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Protocol of an Individual Participant Data meta-analysis to quantify the impact of high ambient temperatures on maternal and child health in Africa (HE²AT IPD)

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Abstract

Introduction

Globally, recognition is growing of the harmful impacts of high ambient temperatures (heat) on health in pregnant women and children. There remain, however, major evidence gaps on the extent to which heat increase the risks for adverse health outcomes, and how this varies between settings. Evidence gaps are especially large in Africa. We will conduct an individual participant data (IPD) meta-analysis to quantify the impacts of heat on maternal and child health in sub-Saharan Africa. A detailed understanding and quantification of linkages between heat and maternal and child health is essential for developing solutions to this critical research and policy area.

Methods and analysis

We will use IPD from existing, large, longitudinal trial and cohort data, on pregnant women and children from sub-Saharan Africa. We will systematically identify eligible studies through a mapping review, searching data repositories, and suggestions from experts. We will obtain the IPD from data repositories, or through collaboration with data providers. Existing satellite imagery, climate reanalysis and station-based weather observations will be used to quantify weather and environmental exposures. IPD will be recoded, harmonized, and then linked with climate, environmental and socio-economic data by location and time. A one and two-stage analysis method will be adopted using analytical models such as time-to-event analysis, generalised additive models, and novel machine learning approaches to quantify associations between exposure to heat, and adverse maternal and child health outcomes.

Ethics and dissemination

The study has been approved by two ethics committees. There is minimal risk to study participants. Participant privacy is protected through the anonymisation of data for analysis, secure data transfer, and restricted access. Findings will be disseminated through conferences, journal publications, related policy and research fora, and data may be shared in accordance with data sharing policies of the National Institutes of Health.

PROSPERO registration: CRD42022346068

Strengths and limitations

Strengths

- Prospectively collected data from cohorts and trials are more likely to be high quality longitudinal data and contain a large number of variables. Longitudinal data enables analysis of temporal relations between repeated exposure-outcomes data, and more detailed causal analysis modelling than data collected at a single time point. The large IPD dataset will have statistical power to assess rare exposures and outcomes, explore high risk sub-groups, and make risk comparison across different areas/regions/countries, enhancing the study's external power and generalisability
- IPD analyses reduces selection bias by drawing on databases regardless of whether the exposure-outcome of interest has been reported or if information is available on the potential presence or size of the association. Individual-level information enables more flexible and robust analyses than are possible in systematic reviews using aggregate study results from published data

Limitations

- Our dataset may not be representative of the entire continent as data availability reflects research capacity across countries and not necessarily size of population, or urban-rural make-up, for example
- Missing data may occur as only data that has been shared by willing investigators will be included in the analysis. We think this this is unlikely to introduce bias because the missing data may be completely at random as these studies had different exposure-outcome assessments, but this will require further assessment when all data has been acquired

Introduction

Background

Climate change is one of the greatest global health threats ever faced by humanity (1, 2). Increasing anthropogenic greenhouse emissions have caused the mean temperature of the world to rise by more than 1°C, and by as much as 2°C in many parts of Africa (3-5). Projected temperature increases in both average temperatures and extreme events, such as heat-waves, are especially concerning. An estimated 54% of the global population will be exposed to more than 20 days of deadly heat per year by 2100 (6).

The climate change crisis, and heat in particular, has a wide range of deleterious effects on health. The indirect impacts of rising temperatures on the burden of infectious diseases are well documented, such as an expanding geographical range of malaria vectors (7-9) and increased soil drying leading to food insecurity and malnutrition due to crop failure and livestock deaths. Heat also indirectly affects health by fomenting wildfires, which destroy ecosystems and infrastructure (10, 11).

The direct impacts on human health due to exposure to high ambient temperatures (referred hereafter as heat) are increasingly recognised, and affect a range of vulnerable populations (2). Heat-waves cause increased rates of emergency room visits and hospitalizations, with an accompanying escalation in healthcare costs (12), and result in substantial excess mortality. Moreover, the mental health sequelae of acute or more prolonged periods of heat exposure are considerable, including generalized anxiety, depression, and eco-anxiety (3, 13).

Heat exposure impacts on maternal and child health

Heat is hazardous for high-risk populations, including pregnant women and children (Figure 1). The physiological and anatomical changes in pregnancy, pregnancy-related weight gain, and heat generated by foetal metabolism and exertion during labour, makes it challenging for pregnant women to maintain a normal temperature range when exposed to heat (14, 15). Manifestations of heat exposure include adverse pregnancy and birth outcomes, such as preterm birth, low birth weight, and stillbirths (13), gestational diabetes (16, 17), and hypertension in pregnancy (18).

Children, and particularly infants, have physiological, anatomic, and social factors that increase their vulnerability to heat, such as increased body surface to volume ratio, higher metabolic rate, and reliance on a caregiver to safeguard them (19-21). Multiple studies have demonstrated a detrimental effect of heat on infant and child mortality (19, 22-26), kidney associated diseases (27), asthma and other respiratory disease (28), and infectious diseases (29, 30). A modelling paper reported that under the high-emission scenario, heat-related child mortality in Africa may exceed 38,000 deaths per year in 2049 (31).

Several studies, including in Ethiopia (32) and Uganda (33), have also shown that exposure to heat *in utero* negatively affects health throughout the life course, such as increased risks of stunting (34). The consequences of heat on maternal and child health outcomes also extend to the larger health systems by increasing the burden on already stretched local health facilities and health resources due to increased rates of caesarean sections (35), hospitalisation (36), emergency department visits (37, 38), and out-and in-patient health facility visits (39-41).

Research gaps

Research on heat and health has been mostly restricted to stand-alone individual studies with relatively small sample sizes, poor-quality data from household surveys or healthcare facilities, considerable variation in research methodology, and limited geographical and temporal coverage (13, 19). Most studies have insufficient power to answer questions about which specific aspects of heat exposures (e.g., timing and duration), and which temperature

patterns/thresholds (e.g., night- or day-time, or averages or cut-off values) are most harmful for different clinical conditions, and in which climate zones, settings and subgroups. In addition, the external validity or generalisability of the findings of these studies may be limited beyond the study's place and time.

Although some of the world's largest clinical trials have been conducted in Africa (42), very little work has focused on heat impacts in key African population groups, such as pregnant women and children. Given the unique demographic profile, disease spectrum, built environment, and resource constraints in Africa, the most at-risk groups in these settings will likely differ from those in the Global North.

Rationale for the Individual Participant Data Meta-Analysis

We propose conducting an Individual Participant Data (IPD) meta-analysis using data collected from longitudinal cohorts and clinical trials on maternal and child health across sub-Saharan Africa. We will use the IPD to quantify the current and future impacts of heat on maternal and child health in sub-Saharan Africa. IPD analyses reduces selection bias by drawing on databases regardless of whether the exposure-outcome of interest has been reported or if information is available on the presence or size of the association (43). Individual-level information enables more flexible and robust analyses than are possible in systematic reviews using aggregate study results from published data (Figure 2) (43, 44). The advantages of the IPD methodology are especially apparent in heat-health research, where larger sample sizes are required to detect relatively small exposure effects.

Public health relevance of the study findings

The study results aim to inform the development of an indicator for the effects of heat on maternal and child health, such as an indicator that could be used in a District Health Information System. The indicator will not be implemented and evaluated in this study. Understanding the patterns of heat-health impacts is an important step towards tracking changes in disease burden over time and projecting future burdens under different climate change scenarios and adaptation responses. A system to track changes over time in the overall burden of heat-related morbidity and mortality are key to a successful health sector response. By performing adequately powered and high-quality 'impact' studies, we will generate the information required to calculate the burden of disease from climate change which, in turn, strengthens arguments for allocating sufficient resources to address climate-related impacts, and for hastening the societal changes required to avert further climate breakdown.

Study objectives

The study's overall objective is to use innovative data science approaches to quantify the current and future impacts of heat exposure on maternal and child health in sub-Saharan Africa.

The specific objectives are:

1. To systematically identify, acquire, collate and integrate prospectively-collected data from cohort studies and clinical trials on maternal and child health in sub-Saharan Africa
2. To link maternal and child health outcome data spatially and temporally with weather and other environmental data, as well as socio-economic and other data
3. To utilise classic statistical and novel machine learning approaches to understand and quantify the impact of heat exposure on maternal and child health
4. To document variations in the relationship between heat exposure and maternal and child health outcomes across different climate zones, settings, and population sub-groups

5. To develop innovative data science solutions for district-level surveillance of the impacts of heat on health

Methods and analyses

Study design and protocol registration

The IPD meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) IPD extension guidelines (45). The study has begun (start date June 2022) and we plan to conclude in June 2026. We have completed the mapping review, started contacting data providers, and have received six datasets. No analyses have been conducted. The protocol has been registered in PROSPERO (registration number: CRD42022346068).

Study population

The study population are women in sub-Saharan Africa in pregnancy, childbirth and up to two years postpartum, and their children up to 2 years of age, exposed to heat.

Eligibility criteria

Eligibility is determined at the study- and individual-level. Study-level inclusion criteria are:

1. Enrolment of at least 1000 pregnant women in one or more study sites, in one or more countries in sub-Saharan Africa
2. Identified through published literature (published between January 2012 and June 2022) from the systematic mapping, or a clinical trial registry, data repository search, or from study investigators and experts
3. Randomised or non-randomised clinical trial, or an observational or interventional cohort with prospectively-collected data
4. At least two of the 'important' maternal and/or child health outcomes[1] have been collected as part of the study (Supplementary 1)
5. Relevant local ethics approvals received, and documented

At the individual level, the following inclusion criteria apply:

1. Enrolment into an eligible study as described above, during pregnancy, or intrapartum
2. Individual participant information is available on the date of birth of the newborn, date of diagnosis/occurrence of an adverse health outcome, or date of the end of pregnancy in cases of maternal deaths or abortion
3. Individual participant information is available on location of birth, or study follow-up

Data sources

Studies are located in several ways. Firstly, we draw on studies identified through a systematic mapping. The search was conducted in 2020 in MEDLINE (PubMed) and updated in 2022, using controlled vocabulary and free-text terms to identify studies. Search terms for maternal health, for World Bank defined sub-Saharan African countries, and for filters to locate cohorts and clinical trials were included (Supplementary 2) (46). The search strategy replicate those used in MASCOT-1, which mapped global maternal health literature from 2000 to 2012 (42, 47-50).

Using EPPI-Reviewer software (51), screening of titles and abstracts was done independently, in duplicate, with differences between reviewers reconciled through discussion, or by a third reviewer. The full text was screened if eligibility could not be

[1] Important maternal and child health outcomes have been selected based on evidence of heat-health impacts, an in alignment with the top causes of maternal and child mortality in sub-Saharan Africa.

ascertained from the title or abstract. Once eligibility was established, the full-text articles were uploaded onto EPPI-Reviewer for data extraction. We extracted the following variables:

- Population: country, number enrolled
- Methods: study design, topic
- Identifiers: name, acronym, clinical registration number, authors, funders

The second way we identify studies is through searching data repositories, such as the Bill and Melinda Gates Foundation Knowledge Integration platform, National Institutes of Health repositories, and ClinicalTrials.gov. Lastly, we will seek additional studies through direct contact with data providers and other experts in the field.

The quality of the studies will be evaluated using the Cochrane risk-of-bias tool for randomised trails (RoB 2), and the risk of bias in non-randomized studies of intervention (ROBINS-I) for cohorts or non-randomised trials. Each study and outcome will have an overall grading, which will be considered in meta-analysis and sensitivity analyses.

Acquisition of individual participant data

Data will be acquired either through data access platforms such as Worldwide Antimalarial Resistance Network (WWARN) (52), or directly from principal investigators or other relevant study custodians. Corresponding authors of the studies will be sent an email request detailing the purpose of our study and study procedures. We will make at least five attempts to contact the study investigators, including through contacting first, last, and other study authors, and funders. The process of obtaining IPD, including the number of attempts made and modes of contact with data providers, will be recorded. Reasons for unattainable IPD data will be included in the IPD flowchart, such as the inability to contact data providers, unwillingness to share their data, or the destruction of data. Data providers who agree to join the collaboration will sign a data sharing agreement that sets out the terms of data sharing, data security, and authorship guidelines. Collaborators will supply meta-data and key documentation, which will be used to confirm eligibility and for data management. Key documentation will include the full study protocol, informed consent forms, codebook, and the ethics approval of the study.

Acquisition of environmental exposure data

Weather data include observational-based datasets (weather station, or satellite remote sensing[2]) and processed or gridded observations. Climate-related data will mostly involve accessing open data repositories such as Copernicus Climate Data Store (CDS) or Earth System Grid Federation data systems.

Air pollution data will be obtained from proxy satellite-derived air quality data such as Aerosol Optical Depth (AOD), in combination with land cover use, to overcome the challenge of gaps in the coverage of ground-based stations (Figure 3). Where available, we will use data on pollutant concentrations, namely of PM_{10}, $PM_{2.5}$, NO_2, SO_2 and CO for developing indices of air quality as well as leveraging global databases of air quality indicators such as the World Air Quality Index (53) and OpenAQ (54).

[2] Remotely sensed data from satellite sensors, mainly optical imagery (e.g., satellite images of urban centres), provide information about physical attributes such as land surface temperature, vegetation characteristics, and land use.

Data management and analysis

Development of the database

In Figure 4, we outline the steps that will result in the comprehensive database formation. In the first phase, the focus is on collecting IPD and metadata, and on data quality and integrity. Once a data transfer agreement has been signed, IPD will be transferred to a secure, password protected platform using a secure data transfer system.

Data from multiple studies will be characterised by differences in quality that must be addressed before the synthesis phase of the meta-analysis. Systematic data quality assessment and remediation guidelines specific to IPD-MA will be used. (55) These have been formulated into a system of five data preparation phases for IPD-MA: Processing, Replication, Imputation, Merging, and Evaluation, also called PRIME-IPD (Table 1).

PRIME	Items
Processing	Convert data into single format for statistical program of choice Compare the total number of participants in the acquired datasets to those reported in published articles Verify the presence of the variables of interest in the acquired dataset Standardise variable names across datasets Identify and standardise the measurement scales used to report the variables of interest Identify and standardise coding for missing values Identify and correct any implausible values that may result from data conversion
Replication	Recalculate reported descriptive and summary statistics using the acquired datasets Calculate the standardised difference to quantitively assess the difference between the replicated and published results If the standardised difference is >10%, investigate and address potential causes
Imputation	Assess the appropriateness of conducting imputation of missing data using missing data theory If multiple imputation is conducted, carefully consider the number of imputations to be run
Merging	Ensure in processing step that variable order and codes are correct Merge the imputed dataset into a single, pooled dataset, taking into consideration the number of imputed datasets, if appropriate
Evaluation	Assess continuous variables for normality by residual analysis either visually or by statistical tests If required, calculate new variables for standardised comparison of effects

Table 1: Checklist for PRIME-IPD tool (58)

The expectation is that the number of covariates available for each study will be large and may differ across studies. The aim of the harmonisation step will be identifying these discrepancies and formulating a strategy, mainly the creation of proxy covariates. The health covariates will be defined using published, reputable sources such as World Health Organisation (WHO), the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) terminology (56), standard ontologies, and local obstetrics and paediatric guidelines.

The second phase of database formation, which will run parallel to the first, will consist of pre-processing the climate and environmental data, to derive variables that will be included in the harmonised health database. Temperature, air pollution, as well as other environmental, and socioeconomic data are merged with the database. The climate data are linked to time (e.g., date of birth, or date of adverse health event) and location. Where we have high resolution location information (GPS coordinates, home addresses), we will aggregate up to the appropriate administrative level that will minimise exposure mischaracterisation while protecting the privacy of the individual participants. Once climate

and other data are merged with health data, potentially identifiable information such as date of birth and location will be removed from the integrated dataset to further protect participant confidentiality. To produce higher resolution daily temperature estimates, a method will be developed using a combination of satellite data, ERA5 land daily temperatures, and weather station data. In this context, further advances based on the exploitation of recent developments in geospatial artificial intelligence (geoAI) will be utilised. Some of the approaches that the team will implement include natural gradient boosting algorithms (57), and quantile random forest spatial interpolations (58), with implementation of maximum covariance analysis (59) to detect the structure of the covariance between these various forms of spatiotemporal datasets.

These two phases will result in an individual participant database consisting of health outcome variables, demographic and health covariates, and climate and environmental covariates. The integrated datasets will be made available to HE^{2}AT Center partners for analysis through an access controlled, Jupyter Hub platform that is managed by the principal investigators and the HE^{2}AT Center data management and analysis core.

Statistical analysis

The baseline characteristics of participants from each of the participating cohorts or trials will be described using R or Python, to compare differences in important baseline characteristics (60, 61).

A two-stage analysis approach will be used primarily, whereby, in the first stage, each study is analysed individually. In the second stage, the data from the individual studies will be aggregated to provide an overall pooled estimate of effect. We will explore analysing each study independently, and in combination with other studies through pooled analyses. We will evaluate heterogeneity of effects and precision of effect estimates and use this information to inform pooled analysis or meta-analysis approaches.

Statistical method for the first stage of the meta-analysis

The core modelling method for this study is linear and non-linear lag-distributed models (62). These models are specifically relevant where the outcome variable is a time series, typical with counts of adverse events such as preterm births. The most valuable characteristics of advanced forms of these models, such as the semi-parametric generalised additive model (GAM) following a quasi-Poisson distribution with a distributed lag non-linear model is the ability to account for non-linear, short-term, and lagged effects of environmental exposures on health outcomes (57). In general, the GAM framework provides the flexibility to account for non-linearity and over-dispersions in the temporal dimension and clustering in the spatial dimension. The additive modelling framework may be expanded further to account for multiple health outcomes, associated uncertainties (58), spatial effects, and interactions (59, 63). Therefore, large geospatial (and spatiotemporal) data from satellites and sensor networks can be leveraged as additional features in testing heat-health outcomes. In addition, the attributable risk of heat to adverse outcomes will be calculated as per IPCC-described methodologies.

Machine learning informed covariate selection

We will consider traditional variable selection approaches for large data, as well as tree-based ensemble learning approaches, namely extreme gradient boosted trees or random forest algorithms. For both approaches, there is a split of the dataset into a training and testing set, the implementation of the tree algorithm and the evaluation of the variable importance ranking, and the possibility to use partial dependence plots to identify the functional form between pairwise or multiple covariates (including interactions) and the response variable. Both forms of tree algorithms can be used for binary, continuous, and time-to-event response variables. While autoencoding algorithms may be implemented for feature engineering from the geospatial or spatiotemporal covariate datasets (climate &

environmental), ensemble tree algorithms may be used for automatic feature (covariate) selection, maintaining a level of explainability required when trying to understand the health effects of environmental exposures (64).

Statistical methods for the second stage of meta-analysis

Using the statistical methods described above, an analysis of outcomes of interest for each study will be performed and a summary statistic will be presented to describe the observed intervention effect. The summary statistic will differ depending on the outcome and the analysis method used.

In the second stage, a weighted average of the effects of heat on maternal and child outcomes will be calculated where possible. This will be illustrated in a forest plot. Forest plots will present the point estimates and uncertainty range for each stratum and the combined estimates where possible.

Exploration of variation in effects across studies and sub-groups

Exploration of variation in effects will be done involving stratified analyses within the following strata: study, geographical area, climate zone, time period, and income group of the country. Data will also be stratified on population characteristics, such as maternal age, socio-economic status, sex, and health conditions such as HIV status. In these analyses, we generate estimates of impact (aggregate data) for each stratum separately and then combine these summary statistics using standard meta-analysis methods, if appropriate.

Risk of bias across the IPD sources

Using the PRISMA-IPD flow chart, we will report the numbers of studies screened and included in the systematic review with reasons for exclusions at each stage. We will describe the distribution of included studies and the characteristics of participants for variables like location and age. We will compare study-level variables between the studies that we collected data from, to those we could not obtain data from. Drawing on this and factors such as the overall rate of participation of eligible studies, we will assess the potential risk of bias associated with non-availability of IPD.

Additional analyses

We will perform sensitivity analyses to assess the robustness of results according to risk of bias in the study, missing data, and quality or accuracy of individual variables. The accuracy of individual variables will be assessed. For example, gestational age is prone to measurement bias and studies that had a poor methodological approach to measuring it may be excluded to assess robustness. This analysis will be applied to other appropriate covariates.

Discussion

This is the first IPD-MA to investigate the impacts of heat on maternal and child health. The IPD-MA will allow us to explore powered and flexible analysis on the different aspects of heat exposure, in many maternal and child health outcomes, across settings, climate zones, and subgroups in sub-Saharan Africa. The study results will inform the development of an indicator for the effects of heat on maternal and child health, that could be used to track changes in burden of disease over time and for monitoring adaptation responses.

Ethics and dissemination

Ethical consideration and protection of human subjects

The study has been approved by the Wits Human Research Ethics Committee, Johannesburg (220605) and the National Ethics Committee for Life and Health Sciences, Cote d'Ivoire (176-22/MSHPCMU/CNESVS-kp). This study follows key guidelines such as the Helsinki Declaration, South Africa Protection of Personal Information Act, US Department of Health and Human Services (HHS) regulations 45 CFR 46, and other country-specific data protection legislation and ethics guidelines. The key ethical and legal considerations are 1) consent for the use of secondary data for research purposes, 2) risks associated with potentially identifiable information, and 3) cross-border data sharing in accordance with country-specific data protection legislation.

For the use of secondary data, we will review informed consent procedures. If a participant signed ''broad consent'' for the use of their data in future research projects, this will allow data sharing without further ethical approvals. Participants that have signed ''narrow consent'', where sharing of data beyond the initial purpose is not permitted, will be carefully considered. If reconsenting is not feasible, impossible, or would involve a disproportionate effort, an informed consent waiver will be requested from the ethics committee.

Secondly, data may contain indirectly identifiable information like date of birth and location data. We will take steps to minimise the risk of a privacy breach. We will not collect names of participants, and no identifiable data will be published. The data will be safeguarded in a password-protected server with limited access. Lastly, where relevant, we will anonymise data through geographical aggregation and jittering of home addresses, and removal of date of birth once climate variables have been linked.

Lastly, the use of health data requires consideration of specific country legislation on the use of personal data and the cross-border transfer of such datasets. Data providers will be required to provide a contractual assurance in the data sharing agreement that informed consent procedures were followed and that sharing of the data follows applicable data protection legislation.

Dissemination

We will promote the project and its findings, guided by Good Participatory Practice guidelines, among communities where the research was conducted, and among maternal and child healthcare practitioners to promote awareness of heat-health risks. Dissemination tools such as newsletters, project posters, community advisory board discussions, and media will be utilised.

Project results will be disseminated to local, provincial, and national authorities to provide technical support, and potentially inform policies. Many HE^{2}AT IPD investigators are active members of the Climate-Health Africa Network for Collaboration and Engagement (CHANCE), which was established to facilitate a channel of communication and to establish coherence in climate change and health in Africa, which will be utilised for engagement. Our engagement plan includes publications in open-access journals and presentations at conferences/meetings such as the International Society for Environmental Epidemiology and DSI-Africa consortium meetings.

Lastly, anonymised data collected from this study may be made available through open-source platforms, with the permission of data providers, and approval from a HE^{2}AT Center data access committee, to promote future research activities.

Authors' contributions

SL and MFC conceptualised the study with inputs from CJ and SM on the methodology. DPL, MFC, SL, KSC, IS, SM and CJ prepared the original draft with all authors contributing to review and editing. All authors have read and agreed to the published version of the manuscript.

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Competing interests statement

DPL MFC, GM, CP and ZM hold investments in the fossil fuel industry through their pension funds. The University of the Witwatersrand holds investments in the fossil fuel industry through their endowments and other financial reserves.

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Supplementary Files

Table S1: Non-exhaustive list of maternal, fetal, newborn and child variables

Variables	Variables essential for study inclusion	Important variables	Desirable variables
Maternal outcomes	To be eligible, data should be available on at least 2 of the important maternal or neonatal outcome variables	• Gestational age at delivery • Preterm premature rupture of the membranes (PPROM) • Prolonged rupture of membranes (PROM) • Antepartum and postpartum hemorrhage estimated blood loss • Hypertensive disorders in pregnancy - gestational hypertension - preeclampsia - preeclampsia with severe features - eclampsia - HELLP syndrome - blood pressure (systolic/diastolic) - proteinuria • Anaemia in pregnancy - hemoglobin, mean cellular volume, hematocrit	• Duration of labor • Caesarean section - emergency - elective • Abortion - spontaneous (miscarriage) - threatened spontaneous - induced • Oligohydramnios • Placental complications - placental abruption - placenta previa - fetal growth restriction • Sexual and gender-based violence - intimate partner violence • Maternal mortality (including cause) • Hyperemesis gravidarum

Variables	Variables essential for study inclusion	Important variables	Desirable variables
		• Adverse events - serious adverse events (SAEs) • Gestational Diabetes Mellitus (GDM) - glucose level in pregnancy (hemoglobin A1c) - Oral Glucose Tolerance Test (OGTT) • Health facility visits - emergency department visits - hospital admissions • Maternal mental health - emotional stress, maternal global severity index (GSI) - Life Event Scale for Pregnant Women - Patient Health Questionnaire-9 (PHQ-9) - Other validated scales/measures	• Maternal cardiovascular disease - ischemic heart disease - stroke - heart failure • Cardiac arrest • Renal function - Glomerular filtration rate (GFR), urea, creatinine • Liver function - ALAT, ASAT, total bilirubin/conjugated bilirubin, GGT • Maternal peripartum infections - pyelonephritis - puerperal sepsis - chorioamnionitis - Group B streptococcus - urinary tract infection/bacteriuria • Infectious disease - malaria - dengue - TB - Other • Maternal immunization • Maternal caregiving practices

Variables	Variables essential for study inclusion	Important variables	Desirable variables
			• Ectopic pregnancy • HIV status - newly diagnosed, chronic - CD4, viral load - treatment
Fetal, neonatal and child outcomes	To be eligible, data should be available on at least 2 of the important maternal or neonatal outcome variables	• Prematurity (see also gestational age at delivery) • Mortality (including cause) - stillbirth (fresh/macerated) - neonatal - perinatal - child (first two years) • Mother-to-child transmission of HIV (MTCT) • APGAR score • Infant growth - small for gestational age - infant height (<2 years) - failure to thrive - stunting • Admission to neonatal intensive care units or paediatric ward • Intrauterine growth restriction • Ultrasound findings	• Birth - singleton/multiple • Meconium staining • Infant sex • Infant feeding practices - exclusive breastfeeding (if yes, duration) • Fetal distress, hypoxia • Infections - neonatal sepsis - TORCH (toxoplasmosis, other (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex) - group B streptococcus - respiratory tract infection (lower/upper/pneumonia) - diarrhea • Early Child Development (ECD) • Bayley's score (<2 years) • Neonatal jaundice

Variables	Variables essential for study inclusion	Important variables	Desirable variables
			• serum and/or transcutaneous bilirubin levels Congenital anomaly
Other variables	To be eligible, data should be available on: • Date of delivery of the newborn OR date of maternal outcome • Location, at a minimum: city of delivery, or city of follow-up (data on location of household, birth facility, or study clinic are preferable)	• Maternal age • Gravidity, parity • Study intervention or exposure • Maternal anthropometry - Maternal weight, height, BMI, MUAC • Date of interviews or examination • Mode of delivery • Facility of delivery location, or catchment area of facility • Location of research site • Type of facility (community health center/hospital) -	• Time of delivery • Location - home address - rural/urban/peri-urban • Housing type - apartment, house, informal - no. of people in household - air-conditioning access • Socio-economic status or income - personal income - household income • Race, ethnicity • Substance use - Smoking, alcohol, or illicit substances • Employment status • Maternal co-morbidities - chronic medication • Education (highest level achieved) • Marital status • Birth attendant (skilled/unskilled)

Variables	Variables essential for study inclusion	Important variables	Desirable variables
			• Religion • Lost to follow-up • Temperature in healthcare facility, incubator, crib, room

Supplemental File S2: PubMed Search Strategy

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AND ("Ambulances"[MeSH Terms] OR "Health Services Accessibility"[MeSH Terms] OR "Transportation of Patients"[MeSH Terms])) OR (("Travel"[MeSH Terms] OR "delivery of health care/organization and administration"[MeSH Major Topic]) AND ("maternal"[Title] OR "pregnant"[Title] OR "pregnancy"[Title] OR "obstetric"[Title] OR "puerperal"[Title] OR "mother"[Title] OR "childbirth"[Title] OR "labour"[Title] OR "labor"[Title] OR "natal"[Title] OR "post-natal"[Title] OR "pre-natal"[Title] OR "prenatal"[Title] OR "antenatal"[Title] OR "ante-natal"[Title] OR "perinatal"[Title] OR "peri-natal"[Title] OR "puerperal"[Title] OR "puerperium"[Title]))) OR ("ectopic pregnancy"[Title/Abstract] OR "pregnancy, ectopic"[MeSH Terms]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR (("maternal"[Title] OR "pregnant"[Title] OR "pregnancy"[Title] OR "obstetric"[Title] OR "puerperal"[Title] OR "mother"[Title] OR "childbirth"[Title] OR "labour"[Title] OR "labor"[Title] OR "natal"[Title] OR "post-natal"[Title] OR 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"partum"[All Fields] AND "Hemorrhage"[All Fields]) OR "post partum hemorrhage"[All Fields]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "Hemorrhage"[All Fields]) OR "Postpartum Hemorrhage"[All Fields] OR ("post"[All Fields] AND "partum"[All Fields] AND "Haemorrhage"[All Fields]) OR "post partum haemorrhage"[All Fields]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "Hemorrhage"[All Fields]) OR "Postpartum Hemorrhage"[All Fields] OR ("post"[All Fields] AND "partum"[All Fields] AND "Hemorrhage"[All Fields]) OR "post partum hemorrhage"[All Fields]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "Hemorrhage"[All Fields]) OR "Postpartum Hemorrhage"[All Fields] OR ("post"[All Fields] AND "partum"[All Fields] AND "Haemorrhage"[All Fields]) OR "post partum haemorrhage"[All Fields])) OR "obstetric hemorrhage"[Title/Abstract] OR "hypertension, pregnancy induced"[MeSH Terms] OR ("obstructed labor"[Title/Abstract] OR "obstructed labour"[Title/Abstract] OR ("obstetric fistula"[Title/Abstract] OR "obstetric fistulae"[Title/Abstract]) OR ("vaginal fistula"[MeSH Terms] OR "vesicovaginal fistula"[MeSH Terms]) OR ("Obstetric Labor Complications"[MeSH Terms] OR "obstetric labor, premature"[MeSH Terms])) OR (("maternal"[Title] OR "pregnant"[Title] OR "pregnancy"[Title] OR "obstetric"[Title] OR "puerperal"[Title] OR "mother"[Title] OR "childbirth"[Title] OR "labour"[Title] OR "labor"[Title] OR "natal"[Title] OR "post-natal"[Title] OR "pre-natal"[Title] OR "prenatal"[Title] OR "antenatal"[Title] OR "ante-natal"[Title] OR "perinatal"[Title] OR "peri-natal"[Title]) AND ("hypertension"[Title] OR "blood pressure"[Title]) AND ("eclampsia"[Title/Abstract] OR "preeclampsia"[Title/Abstract] OR "HELLP"[Title/Abstract] OR "eclampsia"[MeSH Terms] OR "pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[Title/Abstract]))) OR ("pregnancy complications, hematologic"[MeSH Terms] OR "Pregnancy in Adolescence"[MeSH Terms] OR "pregnancy complications, infectious"[MeSH Terms] OR "pregnancy complications, cardiovascular"[MeSH Terms] OR "Pregnancy Complications"[MeSH Terms] OR "pregnancy, prolonged"[MeSH Terms])))

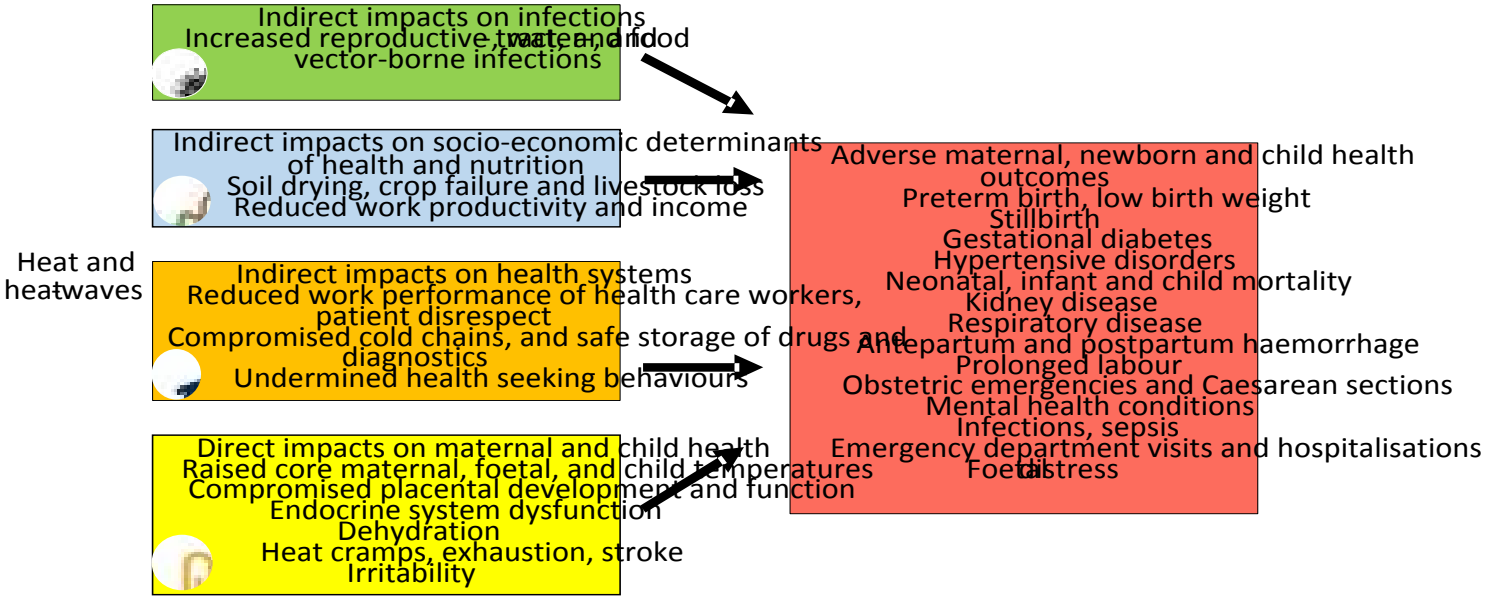

Figure 1: Pathophysiological process of indirect impacts on infections, healthcare systems and socioeconomic determinants of health and nutrition, and direct impacts on maternal and child health

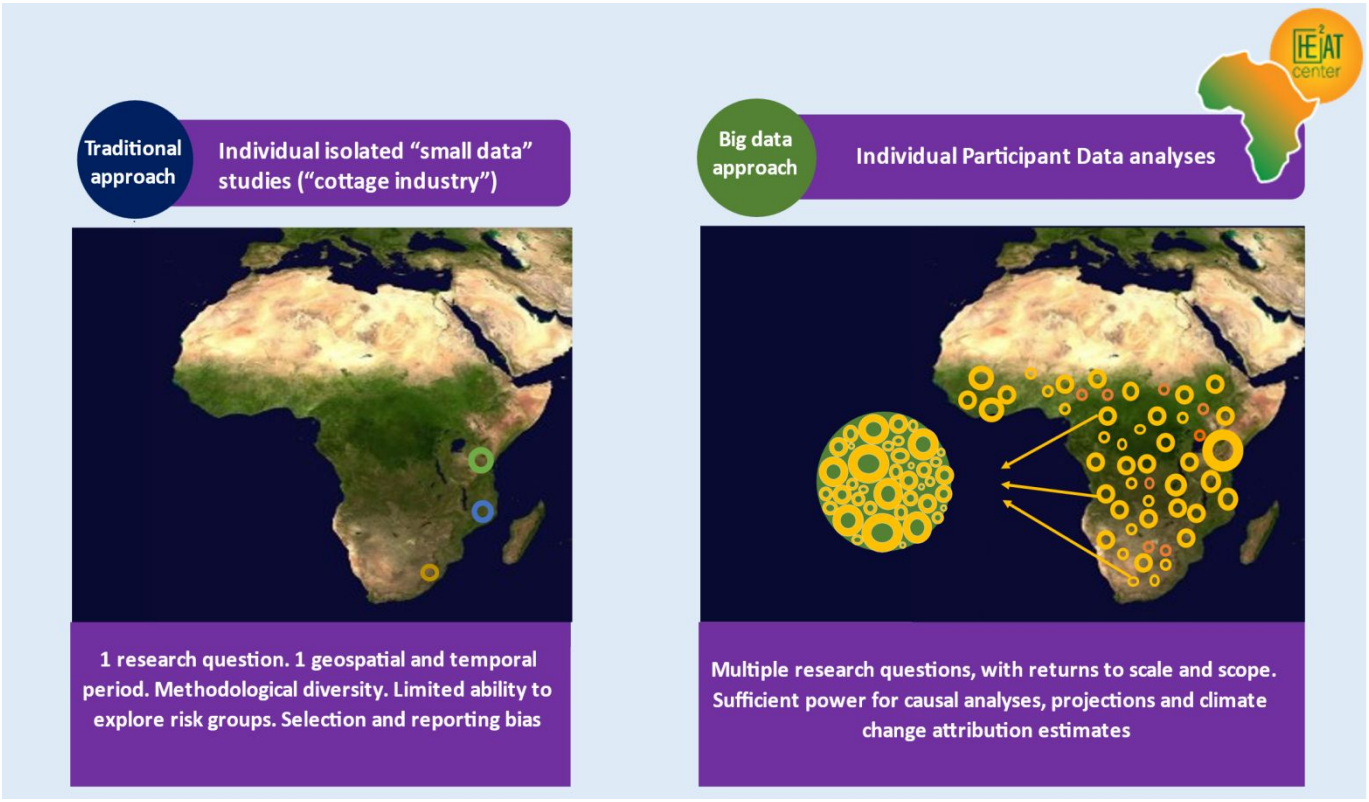

Figure 2: The differences between traditional and IPD analysis approach to heat-health research in sub-Saharan Africa

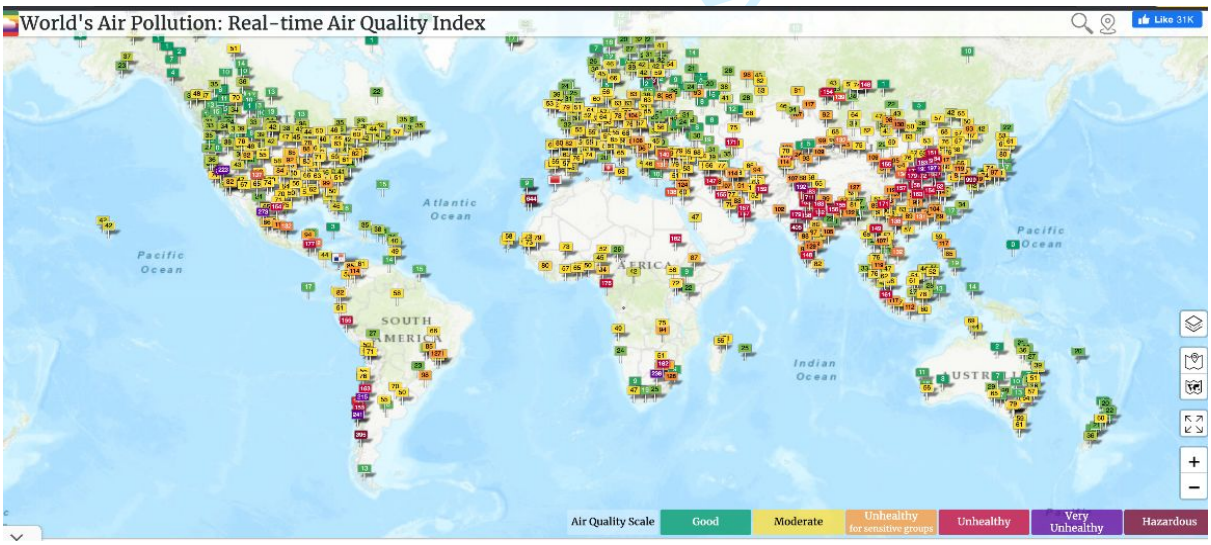

Figure 3 :Real-time air quality index for PM2.5 globally. The map shows the coverage of the monitoring network in Africa (53)

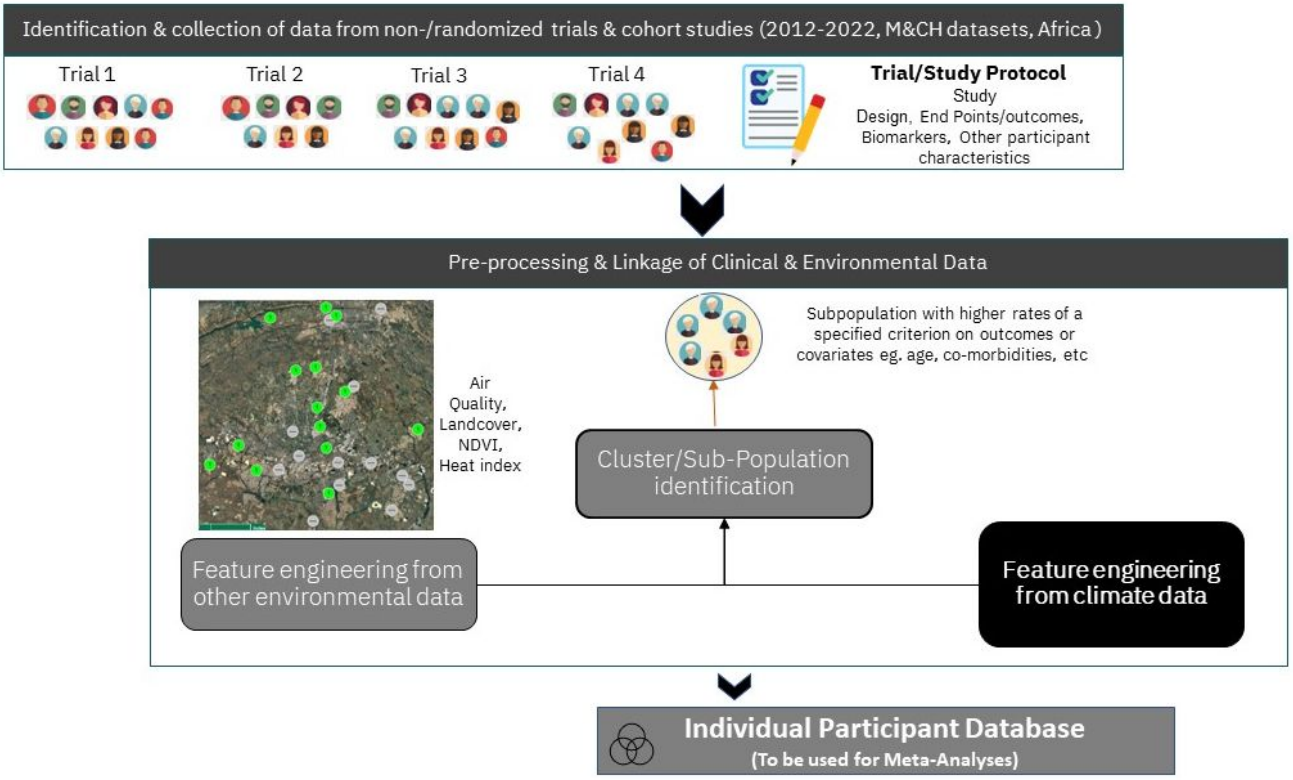

Figure 4: Two phases of the development of the database

PRISMA-IPD Checklist

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD) (68)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	7
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	7
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	7-8
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	7-8

Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	8
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	8 and S1
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	9
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	8-9
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	S1
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	10
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	11
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	11
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	11
Results			

Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	13

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

BMJ Open

Protocol of an Individual Participant Data meta-analysis to quantify the impact of high ambient temperatures on maternal and child health in Africa (HE2AT IPD)

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Protocol of an Individual Participant Data meta-analysis to quantify the impact of high ambient temperatures on maternal and child health in Africa (HE²AT IPD)

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Abstract

Introduction

Globally, recognition is growing of the harmful impacts of high ambient temperatures (heat) on health in pregnant women and children. There remain, however, major evidence gaps on the extent to which heat increases the risks for adverse health outcomes, and how this varies between settings. Evidence gaps are especially large in Africa. We will conduct an Individual Participant Data (IPD) meta-analysis to quantify the impacts of heat on maternal and child health in sub-Saharan Africa. A detailed understanding and quantification of linkages between heat, and maternal and child health is essential for developing solutions to this critical research and policy area.

Methods and analysis

We will use IPD from existing, large, longitudinal trial and cohort studies, on pregnant women and children from sub-Saharan Africa. We will systematically identify eligible studies through a mapping review, searching data repositories, and suggestions from experts. We will obtain the IPD from data repositories, or through collaboration with data providers. Existing satellite imagery, climate reanalysis data and station-based weather observations will be used to quantify weather and environmental exposures. IPD will be recoded, harmonised, and then linked with climate, environmental and socio-economic data by location and time. A one and two-stage analysis method will be adopted using analytical models such as time-to-event analysis, generalised additive models, and machine learning approaches to quantify associations between exposure to heat, and adverse maternal and child health outcomes.

Ethics and dissemination

The study has been approved by two ethics committees. There is minimal risk to study participants. Participant privacy is protected through the anonymisation of data for analysis, secure data transfer, and restricted access. Findings will be disseminated through conferences, journal publications, related policy and research fora, and data may be shared in accordance with data sharing policies of the National Institutes of Health.

PROSPERO registration: CRD42022346068

Strengths and limitations

Strengths

- Prospectively collected data from cohorts and trials provide high quality longitudinal data and contain a large number of variables.
- Longitudinal data enables analysis of temporal relationships between repeated exposure-outcomes data, and more detailed causal analysis modelling than data collected at a single time point.
- The large IPD dataset will have statistical power to assess rare exposures and outcomes, explore high risk sub-groups, and make risk comparison across different areas/regions/countries, enhancing the study's external power and generalisability.

Limitations

- Our dataset may not be representative of the entire continent as data availability reflects research capacity across countries and not necessarily size of population, or urban-rural make-up, for example.

  Missing data may occur due to reliance on the willingness of investigators to share data, however, this bias may be non-differential as the included studies had assessed different exposure outcome relationships than in our study.

Introduction

Background

Climate change is one of the greatest global health threats ever faced by humanity (1, 2). Increasing anthropogenic greenhouse emissions have caused the mean temperature of the world to rise by more than 1°C, and by as much as 2°C in many parts of Africa (3-5). Projected temperature increases in both average temperatures and extreme events, such as heat-waves, are especially concerning. Some estimates indicate that half of the global population will be exposed to more than 20 days of deadly heat per year by 2100 (6), but recent heat extreme suggest these figures may be an under-estimate.

The climate change crisis, and heat in particular, has a wide range of deleterious effects on health. The indirect impacts of rising temperatures are well documented, such as an expanding geographical range of malaria vectors (7-9) and increased soil drying leading to food insecurity and malnutrition. Heat also indirectly affects health by fomenting wildfires, which destroy ecosystems and infrastructure (10, 11).

The direct impacts on human health due to exposure to high ambient temperatures (referred hereafter as heat) are increasingly recognised and affect a range of vulnerable populations (2). Heat-waves cause increased rates of emergency room visits and hospitalisations, with an accompanying escalation in healthcare costs (12), and result in substantial excess mortality. Moreover, the mental health sequelae of heat exposure are considerable, including generalized anxiety, depression, and eco-anxiety (3, 13).

Heat exposure impacts on maternal and child health

Heat is hazardous for high-risk populations, including pregnant women and children (Figure 1). The physiological and anatomical changes in pregnancy, pregnancy-related weight gain, and heat generated by foetal metabolism and exertion during labour, makes it challenging for pregnant women to maintain a normal temperature range when exposed to heat (14, 15). Manifestations of heat exposure include adverse pregnancy and birth outcomes, such as preterm birth, low birth weight, stillbirths (13), gestational diabetes (16, 17), and hypertension in pregnancy (18). Proposed biological mechanisms underlying the impact of heat on preterm birth include a reduction in placental blood flow, dehydration, and inflammatory responses. However, further research is required to describe these biological mechanisms.(15)

Children, and particularly infants, have physiological, anatomic, and social factors that increase their vulnerability to heat, such as increased body surface to volume ratio, higher metabolic rate, and reliance on a caregiver (19-21). Multiple studies have demonstrated a detrimental effect of heat on mortality (19, 22-26), kidney disease (27), asthma and other respiratory disease (28), and infectious diseases (29, 30). A modelling paper reported that under the high-emission scenario, heat-related child mortality in Africa may exceed 38,000 deaths per year in 2049 (31).

Several studies, have shown that exposure to heat *in utero* negatively affects health throughout the life course, such as increased risks of stunting (32). The consequences also extend to the larger health systems by increasing the burden on already stretched health resources due to increased rates of caesarean sections (33), hospitalisation (34), emergency department visits (35, 36), and out-and in-patient health facility visits (37-39).

Research gaps

Research on heat and health has been mostly restricted to stand-alone individual studies with relatively small sample sizes, poor-quality data from household surveys or healthcare facilities, considerable variation in research methodology, and limited geographical and temporal coverage (13, 19). Most studies have insufficient power to answer questions about which specific aspects of heat exposures (e.g., timing and duration), which temperature

patterns/thresholds (e.g., night- or day-time, or averages) are most harmful for different clinical conditions, and in which climate zones, settings and subgroups.

Although some of the world's largest clinical trials have been conducted in Africa (40), very little work has focused on heat impacts in key African population groups, such as pregnant women and children. Given the unique demographic profile, disease spectrum, built environment, and resource constraints in Africa, the most at-risk groups will likely differ from those in the Global North.

Rationale for the Individual Participant Data Meta-Analysis

We will conduct an Individual Participant Data (IPD) meta-analysis using data collected from longitudinal cohorts and clinical trials on maternal and child health across sub-Saharan Africa. We will use the IPD to quantify the current and future impacts of heat on maternal and child health in sub-Saharan Africa. Individual-level information enables more flexible and robust analyses than are possible in systematic reviews using aggregate study results from published data (Figure 2) (41, 42). The advantages of the IPD methodology are especially apparent in heat-health research, where larger sample sizes are required to detect relatively small exposure effects, and effects on rare outcomes.

Public health relevance of the study findings

The study results aim to better understand the heat-health associations among pregnant women and children and will inform the monitoring of the heat-health burden, such as through indicators that could be used in a District Health Information System. Understanding the historical patterns of heat-health impacts is an important step towards monitoring changes in disease burden over time and projecting future burdens under different climate change scenarios and adaptation responses. By performing adequately powered and high-quality 'impact' studies, we will generate the information required to calculate the burden of disease from climate change. This, in turn, strengthens arguments for allocating sufficient resources to address climate-related impacts, and for hastening societal changes required to avert further climate breakdown.

The study forms part of the Data Science Initiative Africa (DS-I Africa) (43) which aims to make optimum use of existing data resources across Africa to address the most pressing health concerns on the continent. The study constitutes one of two research projects within the HEat and HEalth African Transdisciplinary Center (HE^2AT Center)(44) project funded through the DS-I Africa Program.

Study objectives

The study's overall objective is to use innovative data science approaches to quantify the current and future impacts of heat exposure on maternal and child health in sub-Saharan Africa.

The specific objectives are:

1. To systematically identify, acquire, collate, and integrate prospectively collected data from cohort studies and clinical trials on maternal and child health in sub-Saharan Africa
2. To link maternal and child health outcome data spatially and temporally with weather and other environmental data, as well as socio-economic and other data
3. To utilise classic statistical and novel machine learning approaches to understand and quantify the impact of heat exposure on maternal and child health
4. To document variations in the relationship between heat exposure and maternal and child health outcomes across different climate zones, settings, and population sub-groups

5. To develop innovative data science solutions for district-level surveillance of the impacts of heat on health

Methods and analyses

Study design and protocol registration

The IPD-MA will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) IPD extension guidelines (45). The study began in June 2022, and we plan to conclude in June 2026. We completed the mapping review, started contacting data providers, and received thirteen datasets. No analyses have been conducted. The protocol has been registered in PROSPERO (registration number: CRD42022346068).

Study population

The study population are women in sub-Saharan Africa in pregnancy, childbirth and up to two years postpartum, and their children up to two years of age, exposed to heat.

Eligibility criteria

Eligibility is determined at the study- and individual-level. Study-level inclusion criteria are:

1. Enrolment of at least 1000 pregnant women in one or more study sites, in one or more countries in sub-Saharan Africa
2. Identified through published literature (published between January 2012 and June 2022) from the systematic mapping, clinical trial registry, data repository, or from study investigators and experts
3. Randomised or non-randomised clinical trial, or an observational or interventional cohort with prospectively collected data
4. At least two of the 'key' maternal and/or child health outcome variables[1] have been collected as part of the study (Supplementary File 1)
5. Relevant local ethics approvals received, and documented

At the individual level, the following inclusion criteria apply:

1. Enrolment into an eligible study, during pregnancy, or intrapartum
2. IPD is available on the newborn's date of birth, date of diagnosis/occurrence of an adverse health outcome, or date of the end of pregnancy in cases of maternal deaths or abortion
3. IPD is available on location of birth, or study follow-up

Rationale for eligibility criteria

Longitudinal data from clinical trials and cohort studies allows for the assessment of temporal trends and may avoid exposure biases as women are followed up over time, whereas in birth registries for example, the women may have given birth in a place that is some distance away from where she spent much of her pregnancy.

The study only includes cohorts/trials that enrolled more than 1000 participants given that the large amount of time and resources required for data acquisition, preparation, harmonisation, and analysis of each individual study makes it difficult to justify the inclusion of smaller studies. Additionally, a large sample size is required for adequately powered studies for heat-health effect estimates that can be small. We selected recent studies

[1] Key maternal and child health outcomes have been selected based on evidence of heat-health impacts, an in alignment with the top causes of maternal and child mortality in sub-Saharan Africa.

published between 2012 and 2022 to ensure data availability, quality, and relevance. Earlier studies may have used outdated clinical definitions and diagnostic criteria for adverse outcomes, which could complicate data harmonisation. Limiting the time frame improves our ability to identify data providers and their datasets, while also enhancing the quality of available environmental exposure data.

We are including studies where women are enrolled during pregnancy and intrapartum and including child data to the age of two years, if they are followed up as part of the study. Our primary focus is on heat exposure during pregnancy and intrapartum, and how that affects the pregnant mother and their child. Additionally, enrolling women in pregnancy may increase the likelihood of acquiring more accurate gestational age data, to explore windows of susceptibility.

Data sources

Firstly, we draw on studies identified through a systematic mapping. The search was conducted in 2020 in MEDLINE (PubMed) and updated in 2022, using controlled vocabulary and free-text terms to identify studies. Search terms for maternal health, for World Bank defined sub-Saharan African countries, and for filters to locate cohorts and clinical trials were included (Supplementary File 2) (46). The search strategy replicates those used in MASCOT-1, which mapped global maternal health literature from 2000 to 2012 (40, 47-50).

Using EPPI-Reviewer software (51), screening of titles and abstracts was done independently, in duplicate, with differences between reviewers reconciled through discussion, or by a third reviewer. The full text was screened if eligibility could not be ascertained from the title or abstract. We extracted the following variables:

- Population: country, number enrolled
- Methods: study design, topic
- Identifiers: name, acronym, clinical registration number, authors, funders

The second way we identify studies is through data repositories, such as the Bill and Melinda Gates Foundation Knowledge Integration platform, National Institutes of Health repositories, and ClinicalTrials.gov. Lastly, we will seek additional studies, published and unpublished, through direct contact with data providers and other experts.

Risk of bias assessment

The quality of the studies will be evaluated using the Cochrane risk-of-bias tool for randomised trials (RoB 2), and the risk of bias in non-randomised studies of intervention (ROBINS-I) for cohorts or non-randomised trials. Each study and outcome will have an overall grading, which will be considered in meta-analysis and sensitivity analyses.

Data collection

Acquisition of individual participant data

Data will be acquired either through data access platforms such as Worldwide Antimalarial Resistance Network (WWARN) (52), or directly from data providers. We will make at least five attempts to contact study investigators, including through contacting first, last, and other authors, and funders, through multiple communication platforms such as email, phone calls, and LinkedIn. Reasons for unattainable IPD will be included in a flowchart, such as the inability to contact data providers, unwillingness to share data, or the destruction of data. Data providers who agree to join the collaboration will sign a data sharing agreement that sets out the terms of data sharing, data security, and authorship guidelines. Opportunities for authorship, networking and collaboration in study activities will be outlined and continually communicated. Collaborators will supply meta-data and key documentation, which will be

used to confirm eligibility and for data management. Key documentation will include the full study protocol, informed consent forms, codebook, and the ethics approval.

Acquisition of environmental exposure data

Weather data include observational-based datasets (weather station, or satellite remote sensing[2]) and processed or gridded observations. Climate-related data will mostly involve accessing open data repositories such as Copernicus Climate Data Store (CDS) or Earth System Grid Federation data systems.

Air pollution data will be obtained from proxy satellite-derived air quality data such as Aerosol Optical Depth (AOD), in combination with land cover use, to overcome the challenge of gaps in the coverage of ground-based stations (Figure 3). Where available, we will use data on pollutant concentrations, namely PM_{10}, $PM_{2.5}$, NO_2, SO_2 and CO for developing indices of air quality as well as leveraging global databases of air quality indicators such as the World Air Quality Index (53) and OpenAQ (54).

Data management and analysis

Database development

In Figure 4, we outline the steps that will result in the comprehensive database formation. In the first phase, the focus is on collecting IPD and metadata, and data quality and integrity. Once a data transfer agreement has been signed, IPD will be transferred to a password protected platform using a secure data transfer.

Data from multiple studies will be characterised by differences in quality and this will be addressed before the synthesis phase of the meta-analysis, using PRIME-IPD: (55) Processing, Replication, Imputation, Merging, and Evaluation.(Table 1).

PRIME	Items
Processing	Convert data into single format for statistical program of choice Compare the total number of participants in the acquired datasets to those reported in published articles Verify the presence of the variables of interest in the acquired dataset Standardise variable names across datasets Identify and standardise the measurement scales used to report the variables of interest Identify and standardise coding for missing values Identify and correct any implausible values that may result from data conversion
Replication	Recalculate reported descriptive and summary statistics using the acquired datasets Calculate the standardised difference to quantitively assess the difference between the replicated and published results If the standardised difference is >10%, investigate and address potential causes
Imputation	Assess the appropriateness of conducting imputation of missing data using missing data theory If multiple imputation is conducted, carefully consider the number of imputations to be run
Merging	Ensure in processing step that variable order and codes are correct

[2] Remotely sensed data from satellite sensors, mainly optical imagery (e.g., satellite images of urban centres), provide information about physical attributes such as land surface temperature, vegetation characteristics, and land use.

	Merge the imputed dataset into a single, pooled dataset, taking into consideration the number of imputed datasets, if appropriate
Evaluation	Assess continuous variables for normality by residual analysis either visually or by statistical tests If required, calculate new variables for standardised comparison of effects

Table 1: Checklist for PRIME-IPD tool (58)

Data harmonisation

We expect that the number of covariates for each study will be large and variable across studies. The harmonisation step will identify these discrepancies and formulate a strategy, mainly the creation of proxy covariates. The health covariates will be defined using published, reputable sources such as World Health Organisation (WHO), the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) terminology (56), standard ontologies, and local obstetric and paediatric guidelines.

The second phase of database formation, which runs parallel to the first, will consist of pre-processing climate, socioeconomic and environmental data, to derive variables that will be included in the harmonised health database. The climate data are linked to time (e.g., date of birth, or date of health event) and location. Where we have high resolution location information (GPS coordinates, home addresses), we will aggregate up to the appropriate administrative level that will minimise exposure mischaracterisation while protecting the privacy of individual participants. Once climate data are merged with health data, potentially identifiable information such as date of birth and location will be removed from the integrated dataset to further protect participant confidentiality. To produce higher resolution daily temperature estimates, we will additionally combine satellite data, ERA5 land daily temperatures, and weather station data. In this context, further advances based on the exploitation of recent developments in geospatial artificial intelligence (geoAI) will be utilised. Some of the approaches that the team will implement include natural gradient boosting algorithms (57), and quantile random forest spatial interpolations (58), with implementation of maximum covariance analysis (59) to detect the structure of the covariance between these various forms of spatiotemporal datasets.

These two phases will result in an individual participant database consisting of health outcome variables, demographic covariates, and climate and environmental covariates. The integrated datasets will be made available to HE²AT Center partners for analysis through an access controlled, Jupyter Hub platform that is managed by the HE²AT Center data management and analysis core.

Statistical analysis

The baseline characteristics of participants from each of the cohorts or trials will be described using R or Python (60, 61). A two-stage analysis approach will be used primarily, whereby, in the first stage, each study is analysed individually. In the second stage, the data from the individual studies will be aggregated to provide an overall pooled estimate of effect. We will explore analysing each study independently, and in combination with other studies through pooled analyses. We will evaluate heterogeneity of effects and precision of effect estimates to inform our approach.

Statistical method for the first stage of the meta-analysis

The core modelling method for this study is linear and non-linear distributed lag models (62). These models are specifically relevant where the outcome variable is a time series, typical with counts of adverse events such as preterm births. The most valuable characteristics of advanced forms of these models, such as the semi-parametric generalised additive model (GAM) following a quasi-Poisson distribution with a distributed lag non-linear model is the ability to account for non-linear, short-term, and lagged effects of environmental exposures

on health outcomes (57). In general, the GAM framework provides the flexibility to account for non-linearity and over-dispersions in the temporal dimension and clustering in the spatial dimension. The additive modelling framework may be expanded further to account for multiple health outcomes, associated uncertainties (58), spatial effects, and interactions (59, 63). Therefore, large geospatial (and spatiotemporal) climate data from satellites and sensor networks can be leveraged. Further, depending on the type of outcome and duration of exposure, we will use additional statistical methodologies such as case-crossover, time-to-event, and longitudinal random forest methodologies. The case-crossover study design, commonly utilised to assess short-term environmental exposures and health outcomes, adjusts for all observed and unobserved individual level confounders as each case serves as its own control. Time-to-event analyses increases statistical power as all participants at risk are included, there is control of temporal trends (e.g., gestational age), and it can be used to investigate windows of susceptibility (64). Longitudinal random forests are a machine learning approach that can be used to identify longitudinal exposure-related predictors of health (65). In addition, the attributable risk of heat to adverse outcomes will be calculated as per IPCC-described methodologies.

Machine learning informed covariate selection

We will consider traditional variable selection approaches for large data, as well as tree-based ensemble learning approaches, namely extreme gradient boosted trees or random forest algorithms. For both approaches, there is a split of the dataset into a training and testing set, the implementation of the tree algorithm and the evaluation of the variable importance ranking, and the possibility to use partial dependence plots to identify the functional form between pairwise or multiple covariates (including interactions) and the response variable. Both forms of tree algorithms can be used for binary, continuous, and time-to-event response variables. While autoencoding algorithms may be implemented for feature engineering from the geospatial or spatiotemporal climate datasets, ensemble tree algorithms may be used for automatic feature (covariate) selection, maintaining a level of explainability required when trying to understand the health effects of environmental exposures (66).

Statistical methods for the second stage of meta-analysis

Using the statistical methods described above, the association between health outcomes of interest and heat exposure for each study will be performed and a summary statistic presented to describe the estimated effects. The summary statistic will differ depending on the outcome and the analysis method used.

In the second stage, a weighted average of the effects of heat on maternal and child outcomes will be calculated, if levels of statistical heterogeneity are acceptable, and illustrated in a forest plot.

Exploration of variation in effects across studies and sub-groups

Exploration of variation in effects will be done involving stratified analyses within the following strata: study, geographical area, climate zone, time period, and income group of the country. Data will also be stratified on individual characteristics, such as maternal age, socio-economic status, sex, and health conditions such as HIV status. In these analyses, we generate estimates of impact (aggregate data) for each stratum separately and then combine these summary statistics using standard meta-analysis methods, if appropriate.

Risk of bias across the IPD sources

Using the PRISMA-IPD flow chart, we will report the numbers of studies screened and included in the IPD, giving reasons for exclusions. We will describe the distribution of studies and the characteristics of participants for variables like location and age. We will compare study-level variables between the studies that we collected data from, to those we could not. Drawing on this and factors such as the overall rate of participation in eligible

studies, we will assess the potential risk of bias associated with non-availability of IPD from some studies.

Additional analyses

We will perform sensitivity analyses to assess the robustness of results according to risk of bias, missing data, and quality of individual variables. For example, gestational age is prone to measurement bias and studies that had a poor methodological approach to measuring it may be excluded.

The expected outcomes of the study based on our primary and secondary hypotheses are summarised in Supplementary File 3.

Discussion

This is the first IPD-MA to investigate the impacts of heat exposure on maternal and child health. The IPD-MA will allow us to explore powered and flexible analyses on different aspects of heat exposure, in many maternal and child health outcomes, across diverse settings, climate zones, and subgroups in sub-Saharan Africa. The study results will inform monitoring efforts focused on the effects of heat on maternal and child health, that could be used to track changes in burden of disease over time and for assessing adaptation responses.

We acknowledge the potential limitations in the study design. Our IPD-MA may not be geographically representative due to differing research capacity across sub-Saharan African countries. We may not encounter the typical publication bias which occur with meta-analyses of published data as we draw on databases regardless of whether the exposure-outcome of interest has been reported or if information is available on the presence or size of the association (41).Nonetheless, we recognize the potential for published studies to be impacted by publication bias in the outcomes that the study had evaluated.

Further, we are limited to IPD shared by willing investigators from historical studies. We cannot avoid potential biases of the study characteristics (e.g., selection bias by age of study) and of the quality of data collected, which may potentially vary by country, and thus climate zones. Lastly, our study may be at risk of exposure misclassification, common in heat-health research. Individual heat exposure will not have been collected and we assume women remain in one location throughout the study. To mitigate this risk, we employ longitudinal studies ensuring prolonged participant follow-up, leverage appropriate spatiotemporal scales for environmental data, use heat indices to represent heat strain, and may include housing type in some analyses where information is available.

Ethics and dissemination

Ethical consideration and protection of human subjects

The study has been approved by the Wits Human Research Ethics Committee, Johannesburg (220605) and the National Ethics Committee for Life and Health Sciences, Cote d'Ivoire (176-22/MSHPCMU/CNESVS-kp). This study follows key guidelines such as the Helsinki Declaration, South Africa Protection of Personal Information Act, US Department of Health and Human Services (HHS) regulations 45 CFR 46, and other country-specific data protection legislation and ethics guidelines. The key ethical and legal considerations are 1) consent for the use of secondary data for research purposes, 2) risks associated with potentially identifiable information, and 3) cross-border data sharing in accordance with country-specific data protection legislation.

For the use of secondary data, we will review informed consent procedures. If a participant signed ''broad consent'' for use of their data in future research projects, this will allow data sharing without further ethical approvals. Participants that have signed ''narrow consent'', where sharing of data beyond the initial purpose is not permitted, will be carefully considered. If reconsenting is not feasible, impossible, or would involve a disproportionate effort, an informed consent waiver will be requested from the ethics committee.

Secondly, data may contain indirectly identifiable information like date of birth and location. We will take steps to minimise the risk of a privacy breach. We will not collect names of participants, and no identifiable data will be published. The data will be safeguarded in a password-protected server with limited access. Lastly, where relevant, we will anonymise data through geographical aggregation, jittering of home addresses, and removal of date of birth once climate variables have been linked.

Lastly, the use of health data requires consideration of specific country legislation on the use of personal data and the cross-border transfer of such datasets. Data providers will be required to provide a contractual assurance in the data sharing agreement that informed consent procedures were followed and that sharing of the data follows applicable data protection legislation.

Dissemination

We will promote the project and its findings, guided by good participatory practice guidelines, among communities where the research was conducted, and among maternal and child healthcare practitioners to promote awareness of heat-health risks. Dissemination tools such as newsletters, project posters, community advisory board discussions, and media will be utilised.

Project results will be disseminated to local, provincial, and national authorities to provide technical support, and potentially inform policies. Many HE^{2}AT IPD investigators are active members of the Climate-Health Africa Network for Collaboration and Engagement (CHANCE), which facilitates communication among policy makers in Africa, and aims to enhance coherence in climate change and health policy across countries in Africa, which will be utilised for engagement. Our engagement plan includes publications in open-access journals and presentations at conferences/meetings.

Lastly, anonymised data collected from this study may be made available through open-source platforms, with the permission of data providers, and approval from a HE^{2}AT Center data access committee, to promote future research activities.

Authors' contributions

SL and MFC conceptualised the study with inputs from CJ and SM on the methodology. DPL, MFC, SL, KSC, IS, SM and CJ prepared the original draft. DPL, MFC, CJ, GM, GC, IS, KE, KSC, CD, PTM, LvA, BRJ, KAM, MI, SM and SL have contributed to reading, review, and editing of manuscript drafts and have agreed to the published version of the manuscript. The HE^{2}AT Center IPD Study Group are contributors to the project.

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Competing interests statement

DPL MFC, GM, CP and ZM hold investments in the fossil fuel industry through their pension funds. The University of the Witwatersrand holds investments in the fossil fuel industry through their endowments and other financial reserves.

Figure captions

Figure 1: Indirect and direct heat and heat-wave effects on maternal and child health

Figure 2: The differences between traditional and IPD analysis approach to heat-health research in sub-Saharan Africa

Figure 3: Real-time air quality index for PM2.5 globally. The map shows the coverage of the monitoring network in Africa (53)

Figure 4: Two phases of development of the database

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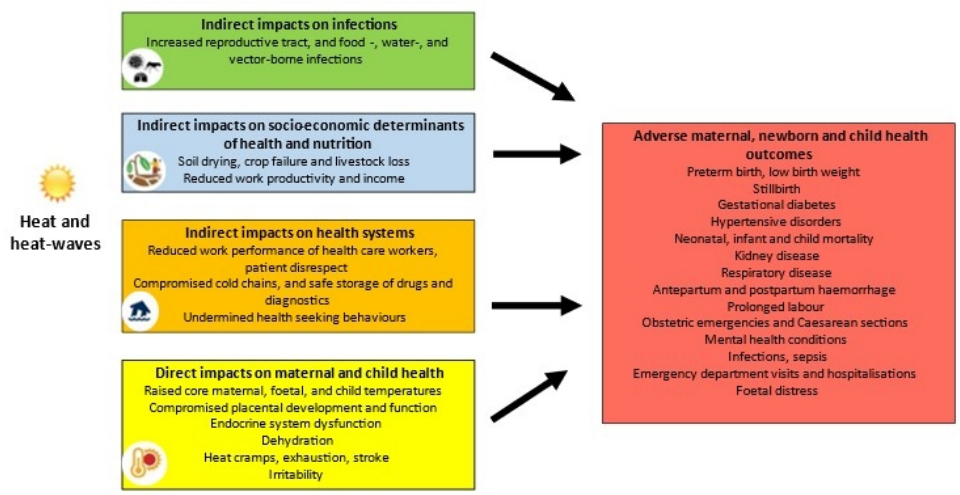

Figure 1: Indirect and direct heat and heat-wave effects on maternal and child health

64x33mm (300 x 300 DPI)

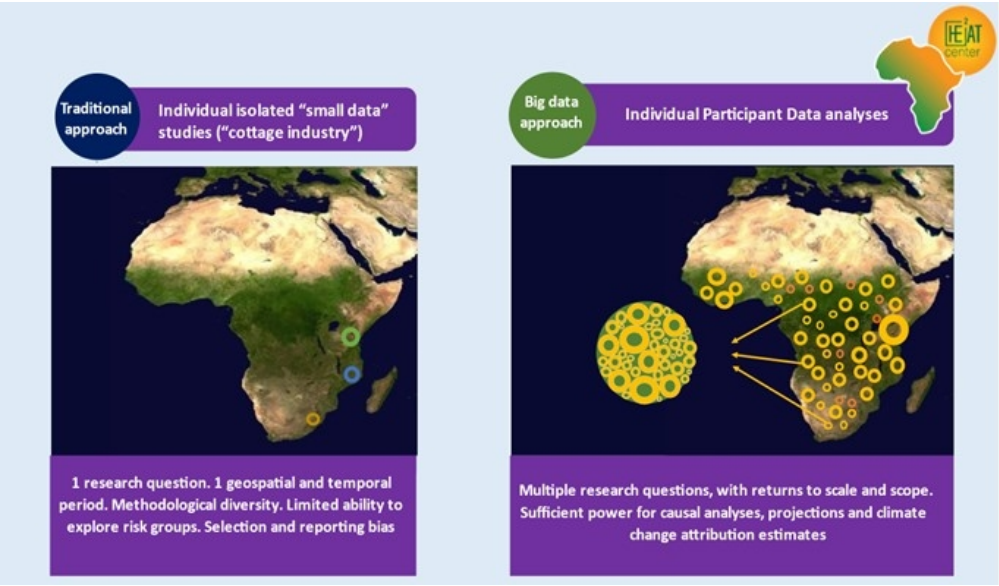

Figure 2: The differences between traditional and IPD analysis approach to heat-health research in sub-Saharan Africa

57x33mm (300 x 300 DPI)

Figure 3: Real-time air quality index for PM2.5 globally. The map shows the coverage of the monitoring network in Africa (53)

50x22mm (300 x 300 DPI)

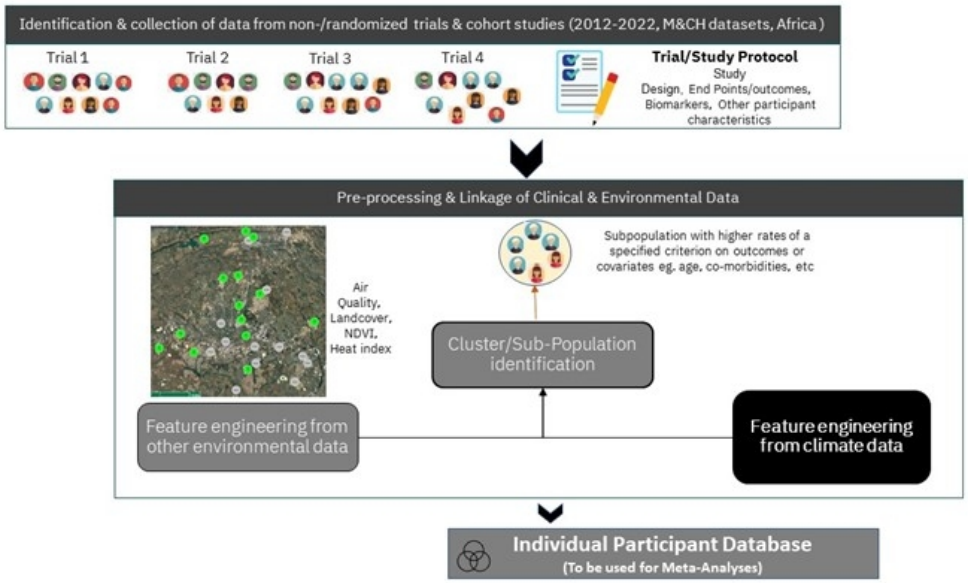

Figure 4: Two phases of development of the database

56x34mm (300 x 300 DPI)

Supplementary Files

Supplementary File 1: Non-exhaustive list of maternal, fetal, newborn and child variables

Variables	Variables essential for study inclusion	Key data variables	Additional data variables of interest
Maternal outcomes	To be eligible, data should be available on at least 2 of the important maternal or neonatal outcome variables	• Gestational age at delivery • Preterm premature rupture of the membranes (PPROM) • Prolonged rupture of membranes (PROM) • Antepartum and postpartum hemorrhage estimated blood loss • Hypertensive disorders in pregnancy - gestational hypertension - preeclampsia - preeclampsia with severe features - eclampsia - HELLP syndrome - blood pressure (systolic/diastolic) - proteinuria • Anaemia in pregnancy - hemoglobin, mean cellular volume, hematocrit • Adverse events - serious adverse events (SAEs) • Gestational Diabetes Mellitus (GDM) - glucose level in pregnancy (hemoglobin A1c) - Oral Glucose Tolerance Test (OGTT) • Health facility visits - emergency department visits - hospital admissions • Maternal mental health - emotional stress, maternal global severity index (GSI) - Life Event Scale for Pregnant Women	• Duration of labor • Caesarean section - emergency - elective • Abortion - spontaneous (miscarriage) - threatened spontaneous - induced • Oligohydramnios • Placental complications - placental abruption - placenta previa - fetal growth restriction • Sexual and gender-based violence - intimate partner violence • Maternal mortality (including cause) • Hyperemesis gravidarum • Maternal cardiovascular disease - ischemic heart disease - stroke - heart failure • Cardiac arrest • Renal function - Glomerular filtration rate (GFR), urea, creatinine • Liver function - ALAT, ASAT, total bilirubin/conjugated bilirubin, GGT • Maternal peripartum infections

Variables	Variables essential for study inclusion	Key data variables	Additional data variables of interest
		- Patient Health Questionnaire-9 (PHQ-9) - Other validated scales/measures	- pyelonephritis - puerperal sepsis - chorioamnionitis - Group B streptococcus - urinary tract infection/bacteriuria • Infectious disease - malaria - dengue - TB - Other • Maternal immunization • Maternal caregiving practices • Ectopic pregnancy • HIV status - newly diagnosed, chronic - CD4, viral load - treatment
Fetal, neonatal and child outcomes	To be eligible, data should be available on at least 2 of the important maternal or neonatal outcome variables	• Prematurity (see also gestational age at delivery) • Mortality (including cause) - stillbirth (fresh/macerated) - neonatal - perinatal - child (first two years) • Mother-to-child transmission of HIV (MTCT) • APGAR score • Infant growth - small for gestational age - infant height (<2 years) - failure to thrive - stunting • Admission to neonatal intensive care units or paediatric ward • Intrauterine growth restriction	• Birth - singleton/multiple • Meconium staining • Infant sex • Infant feeding practices - exclusive breastfeeding (if yes, duration) • Fetal distress, hypoxia • Infections - neonatal sepsis - TORCH (toxoplasmosis, other (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex) - group B streptococcus - respiratory tract infection (lower/upper/pneumonia) - diarrhea • Early Child Development (ECD) • Bayley's score (<2 years)

Variables	Variables essential for study inclusion	Key data variables	Additional data variables of interest
		• Ultrasound findings	• Neonatal jaundice • serum and/or transcutaneous bilirubin levels Congenital anomaly
Other variables	To be eligible, data should be available on: • Date of delivery of the newborn OR date of maternal outcome • Location, at a minimum: city of delivery, or city of follow-up (data on location of household, birth facility, or study clinic are preferable)	• Maternal age • Gravidity, parity • Study intervention or exposure • Maternal anthropometry - Maternal weight, height, BMI, MUAC • Date of interviews or examination • Mode of delivery • Facility of delivery location, or catchment area of facility • Location of research site • Type of facility (community health center/hospital) -	• Time of delivery • Location - home address - rural/urban/peri-urban • Housing type - apartment, house, informal - no. of people in household - air-conditioning access • Socio-economic status or income - personal income - household income • Race, ethnicity • Substance use - Smoking, alcohol, or illicit substances • Employment status • Maternal co-morbidities - chronic medication • Education (highest level achieved) • Marital status • Birth attendant (skilled/unskilled) • Religion • Lost to follow-up • Temperature in healthcare facility, incubator, crib, room

Supplementary File 2: PubMed search strategy

2012/09/01:2020/10/07[Date - Create] AND (("cohort studies"[MeSH Terms:noexp] OR "longitudinal studies"[MeSH Terms:noexp] OR "follow up studies"[MeSH Terms:noexp] OR "prospective studies"[MeSH Terms:noexp] OR "retrospective studies"[MeSH Terms:noexp] OR "cohort"[Title/Abstract] OR "longitudinal"[Title/Abstract] OR "prospective"[Title/Abstract] OR "retrospective"[Title/Abstract] OR ((("Clinical Trial"[Publication Type] OR "Clinical Trials as Topic"[MeSH Terms] OR "clinical trials"[All Fields]) AND "Clinical Trial"[Publication Type:noexp]) OR "clinical trial, phase i"[Publication Type] OR "clinical trial, phase ii"[Publication Type] OR "clinical trial, phase iii"[Publication Type] OR "clinical trial, phase iv"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "multicenter study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "Clinical Trials as Topic"[MeSH Terms:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[MeSH Terms] OR (("randomised"[Title/Abstract] OR "randomized"[Title/Abstract]) AND ("trial"[Title/Abstract] OR "trials"[Title/Abstract])) OR (("single"[Title/Abstract] OR "double"[Title/Abstract] OR "doubled"[Title/Abstract] OR "triple"[Title/Abstract] OR "tripled"[Title/Abstract] OR "treble"[Title/Abstract] OR "treble"[Title/Abstract]) AND ("blind*"[Title/Abstract] OR "mask*"[Title/Abstract])) OR ("4 arm"[Title/Abstract] OR "four arm"[Title/Abstract]) OR "incidence"[MeSH Terms:noexp] OR "incidence"[Title/Abstract])) AND ("angola"[MeSH Terms] OR "benin"[MeSH Terms] OR "botswana"[MeSH Terms] OR "burkina faso"[MeSH Terms] OR "burundi"[MeSH Terms] OR "cabo verde"[MeSH Terms] OR "cameroon"[MeSH Terms] OR "central african republic"[MeSH Terms] OR "chad"[MeSH Terms] OR "comoros"[MeSH Terms] OR "democratic republic of the congo"[MeSH Terms] OR "congo"[MeSH Terms] OR "cote d ivoire"[MeSH Terms] OR "djibouti"[MeSH Terms] OR "equatorial guinea"[MeSH Terms] OR "eritrea"[MeSH Terms] OR "eswatini"[MeSH Terms] OR "ethiopia"[MeSH Terms] OR "gabon"[MeSH Terms] OR "gambia"[MeSH Terms] OR "ghana"[MeSH Terms] OR "guinea"[MeSH Terms] OR "guinea bissau"[MeSH Terms] OR "kenya"[MeSH Terms] OR "lesotho"[MeSH Terms] OR "madagascar"[MeSH Terms] OR "malawi"[MeSH Terms] OR "mali"[MeSH Terms] OR "mauritania"[MeSH Terms] OR "mozambique"[MeSH Terms] OR "namibia"[MeSH Terms] OR "niger"[MeSH Terms] OR "nigeria"[MeSH Terms] OR "rwanda"[MeSH Terms] OR "senegal"[MeSH Terms] OR "sierra leone"[MeSH Terms] OR "somalia"[MeSH Terms] OR "south africa"[MeSH Terms] OR "south sudan"[MeSH Terms] OR "sudan"[MeSH Terms] OR "tanzania"[MeSH Terms] OR "togo"[MeSH Terms] OR "uganda"[MeSH Terms] OR "zambia"[MeSH Terms] OR "zimbabwe"[MeSH Terms] OR "africa south of the sahara"[MeSH Terms] OR "africa, central"[MeSH Terms] OR "africa, southern"[MeSH Terms] OR "africa, eastern"[MeSH Terms] OR "africa, western"[MeSH Terms] OR ("angola"[Text Word] OR "benin"[Text Word] OR "botswana"[Text Word] OR "bechuanaland"[Text Word] OR "burkina faso"[Text Word] OR "burkina fasso"[Text Word] OR "upper volta"[Text Word] OR "burundi"[Text Word] OR "urundi"[Text Word] OR "cabo verde"[Text Word] OR "cape verde"[Text Word] OR "cameroon"[Text Word] OR "cameron"[Text Word] OR "cameroun"[Text Word] OR "central african republic"[Text Word] OR "ubangi shari"[Text Word] OR "chad"[Text Word] OR "congo"[Text Word] OR "zaire"[Text Word] OR "cote d ivoire"[Text Word] OR "cote d ivoire"[Text Word] OR "cote d ivoire"[Text Word] OR "ivory coast"[Text Word] OR "djibouti"[Text Word] OR "french somaliland"[Text Word] OR "equatorial guinea"[Text Word] OR "eritrea"[Text Word] OR "eswatini"[Text Word] OR "swaziland"[Text Word] OR "ethiopia"[Text Word] OR "gabon"[Text Word] OR "gabonese republic"[Text Word] OR "gambia"[Text Word] OR "ghana"[Text Word] OR "gold coast"[Text Word] OR "guinea"[Text Word] OR "kenya"[Text Word] OR "lesotho"[Text Word] OR "basutoland"[Text Word] OR "liberia"[Text Word] OR "madagascar"[Text Word] OR "malawi"[Text Word] OR "nyasaland"[Text Word] OR "mali"[Text Word] OR "mauritania"[Text Word] OR "mozambique"[Text Word] OR "portuguese east africa"[Text Word] OR "namibia"[Text Word] OR "niger"[Text Word] OR "nigeria"[Text Word] OR "rwanda"[Text Word] OR "ruanda"[Text Word] OR "senegal"[Text Word] OR "sierra leone"[Text Word] OR "somalia"[Text Word] OR "south africa"[Text Word] OR "south sudan"[Text Word] OR "sudan"[Text Word] OR "tanzania"[Text Word] OR "tanganyika"[Text Word] OR "togo"[Text Word] OR "togolese republic"[Text Word] OR "tonga"[Text Word] OR

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"partum"[All Fields] AND "Haemorrhage"[All Fields]) OR "post partum haemorrhage"[All Fields]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "Hemorrhage"[All Fields]) OR "Postpartum Hemorrhage"[All Fields] OR ("post"[All Fields] AND "partum"[All Fields] AND "Hemorrhage"[All Fields]) OR "post partum hemorrhage"[All Fields]) OR ("Postpartum Hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "Hemorrhage"[All Fields]) OR "Postpartum Hemorrhage"[All Fields] OR ("post"[All Fields] AND "partum"[All Fields] AND "Haemorrhage"[All Fields]) OR "post partum haemorrhage"[All Fields])) OR "obstetric hemorrhage"[Title/Abstract] OR "hypertension, pregnancy induced"[MeSH Terms] OR ("obstructed labor"[Title/Abstract] OR "obstructed labour"[Title/Abstract] OR ("obstetric fistula"[Title/Abstract] OR "obstetric fistulae"[Title/Abstract]) OR ("vaginal fistula"[MeSH Terms] OR "vesicovaginal fistula"[MeSH Terms]) OR ("Obstetric Labor Complications"[MeSH Terms] OR "obstetric labor, premature"[MeSH Terms])) OR (("maternal"[Title] OR "pregnant"[Title] OR "pregnancy"[Title] OR "obstetric"[Title] OR "puerperal"[Title] OR "mother"[Title] OR "childbirth"[Title] OR "labour"[Title] OR "labor"[Title] OR "natal"[Title] OR "post-natal"[Title] OR "pre-natal"[Title] OR "prenatal"[Title] OR "antenatal"[Title] OR "ante-natal"[Title] OR "perinatal"[Title] OR "peri-natal"[Title]) AND ("hypertension"[Title] OR "blood pressure"[Title]) AND ("eclampsia"[Title/Abstract] OR "preeclampsia"[Title/Abstract] OR "HELLP"[Title/Abstract] OR "eclampsia"[MeSH Terms] OR "pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[Title/Abstract]))) OR ("pregnancy complications, hematologic"[MeSH Terms] OR "Pregnancy in Adolescence"[MeSH Terms] OR "pregnancy complications, infectious"[MeSH Terms] OR "pregnancy complications, cardiovascular"[MeSH Terms] OR "Pregnancy Complications"[MeSH Terms] OR "pregnancy, prolonged"[MeSH Terms])))

Supplementary File 3: Table of primary and secondary hypotheses and expected outcomes

	Hypotheses	Outcome variable	Unit of measurement
Primary hypotheses	The rates of preterm birth are increased when maximum temperatures are above the 90th percentile in the week prior to childbirth.	Preterm birth	Increased odds/risk/relative risk (compared to baseline) of preterm birth with exposure to temperatures above the 90th percentile for lags 0-7 days.
	Exposure to maximum temperatures above the 90th percentile in the three days before childbirth and during childbirth increases the risk of maternal morbidities.	Antepartum and postpartum haemorrhage Infections in pregnancy or postpartum Duration of labour Premature rupture of membranes	Increased odds/risk/relative risk of maternal morbidities associated with exposure to temperature above the 90th percentile for lags 0-3 days.
	Exposure to a higher number of hot days during pregnancy is associated with intrauterine growth restriction and low birth weight.	Intrauterine growth restriction (e.g., head circumference, femur length, abdominal circumference, biparietal diameter, umbilical artery doppler)	Increased odds/risk/relative risk/cumulative relative risk of intrauterine growth restriction and low birth weight with increased exposure to hot days.

		Low birth weight	
	A higher number of hot day exposures during pregnancy and the first two years of childhood is associated with stunting in children under the age of two.	Stunting (e.g., z scores for weight and height)	Increased odds/risk/relative risk/cumulative relative risk of stunting with increased exposure to hot days.
Secondary hypotheses	High ambient temperatures and heatwaves during pregnancy and intrapartum on maternal and child health, vary across key population sub-groups, including maternal age, socio-economic status, geographical area, and climate zone.	Demographic variables: Maternal age, socioeconomic status, geographical area, climate zone Health outcomes: maternal and neonatal adverse health outcomes	Evidence of effect modification by age, socioeconomic status, geographical area, and climate zone
	Exposure to high ambient temperatures increases the burden on health systems due to increased rates of caesarean sections and out- and in-patient health facility visits.	Emergency caesarean section rate Maternal health facility visits Maternal out-patient visits Maternal hospital admissions	Increased odds/risk/relative risk/cumulative relative risk of emergency caesarean sections, health facility visits, out-patient visits, and hospital admissions associated with

			exposure to high ambient temperature.
	High ambient temperature exposure during the first two years of childhood increases the risk of diarrhoea, pneumonia, all-cause out- and in-patient health facility visits, and all-cause mortality.	Gastroenteritis Pneumonia Out-patient visits Health facility visits Hospital admissions All-cause mortality	Increased odds/risk/relative risk/cumulative relative risk of gastroenteritis, pneumonia, health facility visits, out-patient visits, hospital admissions, and all-cause mortality associated with exposure to high ambient temperature

This table presents the expected outcomes based on the primary and secondary hypotheses. However, it is important to note that additional anticipated results will emerge from the inclusion of supplementary variables obtained from individual participant data (IPD) and through the utilisation of machine learning-informed covariate selection.

PRISMA-IPD Checklist

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD) (68)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	7
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	7
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	7-8
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	7-8

Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	8
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	8 and S1
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	9
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	8-9
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	S1
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	10
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	11
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	11
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	11
Results			

Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	13

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.