STUDY PROTOCOL

Impact of Heat on Birth Outcomes and Child Nutrition: Study Protocol using the CIDACS Birth Cohort

[version 1; peer review: 2 approved with reservations]

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Abstract

Background

Pregnant individuals and children are particularly vulnerable to the adverse health consequences of exposure to heat. Leveraging the robust ecosystem of Brazilian linked administrative data, we aim to advance our understanding of how high temperatures and heatwaves influence birth outcomes and child nutrition.

Objectives

Investigate the association between high ambient temperatures/ heatwaves and 1) birth outcomes (low birth weight (LBW), small for gestational age (SGA), large for gestational age (LGA), and preterm birth), 2) child nutrition (growth), and 3) breastfeeding practices and complementary feeding in children.

Methods

We will triangulate results from complementary analytical

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approaches, including time-stratified case-crossover designs and time-to-event techniques. We will explore the influence of high temperatures and heatwaves at different periods (or lags) preceding the event and apply distributed lag non-linear models to account for delayed and non-linear effects. We will conduct subgroup analyses to identify the population groups most at risk.

Results and Conclusions

Our study will generate new insights into the relationship between heat, birth outcomes, and child nutrition in Brazil. By providing evidence from a middle-income country with diverse ecosystems and climate zones in a context of social inequalities, this research will contribute to advancing the current knowledge base. Additionally, by identifying critical windows of vulnerability and at-risk groups, our findings can potentially inform targeted and equitable climate adaptation policies.

Plain summary

Pregnant people and young children are particularly vulnerable to the health impacts of high temperatures. This study uses detailed data routinely collected in Brazil to investigate how high temperatures are associated with outcomes such as babies being born too small or too soon, and how they affect young children's growth and nutrition. Additionally, we will examine how heat influences breastfeeding practices and food intake. To analyse this, we will use advanced statistical methods to understand both immediate and delayed effects of heat exposure and identify the groups most at risk. By studying Brazil, a large middle-income country with diverse climates, and a high level of social inequalities, we aim to provide new insights into the health impacts of high temperatures. Our findings will inform the development of policies that address these risks in an equitable and effective manner, generating evidence to guide policies for the protection of the populations most vulnerable to heat.

Keywords

Ambient temperature, Heat, Heatwaves, Birth outcomes, Child nutrition

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Introduction

The rapid increase in greenhouse gas emissions driven by human activities has led to substantial rise in the average global temperature, with the past decade being the warmest in history[1]. Prolonged exposure to extreme temperatures presents both direct and indirect health risks, particularly to vulnerable populations such as pregnant women, newborns, and children[2]. For example, exposure to elevated temperatures during pregnancy can result in physiological changes such as reduced placental blood flow due to vasodilation and inflammatory responses that may trigger early labour[3]. These changes are linked to an increased risk of adverse birth outcomes, including preterm birth, which remains the leading global cause of neonatal and under-five child mortality[4].

In children, exposure to high ambient temperatures has been associated with a range of acute health issues, including heat stress-induced appetite loss and dehydration[5]. These conditions can impair nutrient retention and absorption, resulting in acute malnutrition characterized by weight loss[6]. Prolonged nutritional deficiencies may lead to chronic malnutrition and stunted growth[7]. Elevated temperatures may also indirectly exacerbate underlying determinants of health by reducing agricultural yields and limiting water availability, contributing to food insecurity and compromised nutritional intake[5].

High temperatures may also impact dietary practices, including breastfeeding[8]. In the context of water insecurity, heat increases the risk of dehydration, raising concerns about its potential effects on lactation[9]. However, the effects of dehydration on lactation in hot climates remain largely unknown. Evidence suggests that exclusively breastfed infants generally maintain adequate hydration in warm conditions, implying that breast milk production may not be significantly affected[10,11]. Nonetheless, experimental animal study indicates that chronic exposure to high temperatures (e.g., 41°C) could impair the milk-producing capacity and reduce the number of mammary epithelial cells[12]. Although no definitive evidence confirms that maternal milk supply is adversely affected, elevated temperatures may influence mothers' perceptions of milk sufficiency. These perceptions can, in turn, affect the timing of introduction of water and complementary foods, which may influence child growth and development.

The effects of extreme high temperatures have undermined progress in improving child health, with the burden disproportionately affecting the most vulnerable populations. These impacts are often exacerbated by existing inequalities and compounded by interactions with other crises. While populations in low- and middle-income countries (LMICs) are particularly vulnerable to the health consequences of rising temperatures[13], most research on heat and birth outcomes is conducted in high-income countries, focusing on populations in temperate climates with greater access to mitigation strategies and adaptive capacities[14].

There is an urgent need to build climate resilience, including enhancing preparedness for climate-related emergencies, and to develop effective adaptation strategies for those most at risk. This includes prioritizing individuals living in poverty, particularly those in extreme poverty and socially or ethnically marginalized groups. To achieve this, it is crucial to generate more evidence-based research from LMICs, with analyses stratified by at-risk groups, to inform targeted and equitable climate adaptation policies.

The Center for Data Integration and Knowledge in Health (*Centro de Integração de Dados e Conhecimentos para Saúde,* CIDACS) has significant potential to advance research on the effects of temperature on birth outcomes and child health by leveraging its robust ecosystem of Brazilian linked administrative data. This includes data from the CIDACS Birth Cohort and the recently launched CIDACS-Clima Climate and Health Data Platform. Using these nationally representative, longitudinal data resources from a large LMIC country is expected to provide critical insights and evidence to support the implementation of adaptation measures that address the adverse health consequences of rising temperatures.

Aims and objectives

- To estimate the association of high ambient temperature and heatwaves on birth outcomes, including low birth weight, small for gestational age (SGA), large for gestational age (LGA), and preterm birth, in the general population and within specific subgroups of interest;
- To estimate the association of high ambient temperature and heatwaves on child nutrition, both in the general population and within specific subgroups of interest;
- To evaluate the influence of high ambient temperature and heatwaves on breastfeeding practices and complementary feeding in children.

Conceptual framework

Our conceptual framework recognizes the complex interplay between multiple mechanisms which may underlie the relationship between high ambient temperatures and heat waves, adverse birth outcomes, and growth faltering in infants and young children. In this protocol, we do not propose novel pathways; this framework builds on existing literature.

Evidence indicates that prenatal exposure to elevated temperatures can have trimester-specific effects on placenta and embryogenesis[15]. In the first trimester, these effects may include epigenetic alterations and physiological, cellular, and metabolic changes. During the second and third trimesters, exposure to higher ambient temperatures may increase the maternal core body temperature, leading to a reduction in maternal metabolic rate, contributing to an increase in birth weight[16]. Additionally, residing in areas with high temperatures may prompt pregnant women to reduce the frequency of physical exercise, which could contribute to elevated levels of glucose, amino acids, and fatty acids, all of which are transferred to the fetus[17,18]. Prenatal exposure to elevated ambient temperatures may also increase maternal leptin levels[19] and contribute to higher birth weight[20]. Additionally, heat may induce elevated levels of pro-inflammatory cytokines and heat shock proteins that may precipitate the onset of early labour and preterm births. These adverse birth outcomes have lasting consequences for infant growth.

For infants and young children, exposure to extremely high temperatures and heat waves are linked to an increased risk of wasting and underweight through various pathways. Hypothesized mechanisms include reduced food intake (including breastmilk due to altered feeding practices), alterations to the gut microbiome, which may be associated with increased risk of diarrheal episodes and diminished nutrient absorption. Food insecurity linked to heat and drought conditions, which may negatively affect crop yields, further exacerbates these risks. The mechanisms contributing to stunting are more complex than those for wasting and often involve indirect pathways such as food insecurity, decreased water availability, and weakened health systems, which can hinder vaccination programs and essential health services—all of which contribute to child malnutrition[6].

These complex relationships have been insufficiently studied in LMICs. The health impacts of climate change are multifaceted, varying across geographic regions and socioeconomic contexts, and are likely to be exacerbated by existing social inequalities. While some outcomes have short-term windows of susceptibility, others reflect the delayed effects of exposure to (prolonged) heat. However, further research is needed to better define these critical windows of vulnerability.

Methods

Study population and data sources

This protocol was developed following the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) guidelines[21]. We will use the CIDACS Birth Cohort[22]. This cohort (N=28,631,394 liveborn children 2001–2018) was established to investigate the impact of prenatal and early life events on health-related outcomes for infants, children, adolescents, and pregnant individuals in the context of social inequalities. A detailed description of the cohort and the list of datasets linked to this data resource can be found in Paixão *et al.* (2021)[22]. It was built through the linkage between:

I) Socioeconomic and demographic data from the National Unified Register for Social Programmes (CadÚnico, Cadastro Único), The National Unified Register for Social Programmes (Cadastro Único) identifies low-income families applying for social assistance in Brazil. The baseline dataset includes 131,697,800 individuals, approximately 62% of the Brazilian population, who entered the cohort during different periods (2001–2018). The CadUnico database originates from an extensive questionnaire completed at the time of application to federal social programs. It contains detailed demographic, economic, and social data at the household and individual levels[23].

II) Live birth records, including information from the Live Birth Information System(SINASC, Sistema de Informação sobre Nascidos Vivos); SINASC is the primary national system recording the data

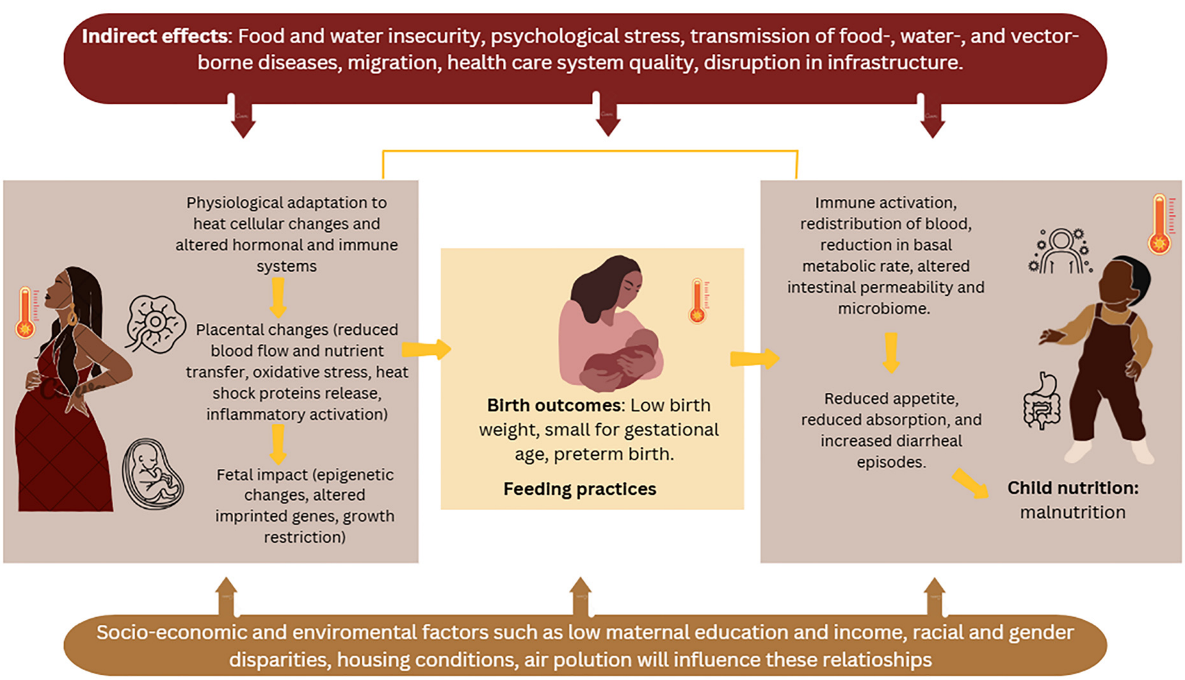

Figure 1. Theoretical framework guiding the investigation of high ambient temperature and heatwaves of birth outcomes, feeding practices and child nutrition.

available in the "declaration of live birth", legally required for every live birth in Brazil. The document is filled by the health worker who assisted the childbirth immediately after birth. In cases where the delivery was not assisted or performed by a registered professional, the declaration is filled in by the Civil Registry Office. The declaration form includes data on maternal characteristics, pregnancy and delivery[24].

The birth cohort was linked to data from the Food and Nutrition Surveillance System (SISVAN, Sistema de Segurança Alimentar e Nutricional)[22]:

III) SISVAN has monitored the Brazilian population's nutritional status since 2008[25]. The system was designed to record information on individual anthropometric indicators and food intake based on data from public healthcare services in all stages of life, including the nutritional status of children whose health is being monitored as part of the Bolsa Família conditional cash transfer program[26]. The main goal of the SISVAN is to inform the evaluation and development of public health nutrition policies. The dataset available at CIDACS includes 307,245,508 records from 59,724,164 individuals from 2008 – 2021.

The climatic variables at municipality level were extracted from two publicly available gridded datasets:

IV) The ERA5-Land reanalysis dataset from The European Centre for Medium-Range Weather Forecasts' (ECMWFs'); the ERA5-Land is a global atmospheric reanalysis for land areas produced by running only the terrestrial component of the ERA5 climate reanalysis model from ECMWF. A spatial subset of the global reanalysis was obtained for Brazil's continental area at a 0.1° x 0.1° (~9 km^2) spatial resolution and hourly frequency[27]. ERA5-Land combines observations and model data to provide consistent spatial and temporal coverage at a global scale. Variables used included hourly 2m air temperature and 2m dew point temperature, from which it was possible to calculate the daily minimum, mean and maximum air temperature and the relative humidity derived by combining the prime variables.

V) The Brazilian Daily Weather Gridded Data (BR-DWGD): The BR-DWGD is a gridded meteorological dataset produced by means of interpolation of observed data from 11,473 rain gauges and 1,252 weather stations across Brazil, obtained from the Agência Nacional de Aguas (ANA) and Instituto Nacional de Meteorologia (INMET). These interpolated data were obtained from a publicly available archive. BR-DWGD provides several variables at a daily time resolution and high spatial resolution of 0.1° x 0.1° by including data on topographic relief in the interpolation process. Variables used included minimum and maximum temperatures and relative humidity.

Data linkage

Two approaches have been employed to perform record linkage between the data sources: **(a)** deterministic linkage and **(b)** probabilistic linkage based on a similarity index.

The record linkage process used to create the CIDACS Birth Cohort is described in detail by Almeida *et al.*[28]. Matching criteria included variables such as maternal name, date of birth or age, and place of residence. This linkage was conducted using CIDACS-Record Linkage, an innovative tool developed at the Center for Data and Knowledge Integration for Health (CIDACS-RL)[29]. CIDACS-RL utilizes a combination of indexing and search algorithms to identify records in the CIDACS Birth Cohort that closely match each record in the other datasets. The tool conducts pairwise comparisons of candidate linking records, ranks them based on similarity scores, and retains the highest-scoring pair as the potential link. To link the CIDACS Birth Cohort baseline with the SISVAN dataset, deterministic linkage was f performed using a unique identifier available in both datasets—the Social Information Number (NIS). For records with missing NIS data, a similar linkage approach to that used to create the CIDACS Birth Cohort was applied.

Climatic data from the CIDACS Climate Platform was incorporated into the cohort database through deterministic linkage, using the municipality code of the mother's residence as a common identifier between datasets.

Before analysis, the final linked dataset will undergo a comprehensive data structuring process.

Exposures

Information on exposure to high ambient temperatures and heatwaves will be assessed at the municipality level. This will be derived by calculating the area-weighted average of values from the geographical cells that intersect each municipality, with weights based on the proportion of the municipality area covered by each cell. The exposures will be defined and operationalized as follows:

1. Ambient air temperature: for each municipality, we will extract daily mean, minimum, and maximum ambient air temperatures (°C). We will compare exposure to high temperatures (95th percentile) to the median temperature value (50th percentile of the municipality-specific baseline temperature distribution). Moreover, we will also investigate exposure to very high temperatures (99th percentiles; with the 75th or 50th percentile as reference values)[30].

2. Heatwaves: adopting the definition used by the *Lancet Countdown*, we will define heatwaves as a period of 2 or more consecutive days on which both minimum and maximum daily temperatures were above the 95th percentile of the municipality-specific baseline temperature distribution[31]. Recognizing the absence of a universally accepted definition[32], we will also define heatwave events by combining other temperature intensity criteria (i.e., 90th and 99th percentile) and

different durations (i.e., at least 3 or 4 consecutive days)[33].

Outcomes
The main outcome variables considered in this study protocol are:

Child and mother variables
Gestational age at birth [GA]: Categorized: [(<22, 22 to 27, 28 to 31, 32 to 36, 37 to 41, and 42 or more weeks); (discrete variable in complete weeks)].

Birth weight [BW]: Categorized: (Low birth weight (<2500g) and Macrosomia (>4000g)[35]); (Very low birth weight (<1500g) and extremely low birth weight (<1000g)[35]); (Continuous variable, in grams)].

Birth size, estimated using gestational age at birth and birth weight: Categorized: [Large (> percentile 90) and Small (< percentile 10) for gestational age, according to Intergrowth-21st sex and gestational age-specific charts[35];

Body Mass Index (BMI) up to 5 years old estimated using weight and height: Categorized: [(BMI-for-age z-scores for sex according to the WHO charts will be used[36]); (Underweight (BMI-for-age<-2 z-score); Normal (BMI-for-age≥-2 and ≤ 2 z-score); Overweight (BMI-for-age>2 and ≤ 3 z-score); Obesity (BMI-for-age>3 z-score)]; (Continuous variable, in kg/m2))].

Nutritional status - Height for age z-scores [HAZ], Weight for-age z-score [WAZ] and Weight for height z-scores [WHZ] according to the WHO charts will be used[38]. Categorized as proposed by the Brazilian Ministry of Health[37]: [(Stunting (HAZ <-2 z-score); (Normal (HAZ ≥-2); (Underweight (WAZ for age <-2 z-score); (Normal (WAZ ≥-2 and ≤3 z-score); (Obesity (WAZ for-age >3 z-score). (Wasting (WHZ <-2 z-score); (Normal (WHZ>-2); (Continuous variable, in z scores)].

SISVAN Food Intake Markers: For children < 6 months old: consumption of breast milk; porridge; water/ tea; cow milk; infant formula; fruit juice; fruits; other food/ beverages. For children 6 – 23 months old: consumption of breast milk; whole fruit in pieces or mashed (and the daily frequency); food (and the daily frequency and how the food was offered); milk other than breast milk; porridge; yogurt; vegetables; or fruit or dark green leaves (spinach, kale); leaf greenery (lettuce, cabbage); meat (beef, chicken, pork, fish) or eggs; liver; beans; rice, root vegetable or pasta; hamburger and/or sausages; sugar-sweetened beverages; instant noodles, packaged snacks, or crackers; biscuits/cookies or candies. For children > 24 months old: beans; fresh fruits (excluding fruit juice); vegetables and/or greens (excluding potatoes, cassava, yams, taro, and sweet potatoes); sweetened beverages (soft drinks, boxed juice, fruit juice with added sugar); instant noodles, packaged snacks or savory biscuits; and filled biscuits, sweets.

The response options are: “yes,” “no,” and “do not know” if consumed in the previous day.

Food consumption records from SISVAN will be used to calculate the following child feeding practice indicators: exclusive breastfeeding; mixed breastfeeding; continued breastfeeding; introduction of solid, semi-solid or soft foods (ISSSF); minimum meal frequency; minimum dietary diversity (MDD); minimum acceptable diet (MAD); consumption of meat and/or eggs; consumption of sweetened beverages; consumption of ultra-processed foods (UPF); and zero consumption of fruit and vegetables[39,40].

These variables will be outcomes for some objectives proposed but can also be confounders or effect modifiers for other objectives. Whenever possible, we plan to explore outcomes as both continuous and categorical variables, according to the proposed aim.

Analytical approach
For most of the outcomes to be studied, there is limited evidence, which makes it challenging to predefine key methodological aspects, such as the expected shape of the exposure-response curve and lag periods. Additionally, some analyses will focus on the short-term exposure (e.g., one-week preceding outcome), while others will consider lags of up to one year to try to understanding window of susceptibility. Therefore, this protocol outlines a general analytical approach, with more detailed analysis plans to be published for each paper in online repository, providing specific information included sensitivity analyses.

For each analysis, we plan to construct directed acyclic graphs (DAGs) with the program dagitty (http://www.dagitty.net/) and to include confounders defined *a priori*. The identification of potential confounders and effect modifiers will be guided by existing literature and the substantive expertise of the research team and collaborators. Confounders will include both environmental factors (e.g., humidity) and individual-level sociodemographic variables (e.g., maternal education). Although the exposure will be measured at the ecological level, it will be considered as a proxy for individual-level exposure. Consequently, we will adjust for individual-level covariates in the analysis, when appropriate based on the study design. Adjustment for seasonality and long-term time trends will be accounted for by design (e.g., by conducting case-crossover analyses) or by including covariates in the model with time terms, allowing for non-linearity. DAGs will also be used to identify potential residual confounding, which will inform sensitivity analyses to ensure robust findings.

We will triangulate findings from complementary methodological approaches to address our research objectives and investigate the influence of high temperatures and heatwaves across various time periods (or lags) leading up to the event. To capture non-linear and delayed effects of high ambient temperature/heatwaves, we will integrate distributed lag nonlinear models

(DLNMs) into our analyses[41]. Applying DLNMs involves defining a cross-basis which describes the exposure-response relationship along two dimensions: the predictor space and the lag dimension. The specification of the cross-basis will be informed by existing evidence about the temperature-outcome relationship, where possible. We will also use the Akaike Information Criterion (AIC) to guide model selection, with lower AIC values indicating the preferred model fit. To test the robustness of our findings, we will conduct sensitivity analyses with different cross-basis specifications, when appropriate.

DLNMs will be integrated into a suite of complementary methodological approaches based on case-crossover and time-to-event analyses. Additionally, other models and study designs may be incorporated as needed.

1. Case-crossover studies: this design will be used to study the effect of short-term exposure on acute events (e.g., preterm birth). In case-crossover studies, only individuals with the outcome are included and the exposure level on the day of the health event ("case day") is compared with exposure levels on proximate days when the health event did not occur ("control days"). We will adopt the time-stratified approach and select control days within the same year, same month, and on the same day of the week as the case day[42]. The case-crossover design controls confounding factors that are stable (or vary slowly) over time (e.g., individual characteristics such as race/ethnicity or education) by design. However, we will adjust for time-varying confounders such as relative humidity. As a primary statistical model, we plan to use conditional Poisson regression, which will allow us to adjust for overdispersion using quasi-likelihood functions[43].

2. Time-to-event analyses: This design leverages the longitudinal structure of the data and is particularly well-suited for handling censored observations. It is ideal for scenarios where accounting for the timing of an event is critical, such as gestational age at birth (e.g., preterm delivery) or the time elapsed since childbirth (e.g., feeding practices). We will use gestational age or time since childbirth as the timescales[44]. Aligning exposure data with the at-risk window breaks the dependence of exposure assignment and gestational age/time since childbirth, thereby preventing immortal time bias[44]. This is important where the likelihood of an outcome increases with gestational age or age of the child and where time trends in ambient temperature exposure (i.e., seasonality and long-term trends) cause average exposure over longer windows to systematically differ from exposure over shorter windows[45]. Models can be fitted with time-dependent exposures with short (e.g., lag: 0–2 days) or longer lag structures (e.g., lag: 0–4 weeks)[45]. Using this approach, we can investigate critical windows of exposure across the entire pregnancy and/or the child's lifespan using a modified version of an approach suggested by Leung *et al.*[44]. Our approach will consist of the following steps:

   a. Define the start of follow-up as conception or birth and split the data into different risk sets for each week of follow-up.

   b. For each risk set, fit a distributed lag nonlinear model (described below) with weekly (or monthly) lags ranging from the start of follow-up to the risk set. This allows the length of exposure to increase over the course of follow-up.

   c. Extract the lag-specific risk estimates for each risk set[41].

   d. Combine the lag-specific risk estimates across risk sets using a meta-analysis. Lag-specific risk estimates need to be aligned at the start of follow-up to ensure that they correspond to the same window of exposure (e.g., gestational week 1).

3. Other models: We might also apply the DLNM approach to model the matrix of exposure history in other models, such as general linear models, generalized linear mixed models and generalized additive models, inside the labelled DLNM extended applications. We will follow the applications in the literature, accounting for confounders and seasonality/long-term time trends.

Brazil has approximately 5,570 municipalities, which vary, for example, in terms of size and climate. To account for this heterogeneity, independent of the methodological approach, we will adopt a two-stage design, which is a common method for the analysis of multi-location data within environmental research[46–48]. In the first stage, we will estimate location-specific exposure-response associations (at the municipality level). In the second stage, we will pool the estimates to the regional level using meta-analytical methods. Alternatively, we might use alternative ways to aggregate such as Köppen climate classification to pool effect estimates[49]. We will also explore other methods which have been suggested for multi-location studies (e.g., the space-time-stratified design for case-crossover studies and case times series)[42,50].

We will conduct a series of subgroup analyses to characterize those women and children at greatest risk of the adverse health consequences of high temperatures. As the data allow, we will stratify by maternal characteristics (e.g., education level, race/ethnicity, gestational age at delivery), infant characteristics (e.g., sex, birth weight categories) and family characteristics (e.g., area of residence – rural/urban, beneficiary or not of social programs) and test for interaction effects with the exposure.

The proposed analyses will be conducted using R or Stata.

Ethics approval and consent to participate

The objectives described in this protocol are subprojects of the 100 Million Brazilian Cohort and CIDACS Birth Cohort, which was approved by the Research Ethics Committees of the Gonçalo Moniz Institute, Oswaldo Cruz Foundation (CAAE:

56003716.0.0000.0040) and [CAAE: 18022319.4.0000.5030]. As the study will exclusively use routinely collected and de-identified data, in accordance with Resolution no. 466/2012 established by the Brazil National Health Council's Commission for Ethics in Research Brazil, the requirement for study participants to provide informed consent is waived. The objectives described in this protocol were approved by the Research Ethics Committee from Nutrition School/Federal University of Bahia (CAAE: 76672823.8.0000.5023; V2).

Consent for publication
Not applicable.

Availability of data and materials
The data that will support the findings derived from this study protocol are available from the Centre for Data and Knowledge Integration for Health (CIDACS), Oswaldo Cruz Foundation, but restrictions apply to the availability of these data, which will be used under license for the current study protocol, and so are not publicly available. Data are however available upon reasonable request (using this email: cidacs.comunicacao@fiocruz.br) and with permission of CIDACS.

*Bolsa Familia is the conditional cash transfer program implemented in Brazil since 2004. ** In 2010, the system's coverage was estimated to be 95% in some Brazilian regions (58).

Contributions
Authorship: RCRS., PRFC., MP., ESP., LS., LHR., LPL., IF., PR., DR., ASR. conceptualized and designed the protocol, drafted the initial manuscript, and reviewed and revised the manuscript. OTR., IS., JMP., LS., EBB., TRC., and MLB. critically reviewed the intellectual content of the manuscript. All authors approved the final submitted version of this manuscript and accepted accountability for all aspects of the work.

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Reviewer Report 23 June 2025

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John Molitor
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This study protocol outlines a highly promising and timely investigation into the health impacts of heat exposure on birth outcomes, child nutrition, and feeding practices in Brazil. The research team leverages a remarkable array of linked administrative datasets, and the analytical plan demonstrates thoughtful consideration of time-varying exposures and lagged effects. The project is especially important in the context of low- and middle-income countries, where such large-scale evidence is scarce yet urgently needed.
The proposed methodology is largely sound and appropriately ambitious, including use of distributed lag non-linear models (DLNMs), case-crossover designs, and time-to-event analyses. However, one critical limitation is the absence of spatial statistical modeling. The current approach aggregates exposures at the municipality level, but this overlooks two important concerns: spatial correlation in both exposures and outcomes and how these correlations affect associations.

To address this, the authors should consider spatially varying coefficient (SVC) models, ideally within the R-INLA framework, which is well-suited for large-scale hierarchical models with spatial components. Incorporating spatially structured random effects (e.g., using BYM2) or allowing exposure effects to vary geographically would offer two major advantages: First, it would account for spatial dependence and unmeasured area-level confounding; second, it would allow the team to detect regional variation in the heat-health relationship—variation that is likely to be highly relevant for targeted adaptation policy. Given the availability of rich spatial data through CIDACS, this is a missed opportunity and should be considered as and addition to the analysis strategy.
The authors state: "Two approaches have been employed to perform record linkage between the data sources: (a) deterministic linkage and (b) probabilistic linkage based on a similarity index." Only the deterministic linkage method appears to be described in the protocol; it would be helpful to clarify whether the probabilistic approach was used in this study.
Other aspects of the protocol could benefit from clarification. For instance, it is not clear how the two climate datasets (ERA5-Land and BR-DWGD) will be integrated or reconciled; more detail would be helpful. The representativeness of SISVAN data, which appears to be limited to children engaging with the health system, raises concerns about selection bias.

Finally, a dedicated limitations section would improve the transparency of the protocol, especially around spatial misclassification, data representativeness, and the ecological nature of some exposure assignments. Similarly, the growth and nutrition analyses should reflect the biological distinctions between wasting and stunting and their likely differing relationships with heat exposure across child age groups.
In summary, this protocol represents an important and well-constructed study with the potential for significant impact. Incorporating spatially structured and spatially varying effects would substantially strengthen its methodological rigor and real-world relevance, and should be seriously considered as part of the core analytical strategy.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Spatial varying effect of exposure; Bayesian spatial modeling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 19 May 2025

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Ana Bonell
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This study protocol details the use of extensive datasets from Brazil to explore the association between high temperature exposure and the following: birth outcomes (LBW, preterm birth, SGA, LGA); child growth (HAZ, WHZ,WAZ); and child feeding practices. The datasets are explained with the planned linkages between them. This is a well-written and well explained study protocol. The outcome of these studies will be important in understanding the risk of pregnant women and infants to extreme heat. There are a few minor points to consider:

1. Exposure determination is based on area-weighted average values for the municipality. It appears that individual residence data is available in CIDACS (as indicated by the linkage of datasets process). Could individuals rather than municipality be linked to climate exposure? If this is not possible then are there plans to undertake a sensitivity analysis to understand if the described method would misusing exposure, for example due to the heat island effect?

2. It is unclear if the SISVAN survey could introduce bias. Is the data only collected when individuals attend a health centre? If this is the case then it would be important to understand the implications of this?

3. It is unclear how the two climate datasets will be used - both seem to have good coverage of the country.

4. In the conceptual framework there is the following statement: "*During the second and third trimesters, exposure to higher ambient temperatures may increase the maternal* core body temperature, leading to a reduction in maternal metabolic rate, contributing to an increase in birth weight." Please expand the physiological reasoning behind this statement, since it is not clear how a reduction in maternal metabolic rate would result in an increased birth weight.

5. Please add a limitations section.

6. For the nutritional status/growth analysis - is this planned over a specific age range? Please consider the high likelihood that heat effects growth differently at different ages (https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(24)00208-0/fulltext). In addition, the analysis plan does not expand on the potentially different biological and environmental pathways found in the association between extreme heat and wasting versus stunting. Please explain how this will be taken into account.

7. For the food intake/breast-feeding analysis - is the same analytical approach being taken? Please add a little detail on this study.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Maternal health and climate change.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.