

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Lakhoo, Darshnika; Chersich, Matthew; Jack, Chris; Maimela, Gloria; Cissé, Guéladio; Solarin, Ijeoma; Ebi, Kristie; Chande, Kshama; Dumbura, Cherlynn; Makanga, Prestige; van Aardenne, Lisa; Joubert, Bonnie; McAllister, Kimberly A.; Ilias, Maliha; Makhanya, Sibusisiwe; Luchters, S; IPD Study Group, HE2AT Center

VERSION 1 – REVIEW

REVIEWER	Szenderák, János University of Debrecen
REVIEW RETURNED	06-Aug-2023

GENERAL COMMENTS	<p>The topic of the protocol sounds extremely interesting and important. I see two main sources of uncertainty. As the authors suggest, there is a large evidence gap in this area. First, we don't fully understand how environmental stressors, such as heat, affect maternal and child health. The mechanism should and could be further detailed. Second, there could be several other factors that contribute to maternal and child health, including, first and foremost, nutritional status. Without this information, it is impossible to isolate the effects of high temperatures. Your proposed machine learning approach may help in this regard. I think the problem should be discussed within this framework because already existing problems (like a lack of sufficient nutrition) increase the vulnerability of the focus group with possible feedback effects. In addition, study limitations should be further elaborated. Overall, I believe it is a great idea to analyze all datasets individually and summarize the information with a meta-analysis. As a methodological suggestion, meta-analysis has a serious drawback since it assesses only already published articles. In the current academic environment, significant results have a higher chance of being published, which reduces the chance of seeing high-quality studies with non-significant results. This selection bias can result in an enlarged effect size since meta-analysis involves only those articles that were published (with possibly</p>
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	<p>significant results) and excludes those that were not even published in the first place. There is hardly anything that can be done here, but I think it is extremely important to mention these issues in the manuscript to avoid unreasonable and unrealistically large effect sizes.</p> <p>Furthermore, the resulting effect size should be discussed (how large, is it possible etc.) to avoid the mentioned issues, and more importantly, it should not be overstated.</p> <p>Minor comments:</p> <p>Strengths and limitations</p> <ul style="list-style-type: none"> o Line 8: What type of longitudinal data do you plan to use? Repeated measurement of random samples in time or follow-up studies (where the same individuals measure over time). o Line 13: "The large IPD dataset will have statistical power to assess rare exposures and outcomes" Large data does not always translate to higher statistical power. It is more like the quality of the data, than the quantity. o Line 29: Data is usually never "missing completely at random", especially in these studies, where I expect a high level of non-cooperation. Especially in poorer regions, studies have shown that citizens do not trust outsiders (even medical professionals). Furthermore, there could be several cultural or traditional obstacles that may affect the participation rate (especially in follow-up studies). Public health relevance of the study findings o Line 28: "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..." I'm not sure heat effects can be summarized in a single indicator because of the complexity and heterogeneity associated with the heat – health relationship. <p>Acquisition of individual participant data</p> <ul style="list-style-type: none"> o What do you plan in case of a high non-response rate among authors? Unfortunately, data sharing and open access movements are not popular in the case of confidential (and probably expensive) datasets. <p>Acquisition of environmental exposure data</p> <ul style="list-style-type: none"> o A possible gap I see here is the difference between observed or recorded temperatures and experienced temperatures (how the individual was affected by the high temperature). In my opinion, high temperatures do not always translate to heat stress because its effects can be mitigated. Is there any information available about the individual's experience (like questions about how they tolerated high heat or how much they were exposed to it)? <p>Data management and analysis</p> <ul style="list-style-type: none"> o The PRIME approach seems really appropriate here (although I'm afraid the replication
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	crisis will affect high share of these studies as well). o How do you plan to analyze and compare observational data and randomized controlled trials?
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REVIEWER	Levy, Barry Tufts University
REVIEW RETURNED	11-Aug-2023

GENERAL COMMENTS	<p>Your protocol is important for addressing key issues concerning the impacts of climate change on vulnerable populations. I commend you for a carefully developed and well written protocol.</p> <p>I have only one very minor comment: In Table S1, you label the right hand column "Desirable variables." While these are desirable in terms of the research objectives, they are clearly not desirable for the people affected by these serious health outcomes. I suggest that you relabel this column heading.</p> <p>I am recommending that the protocol be published without any significant revision.</p>
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REVIEWER	Lokmic-Tomkins, Zerina Monash University Faculty of Medicine Nursing and Health Sciences, School of Nursing and Midwifery
REVIEW RETURNED	31-Aug-2023

GENERAL COMMENTS	<p>Thank you for providing the opportunity to review the '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)'. I hope that the following comments will be valuable to the authors, particularly in terms of the protocol's readability:</p> <p>Page 4, Lines 31-34: Consider including new mothers and providing examples of how heat exposure can manifest in this group.</p> <p>Page 5, Lines 28-31: The study's aim to develop an indicator for the effects of heat on maternal and child health is not clearly linked to the study objectives. Please connect these aspects more explicitly, as readers may not intuitively grasp this connection.</p> <p>Page 7, Line 14: Provide a rationale for focusing on children up to 2 years of age, especially since WHO reporting on child health typically spans up to 5 years of age (https://www.who.int/health-topics/maternal-health#tab=tab_1).</p> <p>Page 7, Line 18: Separate the 'Eligibility criteria' as a distinct heading rather than a subheading for enhanced readability.</p> <p>Rationale for 10-year limit on published literature: Justify the decision for a 10-year limit on literature, especially considering the relevance of climate change-related extremes over a longer period.</p> <p>Rationale for enrolling at least 1000 pregnant women: Provide reasoning behind the need for this number, considering the absence of a universally agreed minimum for IPD meta-analysis and the under-studied nature of this population.</p> <p>Page 7, Line 44, Section on data sources: Introduce more</p>
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	<p>subheadings to improve readability, such as separating the quality of studies and risk of bias from the data sources.</p> <p>Overall, consider if the structure of the methods could be refined and simplified so that it is more logically presented, possibly with the inclusion of a figure depicting the IPD meta-analysis flow, similar to the approach in Hunter KE et al.'s study. (2022) Development of a checklist of standard items for processing individual participant data from randomised trials for meta-analyses: Protocol for a modified e-Delphi study. PLoS ONE 17(10): e0275893. https://doi.org/10.1371/journal.pone.0275893.)</p> <p>The methods description could be refined as:</p> <p>Data Sources Data Collection (subheadings: Acquisition of individual participant data; Acquisition of environmental exposure data) Data Management and Analysis (subheadings: Database development; Data Harmonization; Addressing data quality and validity; Addressing heterogeneity) Statistical Analysis (as already presented by the authors) Supplementary Table 2: Organize this table in a clear format outlining how the search strategy was tested. This will improve transparency and enable independent replication of the search strategy.</p> <p>Figure 1: If individual concepts are spilling over and impacting readability, consider submitting the figure as a separate file to the publisher to ensure clarity.</p> <p>I trust that these suggestions will contribute to enhancing the clarity, structure, and overall quality of the protocol, thereby likely improving the accessibility of your work to readers.</p> <p>Thank you once again for the opportunity to review this important work.</p>
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REVIEWER	Bonell, Ana London School of Hygiene & Tropical Medicine, Centre on Climate Change and Planetary Health
REVIEW RETURNED	31-Aug-2023

GENERAL COMMENTS	<p>Thank you for the opportunity to review this study protocol of individual participant level-data meta-analysis to understand the impact of heat on maternal and child health in SSA. It is extremely well thought out and will add valuable estimates of health impacts of climate change in SSA which are currently missing.</p> <p>I feel the protocol would benefit from expanding on the following points:</p> <ol style="list-style-type: none"> 1. Please explain and justify the stated cut-off of only including studies that have recruited 1000 pregnant women and more. I would be interested to understand if consideration of bias in geographical region was factored into this decision. 2. Would you consider studies of 0-2 year olds without information on pregnancy? If yes, then please add this to the eligibility criteria and if no then please explain the rationale for this.
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	<p>3. In the statistical analysis plan it would be good to expand on other methodologies that you would consider if time series is not an option due to sparsity in the data. For example, would a case-crossover design be something that would be adopted? If so it would be helpful to briefly describe this methodology.</p> <p>4. It would be good to see a table of expected outcomes that will be evaluated for both maternal and child health.</p> <p>5. I am unclear on the methodology that will be used to estimate the effect of heat on specific child health outcomes as these may differ from clear time specific outcomes (i.e. preterm birth) and may develop gradually over some months (i.e. stunting, kidney disease etc.)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment	Response	Place in manuscript where changes were made
<p>I see two main sources of uncertainty. As the authors suggest, there is a large evidence gap in this area. First, we don't fully understand how environmental stressors, such as heat, affect maternal and child health. The mechanism should and could be further detailed. Second, there could be several other factors that contribute to maternal and child health, including, first and foremost, nutritional status. Without this information, it is impossible to isolate the effects of high temperatures. Your proposed machine learning approach may help in this regard. I think the problem should be discussed within this framework because already existing problems (like a lack of sufficient nutrition) increase the vulnerability of the focus group with possible feedback effects. In addition, study limitations should be further</p>	<p>Thank you for your valuable comments. We acknowledge the uncertainty in how environmental stressors impact on maternal and child health. To address this, we have added to the introduction some potential biological mechanisms, while highlighting the limited research in this area.</p> <p>Regarding confounding factors such as the influence of nutritional status, we do recognise their importance. In the field of environmental epidemiology, much work has been done in recent decades to develop analytical techniques that can isolate the impacts of temperature and other environmental exposures on health. One such study design in this field is a case-crossover, which corrects for any known or unknown individual risk factors as each case is its own control. Using appropriate analytical models, we can effectively dissect out the impacts of temperature on health outcomes, not unlike how one might do any other analysis. Additionally, we could investigate the effects of nutrition by analysing variables such as haemoglobin, MUAC and other variables reflecting nutritional status if they are available in the</p>	<p>Introduction Page 4</p> <p>Discussion page 12-13</p>

<p>elaborated.</p>	<p>datasets we acquire.</p> <p>Lastly, we have expanded on study limitations in the discussion section to provide a more comprehensive assessment of potential constraints.</p>	
<p>Overall, I believe it is a great idea to analyze all datasets individually and summarize the information with a meta-analysis. As a methodological suggestion, meta-analysis has a serious drawback since it assesses only already published articles. In the current academic environment, significant results have a higher chance of being published, which reduces the chance of seeing high-quality studies with non-significant results. This selection bias can result in an enlarged effect size since meta-analysis involves only those articles that were published (with possibly significant results) and excludes those that were not even published in the first place. There is hardly anything that can be done here, but I think it is extremely important to mention these issues in the manuscript to avoid unreasonable and unrealistically large effect sizes. Furthermore, the resulting effect size should be discussed (how large, is it possible etc.) to avoid the mentioned issues, and more importantly, it should not be overstated.</p>	<p>We have edited the manuscript to describe and elaborate on the limitations in the strengths and limitations section as well as the discussion section.</p> <p>In our study, it's worth noting that we may not encounter the typical publication bias issue associated with meta-analyses. The studies included in our IPD-MA have primarily focused on different exposure-outcome assessments. Specifically, they have not explored the specific relationship between heat exposure and adverse health outcomes, which differentiates our approach from traditional meta-analyses that pool published articles. Additionally, we are seeking unpublished studies through data provider, which I have clarified in the Data sources section, "Lastly, we will seek additional studies, published and unpublished, through direct contact with data providers and other field." Nonetheless, we recognize the potential for published studies to be impacted by publication bias for their evaluated associations and have noted this in the limitations section of the manuscript.</p>	<p>Date sources, page 8</p> <p>Discussion page 12-13</p>
<p>Line 8: What type of longitudinal data do you plan to use? Repeated measurement of random samples in time or follow-up studies (where the same individuals measure over</p>	<p>We will use longitudinal data from clinical trials and cohorts where the same individuals are followed up over a period of time, with multiple measurements.</p>	

time).		
<p>Line 13: “The large IPD dataset will have statistical power to assess rare exposures and outcomes” Large data does not always translate to higher statistical power. It is more like the quality of the data, than the quantity.</p>	<p>In our strengths, and methodological considerations, we highlight the use of data from clinical trials and cohorts. Our choice of utilising data from clinical trials and cohorts is intentional, as these sources are generally associated with higher data quality compared to data from hospital or routine data collection sources in sub-Saharan Africa. We recognise that the quality of data can significantly impact the validity of our analyses. We will also assess the quality of the studies using risk of bias assessments, as described on page 8.</p> <p>Furthermore, both traditional statistical approaches in environmental epidemiology and machine learning methods often require substantial amounts of data to produce reliable results. By aiming to collect large amounts of high-quality data, our goal is to fulfil the requirements for conducting in-depth and robust analyses.</p>	
<p>Line 29: Data is usually never "missing completely at random", especially in these studies, where I expect a high level of non-cooperation. Especially in poorer regions, studies have shown that citizens do not trust outsiders (even medical professionals). Furthermore, there could be several cultural or traditional obstacles that may affect the participation rate (especially in follow-up studies).</p>	<p>When we mentioned "missing at random" in this context, we were specifically referring to the IPD that we may not obtain from investigators who are unwilling or whom we cannot contact. It is possible, however, that there are factors that influence the willingness of a data holder to participate in the study that might introduce bias. For example, an investigator on a study that was done in a particular hot part of Africa may be more likely to join than investigators of studies in cooler regions. In our experience factors such as data being lost or authors not contactable are the principal reasons for "missing" studies. Nevertheless, we say missing at random, rather than missing completely at random given some uncertainty.</p> <p>However, it's important to emphasize that the primary focus of our study is on different exposure-outcome assessments as compared to the original study. Our ability to contact and obtain IPD from investigators is unlikely to be biased in a specific direction. While we acknowledge the potential for missing data due to non-cooperation and</p>	

	<p>related factors, our analyses aim to account for this possibility and assess its potential impact on our results, as described on page 12 under risk of bias across the IPD sources</p>	
<p>Line 28: “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...” I’m not sure heat effects can be summarized in a single indicator because of the complexity and heterogeneity associated with the heat – health relationship.</p>	<p>We agree that it is complex to develop an indicator, and different health outcomes will likely have different thresholds, in different regions and populations. In collaboration with a WHO-led Expert Panel, we aim to identify a suitable indicator for measuring heat-related burden. Our study will inform this process.</p> <p>We have edited the text to represent the broader aims of informing monitoring systems “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.”</p>	<p>Public health relevance of the study findings, page 5</p> <p>Discussion (page 12).</p>
<p>What do you plan in case of a high non-response rate among authors? Unfortunately, data sharing and open access movements are not popular in the case of confidential (and probably expensive) datasets.</p>	<p>We are trying to mitigate the non-response rates through multiple attempts at contacting data providers, and through the use of different communication channels such as email, phone call, mutual networks, and LinkedIn. I have elaborated on this in acquisition of individual participant data on page 8, “We will make at least five attempts to contact the study investigators, including through contacting first, last, and other study authors, and funders through multiple communication platforms such as email, phone calls, and LinkedIn.”</p> <p>We have a data sharing agreement to ensure data providers understand any risks and how their data will be used. Further, we provide opportunities for data providers to collaborate, contribute, and get access to data, to ensure a mutually beneficial relationship. We have elaborated on this further on pages 8-9, under acquisition of individual participant data, “Opportunities for authorship, networking and collaboration in study activities will be outlined and continually communicated.”</p> <p>There is an increasing recognition and</p>	<p>Acquisition of individual participant data, pages 8-9</p>

	interest in climate change impacts on health, but a lack of capacity, which we think has increased data provider's interest in participating (this has been our experience so far). Additionally, our analyses do not compete with their research objectives which has resulted in less hesitancy to share.	
<p>A possible gap I see here is the difference between observed or recorded temperatures and experienced temperatures (how the individual was affected by the high temperature). In my opinion, high temperatures do not always translate to heat stress because its effects can be mitigated. Is there any information available about the individual's experience (like questions about how they tolerated high heat or how much they were exposed to it)?</p> <p>The PRIME approach seems really appropriate here (although I'm afraid the replication crisis will affect high share of these studies as well).</p>	<p>We will not have access to individual experiences or measurements of heat exposure as all the studies included the IPD-MA would not have measured this. Ambient temperature, heat indices and land surface temperature are used as proxies for actual temperature exposure, which varies by housing type and access to cooling through air conditioning or ventilation, for example. Coverage of air conditioning is very low in most parts of Africa. In South Africa, for example, which is a middle-income country, only 6% of the population have access to air conditioning, with coverage much lower in other African countries. Air conditioning access is becoming a major limitation in temperature-health association research, but not among our study populations. In some analyses we may take housing type into account, where such information is available (or use a variable such as predominant housing type in a particular location). We have edited the text in the discussion section to reflect this: "To mitigate exposure misclassification, we employ longitudinal studies, ensuring prolonged participant follow-up, leverage appropriate spatiotemporal scales for environmental data, use of heat indices to represent heat strain, and may include housing type in some analyses where such information is available."</p>	Discussion, pages 12-13
How do you plan to analyze and compare observational data and randomized controlled trials?	We will not be comparing observational data from cohorts with data from randomised controlled trials. We are instead harmonising the longitudinal IPD from these studies.	

Reviewer 2

Comment	Response	Place in manuscript where changes

		were made
In Table S1, you label the right hand column "Desirable variables." While these are desirable in terms of the research objectives, they are clearly not desirable for the people affected by these serious health outcomes. I suggest that you relabel this column heading.	Your point about the potential insensitivity of the term "Desirable variables" for individuals experiencing serious health outcomes is well taken. We have edited the table column headings accordingly to "Key data variables" and "additional data variables of interest"	Table S1

Reviewer 3

Comment	Response	Place in manuscript where changes were made
Page 4, Lines 31-34: Consider including new mothers and providing examples of how heat exposure can manifest in this group.	Thank you for this suggestion. We could consider effect modification by parity if we are powered to do this analysis. However, this is not a primary or secondary outcome, and will be included in our exploratory analyses.	
Page 5, Lines 28-31: The study's aim to develop an indicator for the effects of heat on maternal and child health is not clearly linked to the study objectives. Please connect these aspects more explicitly, as readers may not intuitively grasp this connection.		
Page 7, Line 14: Provide a rationale for focusing on children up to 2 years of age, especially since WHO reporting on child health typically spans up to 5 years of age (https://www.who.int/health-topics/maternal-health#tab=tab_1).	We have added in additional lines to describe the rationale for our eligibility criteria on pages 7-8. In response to your comment, we have added the following lines: "We are including studies where women are enrolled during pregnancy and intrapartum and including child data to the age of two 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.	Rationale for eligibility criteria, pages 7-8.

	Additionally, enrolling women in pregnancy may increase the likelihood of acquiring more accurate gestational age data, to explore windows of susceptibility.”	
Page 7, Line 18: Separate the 'Eligibility criteria' as a distinct heading rather than a subheading for enhanced readability.	The eligibility criteria has been labelled as a distinct heading.	Page 7
Rationale for 10-year limit on published literature: Justify the decision for a 10-year limit on literature, especially considering the relevance of climate change-related extremes over a longer period.	In response to the rationale for a 10-year limit and for enrolling 1000 pregnant women, we include a section detailing the rationale for our eligibility criteria. On page 7-8, we have added the following text: Longitudinal data from clinical trials and cohort studies allows for the assessment of temporal trends and the use of statistical approaches like time-to-event analyses which are valuable in assessing heat-health associations. Including data from longitudinal studies, where women are followed over pregnancy in one location, may avoid biases in birth registries where a women may have given birth in a place that is some distance away from where she may have spent much of her pregnancy.	Page 7-8
Rationale for enrolling at least 1000 pregnant women: Provide reasoning behind the need for this number, considering the absence of a universally agreed minimum for IPD meta-analysis and the under-studied nature of this population.	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, and analysis of each individual study makes it difficult to justify the inclusion of smaller studies. We selected studies published between 2012 and 2022 to ensure the data's quality and relevance. Earlier studies may have used outdated clinical definitions and diagnostic criteria for adverse outcomes, which could complicate data	

	<p>harmonisation. Limiting the time frame improves our ability to identify data providers and access their datasets, while also increasing the likelihood of obtaining environmental exposure data.</p>	
<p>Page 7, Line 44, Section on data sources: Introduce more subheadings to improve readability, such as separating the quality of studies and risk of bias from the data sources.</p>	<p>We have added a risk of bias assessment sub-heading to improve readability.</p>	<p>Page 8</p>
<p>Overall, consider if the structure of the methods could be refined and simplified so that it is more logically presented, possibly with the inclusion of a figure depicting the IPD meta-analysis flow, similar to the approach in Hunter KE et al.'s study. (2022) Development of a checklist of standard items for processing individual participant data from randomised trials for meta-analyses: Protocol for a modified e-Delphi study. PLoS ONE 17(10): e0275893. https://doi.org/10.1371/journal.pone.0275893.)</p>	<p>The checklist presented in the Hunter paper is a great resource, thank for your sharing. Figure 4 that we developed does not incorporate all processes, but describes the main activities for data preparation and harmonisation.</p>	
<p>The methods description could be refined as:</p> <p>Data Sources Data Collection (subheadings: Acquisition of individual participant data; Acquisition of environmental exposure data) Data Management and Analysis (subheadings: Database development; Data Harmonization; Addressing data quality and validity; Addressing heterogeneity) Statistical Analysis (as already presented by the authors) Supplementary Table 2: Organize this table in a clear format outlining how the search strategy was tested. This will improve transparency and enable independent replication of the search strategy.</p>	<p>Thank you for your thoughtful suggestions on improving the flow and readability of the manuscript. We have taken your comments into consideration and made edits to the methodology to improve headings and structure.</p>	
<p>Figure 1: If individual concepts are spilling over and impacting readability, consider submitting the figure as a separate file to the publisher to ensure clarity.</p>	<p>Thank you for your suggestion. We will submit this figure separately to the editors.</p>	

Comment	Response	Place in manuscript where changes were made
<p>Please explain and justify the stated cut-off of only including studies that have recruited 1000 pregnant women and more. I would be interested to understand if consideration of bias in geographical region was factored into this decision.</p>	<p>We have added a paragraph detailing the rationale for our exclusion criteria on page 7-8. Pertaining to the sample size criteria, this is our rationale: "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, and analysis of each individual study makes it difficult to justify the inclusion of smaller studies." We do acknowledge the limitations of this approach on for geographical representativeness in the strengths and limitations and discussion sections.</p>	<p>Rationale for eligibility criteria, page 7-8</p> <p>Discussion, page 12-13</p>
<p>Would you consider studies of 0-2 year olds without information on pregnancy? If yes, then please add this to the eligibility criteria and if no then please explain the rationale for this.</p>	<p>In the additional information added on pages 7-8, under rationale for eligibility criteria, we describe the following: "We are including studies where women are enrolled during pregnancy and intrapartum and including child data to the age of two 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."</p>	<p>Rationale for eligibility criteria, page 7-8</p>
<p>In the statistical analysis plan it would be good to expand on other methodologies that you would consider if time series is not an option due to sparsity in the data. For example, would a case-crossover design be something that would be adopted? If so it would be helpful to briefly describe this methodology.</p>	<p>Thank you for this suggestion. It is our plan to use multiple statistical methodologies depending on the outcome and the window of exposure. We have added some additional lines in the statistical analysis section on page 11 to clarify and elaborate: "Additionally, 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</p>	<p>Statistical methods for the first stage of the meta-analysis, page 11</p>

	included, there is control of temporal trends (can control for gestational age for example), 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).”	
It would be good to see a table of expected outcomes that will be evaluated for both maternal and child health.	Thank you for this suggestion. We have added a table of some expected outcomes based on our primary and secondary hypotheses in the supplementary files. 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.	
I am unclear on the methodology that will be used to estimate the effect of heat on specific child health outcomes as these may differ from clear time specific outcomes (i.e. preterm birth) and may develop gradually over some months (i.e. stunting, kidney disease etc.)	In our analyses, we plan to explore various lagexposure times and windows of susceptibility, some of which may span days, and others months. We will use cumulative risks over time, such as described in a paper by Yang 2022. The various statisticalmethodologies used will depend on the type of variable and investigation of plausible windows of exposure.	

VERSION 2 – REVIEW

REVIEWER	Szenderák, János University of Debrecen
REVIEW RETURNED	26-Oct-2023

GENERAL COMMENTS	Thank you for the changes made, I have no further comments on the manuscript.
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REVIEWER	Lokmic-Tomkins, Zerina Monash University Faculty of Medicine Nursing and Health Sciences, School of Nursing and Midwifery
REVIEW RETURNED	05-Nov-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript again. All my comments have been addressed in details and there are nil further concerns.
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REVIEWER	Bonell, Ana London School of Hygiene & Tropical Medicine, Centre on Climate Change and Planetary Health
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REVIEW RETURNED	31-Oct-2023
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GENERAL COMMENTS	Thank you for addressing the comments fully.
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