affects human health in LMICs. This dissertation was able to study these relationships across many LMICs. Several systematic literature reviews have identified very few studies examining wildland smoke and dust and respiratory outcomes in children in sub-Saharan Africa. This dissertation has bolstered the existing evidence from LMICs, which showed that extreme heat, wildland fire smoke, and dust are linked with increased risk of adverse health outcomes.

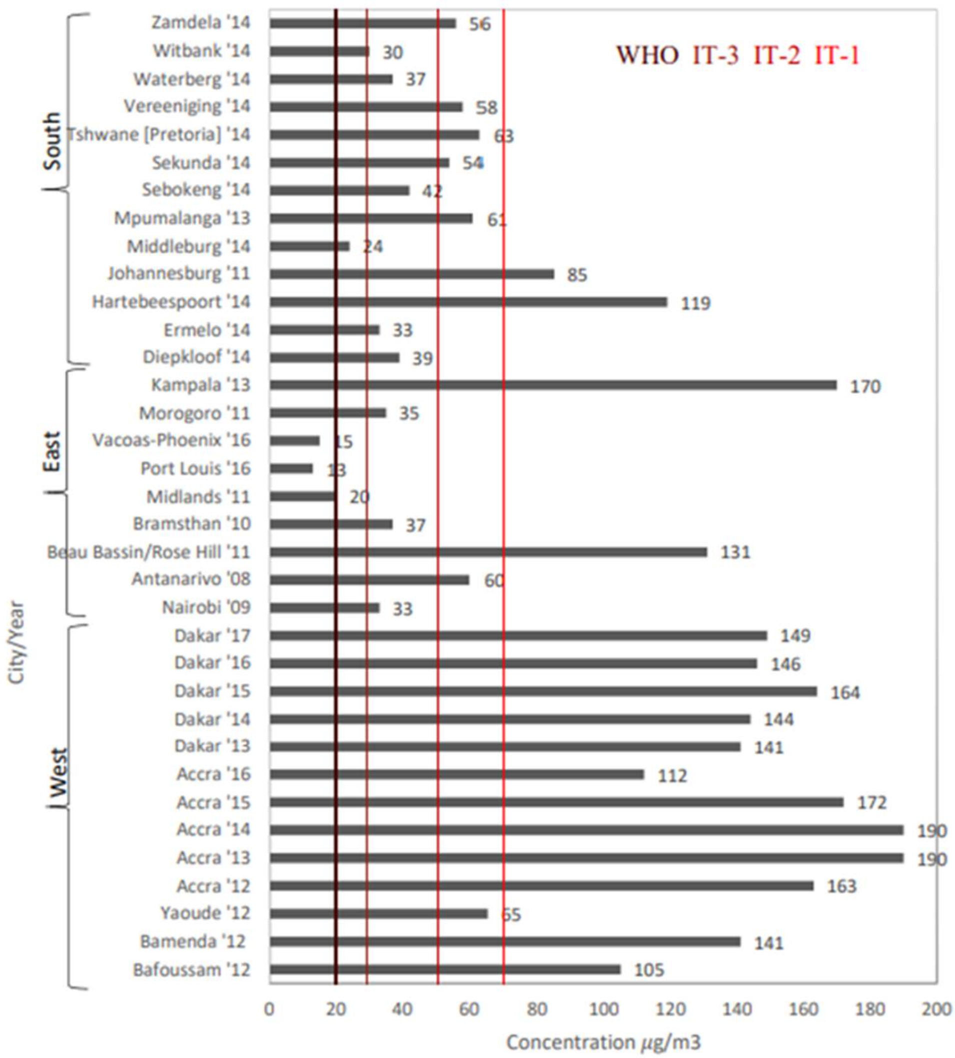


Figure 7a. SSA mean annual PM10 concentrations.

Figure 5. 1: Mean annual PM10 concentration in several sub-Saharan African cities.

<u>5.3.3 Daily outcome assessment for phase 7 of the DHS survey:</u>

Chapter 4 examined acute exposure to extreme heat and adverse birth outcomes daily, using globally gridded meteorological products to measure acute exposure to heat with fine spatiotemporal resolution. Data on adverse birth outcomes was obtained from Demographic Health Surveys (DHS) and linked with global telecommunications meteorological data. With the release of the newest phase of the survey came a unique opportunity to capitalize on the fact that this version added the day of birth (or death) for each child, not just the birth month. This new attribute allows for the performance of analyses on a more acute and specific level, i.e., daily measurements that have shown to be relevant for considering critical windows of susceptibility. This study was one of the first studies to examine these outcomes at a daily level compared to previous literature, which assessed exposure as monthly averages.

5.4 Limitations:

We acknowledge that this dissertation is not without its limitations. We relied on remotely sensed satellite data to measure exposure to wildland fire smoke and dust. There are three primary constraints when using satellite data, which one needs to consider: cloud cover, surface reflectance, and molecular scatter[244]. These three constraints can cause missing data or inaccurate measurements. In addition, since there is a current paucity of ground monitors located in LMICs, we could not validate our measures with ground measurements. However, these products have been shown to be valid in previous studies[198-200]. Using remote sensing information may reduce exposure misclassification compared to the previous standard of measurement of interpolating from ground monitors. Nevertheless, this exposure misclassification is independent of outcome assessment and thus nondifferential.

We acknowledge that there are other alterative measures that could have been used in accessing the presence of wildland fire smoke or dust, such as chemical transport models. However, these models have had a crucial problem of spatial resolution[245]. The spatial resolution of these models ranges from 4°x 5°-28km x 25km. Also, some chemical transport models fail to capture variations in daily changes and spatial distribution due to imperfect data and chemistry[246]. Finally, in order for chemical transport models to be accurate, they need accurate levels of the initial concentration of pollutants[247], which is problematic in areas that do not have ground monitors. Additionally, land use regression models have been suggested, but the land use regressions have problems capturing temporal variations[248]. Since we aimed to study the acute effects of extreme environmental events, we needed the methodology to be able to handle daily spatiotemporal changes.

Another limitation of this dissertation is the non-clinical definition of outcome ascertainment. All health outcomes were classified from the DHS questionnaire, and thus self-reported, which could lead to outcome misclassification. Since we could not obtain medical records to validate the DHS data for this dissertation outcome, misclassification was highly probable. Additionally, preterm birth was only measured at the month level, which does not allow for precise estimates of gestational age. Although, even when gestational age is measured weekly, there have been many documented problems with the measurement because it is reported primarily from a mother's recall of her last menstrual period[249]. It has been suggested to use birth weight as a proxy for gestational age but a study examining the validity of the DHS birth weight variable found it to be highly unreliable[250]. Qualitative data indicated that this discrepancy in mothers' reported birth weight and clinical birth weight was because of lack of measurement, poor communication, social perceptions, and spiritual beliefs surrounding birth weights.

In order to obtain large enough sample sizes to detect effects when studying adverse birth outcomes, we needed to pool cases from many LMICs. To do this, we needed to use a standardized survey across all LMICs, which was the DHS survey. Unfortunately, this survey does not measure gestational age at the weekly level and with the evidence of the unreliability of the birth weight variable, we decided to use this monthly measure. If future phases of the DHS survey start ascertaining gestational age, this research should be replicated using those measures.

Another problem with outcome assessment that we acknowledge is the underreporting of stillbirths. There is still an observed stigma associated with stillbirths across the globe. We believe that this could have led to many unreported stillbirths, making for more conservative effect estimates in our study. A study examining stillbirths in Tanzania and Zambia found the stillbirth rate within their study population was 16% in Tanzania and 10% in Zambia, which is much higher than the previous estimates of 2.24% and 2.09%, respectively[251]. This discrepancy in rates could be attributed to underreporting and poor communication from health care professionals. Improving education about stillbirths in LMICs could help address this stigma and may lead to more accurate reporting of these outcomes in the future.

Finally, the DHS survey is cross-sectional in nature and did not measure exposure and outcomes across time. This does not allow us to ascertain the temporal relationship between when symptoms started, but we do know the exact timing of the dust or smoke event. Since, the survey was done at one specific time, we were not able to see the progression of an extreme weather event to symptoms of respiratory problems, which again could lead to bias in our effect sizes. Additionally, we were limited in our methodologies for analyzing these data due to the nature of the DHS survey. Unfortunately, there was not enough temporal variation in survey times to employ quasi-experimental methods, which were first proposed. Sample size issues and timing of surveys inhibited this dissertation from examining adverse birth outcomes in the context of wildfire smoke and dust exposure. Future research should combine many of the DHS surveys to obtain a large sample of adverse birth outcomes.

5.5 Future Research:

There are many ways that future research can build on top of this dissertation. In addition to acute exposure to wildland fire smoke and dust, there is also a lack of studies examining how chronic exposure can affect child health outcomes in LMICs. There has been plenty of evidence that has previously linked chronic exposure to air pollution and adverse respiratory outcomes, but research in this area is sparse in LMICs. As LMICs experience rapid development[252], we see an increase in air quality in urban areas[240] , and this pattern is predicted to keep increasing in the future. Thus, it will be important to understand the mechanisms of how chronic exposure to poor air quality can affect child health outcomes. This future work should focus on adverse respiratory outcomes and significant risk factors for respiratory infections such as stunting and wasting[253].

Another way this dissertation research could be extended is to examine how acute exposure to wildland smoke and dust storms can impact the risk of adverse birth outcomes such as preterm birth, stillbirth, and low birth weight. This future research will need to obtain outcome ascertainment from additional sources because the sample size for the reported preterm births and stillbirths reported within a month of the survey interview was too small. Many previous studies have tied exposure to wildland smoke and adverse birth outcomes in HICs[254-256]. One recent study currently in preprint examined exposure to landscape fire smoke and low-birth-weight in LMICs[257] and found an 11% increase in risk for very low birth weight. This study will be the first comprehensive study of wildland smoke and adverse birth outcomes across 54 LMICs. However, this study does not examine preterm birth and stillbirth, which are important maternal and child health outcomes. Additional research could also examine how maternal exposure to chronic air pollution during pregnancy can result in stunting, wasting, or other adverse child health outcomes. As the climate continues to change in LMICS, it is crucial that we focus future research on vulnerable populations such as children and pregnant women.

Future research also can focus on these critical environmental exposures and infectious diseases outcomes. There is evidence that climate zones are shifting in nature and size, allowing for the habitat of mosquitos to grow. In 2015-2019, the suitability for malaria in the highland areas of Sub-Saharan Africa was 38.7% higher than the previously known[238]. Rising temperatures are making elevation irrelevant, and mosquitos are being found at much higher altitudes because of the higher temperatures. We need to focus research on how these changes in the climate zones can alter the pattern of malaria infections in LMICs. More specifically, we need to focus on how these changes in malaria can affect children and pregnant women.

Finally, a major public health concern is how climate change will influence the spread of COVID-19, especially in LMICs. They lack infrastructure and access to basic health care resources to tackle a global pandemic. Climate change and COVID-19 act to exacerbate the existing inequalities within and between countries[258]. In addition to COVID-19, LMICs countries also have to deal with co-morbidities such as HIV and malnourishment, which could affect vulnerable populations such as children and pregnant women more than others. We have already witnessed inequalities in the action plans and preparedness for pandemics in LMICs. One such example is unequal access to the vaccine. LMICs are the last to get the vaccine, and we should make it a priority and have a moral responsibility to support developing nations through this global pandemic. It is vital that we focus on this research and consider the ethical concerns regarding preparedness, knowledge sharing, intellectual property rights, environmental health, and constraints in the health care system.

5.6 Concluding remarks:

In conclusion, this dissertation provides a thorough epidemiological examination of the effect of wildland fire smoke, dust, and extreme heat on adverse child health outcomes by building upon the paucity of the existing evidence base in LMICs and utilizing modern exposure assessment techniques. This body of research advances the field of climate and health by overcoming previous methodological challenges in exposure and outcome ascertainment and provides a detailed overview of how extreme weather events affect children and mothers in LMICs.

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