STUDY PROTOCOL

Effects of maternal stress during pregnancy and up to two years after birth on risk of child overweight and obesity: Protocol for a Systematic Review [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Childhood obesity presents a significant public health challenge globally. The period from conception to two years after birth, the first 1000 days, represents a critical period during which the experience of maternal stress may be related to the development of childhood obesity. Research to date suggests some positive associations between maternal stress during the first 1000 days and childhood obesity, but findings are inconsistent and have not yet been comprehensively synthesised. The purpose of this review is to systematically examine the association between maternal stress during the first 1000 days and the risk of child overweight and obesity.

Methods: The following electronic databases will be searched from inception using a detailed search strategy: the Cochrane Library, MEDLINE, PsycINFO, EMBASE, CINAHL, Maternity and Infant Care, and Web of Science. Cohort, case-control, and cross-sectional studies examining maternal stress during the first 1000 days and child obesity, but findings are inconsistent and have not yet been comprehensively synthesised. The purpose of this review is to systematically examine the association between maternal stress during the first 1000 days and the risk of child overweight and obesity.

The Cochrane Collaboration’s bias classification tool for observational studies will be used to assess study quality. This protocol is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol (PRISMA-P) checklist, and the systematic review will be conducted and reported following the PRISMA checklist. If possible, random effects models will be used to perform meta-analyses.
Ethics and dissemination: Ethical approval is not required for this study as it will not involve conducting experimental research, nor include identifying personal data. The systematic review will be disseminated in peer-reviewed journals.

PROSPERO registration number: CRD42018100363

Keywords
Stress, 'First 1000 days', pregnancy, postpartum, 'childhood obesity', 'childhood overweight'

This article is included in the Maternal and Child Health collection.

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Author roles: Cooney J: Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Flannery C: Methodology, Writing – Review & Editing; Khashan AS: Methodology, Writing – Review & Editing; Huizink AC: Methodology, Writing – Review & Editing; Matvienko-Sikar K: Conceptualization, Funding Acquisition, Methodology, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Introduction
Childhood obesity presents a significant public health challenge globally. 41 million children under the age of five, and 340 million children and adolescents aged between 5 and 19, were overweight or obese in 2016 (WHO, 2017). While in recent years, rates of childhood obesity appear to be levelling off in some countries such as Ireland and the US, childhood obesity remains a serious health burden. Obesity during childhood tracks into adulthood and is associated with, for instance, higher incidences of type II diabetes, many types of cancer, cardiovascular disease, and osteoarthritis (Guh et al., 2009; WHO, 2017).

There is increasing evidence that the period from conception to two years after birth, the first 1000 days, may be a critical period for the development of childhood, and subsequently adult, obesity (Gillman et al., 2008; Stettler, 2007; Woo Baidal et al., 2016). One recent systematic review indicated a number of factors consistently associated with childhood obesity, such as a higher maternal pre-pregnancy BMI, excess maternal gestational weight gain, prenatal smoking, high infant birth weight and infant antibiotic exposure (Woo Baidal et al., 2016). Maternal psychological factors, including maternal stress, are less frequently examined in the context of childhood obesity; however, a need for further prospective studies examining both perceived and biological stress measures has been noted in the literature (Woo Baidal et al., 2016). Maternal stress during pregnancy has been found to be related to low gestational weight or infant birth weight, and gestational age (Bussières et al., 2015; Littleton et al., 2010). Such early birth outcomes may set the stage for childhood developmental of weight patterns such as catch-up, or compensatory growth (Brenseke et al., 2013). In terms of postnatal maternal stress, a recent meta-analysis (Tate et al., 2015) found a positive relationship between postnatal maternal stress and child obesity. However, many of the included studies measured maternal stress when the child was over the age of two years therefore missing the critical window of the first 1000 days (Woo Baidal et al., 2016). Thus, there is some evidence that maternal stress may be implicated in the aetiology of childhood obesity but findings are inconsistent.

It is important to note that while the first 1000 days as a whole may be a critical period during which the experience of maternal stress may be related to the development of childhood obesity, the associated mechanisms may differ significantly between prenatal and postnatal stress. During the first 1000 days, stressors experienced by women may change over time due to the transitional nature of pregnancy and early parenting, and in this way may be associated with childhood obesity via different mechanisms (Huizink & de Rooij, 2018; Huizink et al., 2017). For example, prenatal maternal stress may have programming effects on the foetus via gestational exposure to maternal stress hormones, which can track into childhood and adult life, as suggested by the Developmental Origins of Health and Disease (DOHaD) approach (Brenseke et al., 2013; Wadiwa et al., 2009). On the other hand, postnatal maternal stress may be associated with child weight via maternal health behaviours, such as feeding practices and physical activity (Park & Walton-Moss, 2012), maternal attachment style (Anderson & Whitaker, 2011), or via infant exposure to maternal stress hormones such as cortisol through breastfeeding (Hinde et al., 2015). Thus it is important to examine the multiple ways in which maternal stress across the first 1000 days may impact on child obesity outcome. This is essential to tease out existing inconsistencies and provide insight into potential associations between maternal stress and childhood obesity.

While the research examining the relationship between prenatal and postnatal stress and child obesity appears to indicate a positive association, findings are inconsistent and do not fully examine maternal stress during the critical period of the first 1000 days. The relationship between maternal stress during this period and childhood obesity has therefore not yet been comprehensively synthesised to elucidate potential associations and pathways of maternal stress effects. Therefore, this study aims to examine the relationship between maternal stress during the first 1000 days and the risk of child overweight and obesity.

Methods

Study registration. This study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO). Registration number CRD42018100363.

Study design. This review will follow the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) checklist (Moher et al., 2015) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). A PRISMA flow diagram will be utilised to illustrate the study selection process, including rationale for the inclusion and exclusion of studies.

Ethics. As no experimental or observational research will be carried out as part of this review, and no identifying personal information will be collected or present, ethical approval is not required.

Types of studies. Cohort studies, case-control studies, and cross-sectional studies will be included. Studies must examine maternal stress during the first 1000 days (either during the prenatal period, from birth up to two years, or during both periods), and subsequent child overweight and obesity up to the age of 12 years. Only studies published in English, German, French, and Dutch will be included due to limited translating resources. Studies in languages other than those listed, which provide an English abstract will be described and reported in the review. No restrictions on date of study publication will be included in the search. The review will include peer-reviewed published studies and grey literature including unpublished papers, theses, and/or data provided by contacted authors.

Inclusion criteria. Inclusion criteria for the review are as follows:

Population. Studies need to include women who have experienced maternal stress in first 1000 days; non-stressed comparator groups used in some studies will also be included where relevant. Studies also need to include these women’s infants from birth up to 12 years of age. A cut-off of 12 years was chosen to examine obesity outcomes in childhood, prior to pubertal weight changes. This is because during puberty, around 50% of adult body
weight is gained, with ‘peak weight velocity’ (PWV) occurring for girls at approximately 12.5 years and at approximately 14 years for boys (Barnes, 1975). In addition, body composition changes occur throughout puberty, with changes in body-fat distribution, muscle mass, and bone mineral content (Rogol et al., 2002).

Exposure. Maternal stress during the first 1000 days will be defined as the experience of any psychological stress (including: stress; distress; and anxiety), as measured by validated self-report questionnaires, biological measures of stress (e.g. cortisol; corticotropin-releasing hormone; heart rate variability), or environmental stress (including: natural disaster; bereavement).

Comparison. Women who experience low or no form of stress, as defined by the original studies, during the first 1000 days.

Outcomes. Child anthropometrics as measured by, but not limited to: Weight, Body Mass Index [BMI]; Waist-Hip Ratio [WHR]; waist circumference; and body composition.

Method for identifying studies for inclusion

The following databases will be searched from inception: The Cochrane Library, MEDLINE, PsycINFO, EMBASE, CINAHL, and Maternity and Infant Care. Conference Proceedings will be searched on Web of Science. All databases will be searched using the comprehensive list of search terms below, including different combinations of phrases/Mesh headings. Following consultation with a subject-specialist librarian, it has been decided that non-human search terms will be excluded using the Boolean operator ‘NOT’. Scoping searches will be carried out and the search strategy will be tested and amended based on results of the scoping searches and on consultation with a subject-specific librarian. The search will be supplemented by cross-checking the reference lists of all relevant articles. Finally, the searches will be re-run just before final analysis to ensure all eligible studies are included in the review.

Search strategy

The following search strategy will be utilised:

(Maternal OR Mother OR Mothers OR Parent OR Parental OR Parenting OR Antenatal OR Prenatal OR Pregnant OR Gestation OR Gestational OR Pregnancy OR In-utero OR Postnatal OR Postpartum OR Antepartum) AND (Stress OR Stressor OR Stressors OR Distress OR Anxiety OR “Corticotropin-releasing hormone” OR CRH OR Glucocorticoids OR Cortisol) AND (Child OR Childhood OR Children OR Infant OR Infants OR Pediatric OR Paediatric OR Baby OR Youth OR Offspring OR Preschool OR Toddler) AND (Obesity OR Obese OR Overweight OR Weight OR Body Mass Index OR BMI OR Adiposity OR Anthropometric OR “Waist Circumference” OR “Waist-to-Hip Ratio” OR “Waist-to-Height Ratio” OR “Body composition” OR “Body Fat Mass” OR “Fat Mass Index”) NOT (rats OR mice OR animal OR non-human).

Data collection, extraction and assessment

Study selection. All references will be imported into Endnote and duplicates will be removed using the “remove duplicates” function, as well as being manually screened for duplicates. Titles and abstracts of identified articles will be imported into Rayyan (Ouzzani et al., 2016) and screened by a single reviewer (JC), with a random third of all identified articles checked by a second reviewer (KMS); should any discrepancies be noted, the second reviewer will screen all remaining titles and abstracts. In cases of uncertainty, studies will be included in the full text review stage. Articles identified for full-text review will be transferred into Covidence. All full texts will be individually reviewed by at least two reviewers to identify eligible studies, with JC reviewing all the full-text articles, and KMS and CF each screening approximately half of all studies. Discrepancies will be resolved through consensus discussion with all three reviewers.

Data extraction. Data from full-text articles will be extracted using a pre-designed data extraction tool (Extended data (Matvienko-Sikar, 2018)) which will include main author, publication year, and study characteristics including: study design; maternal stress exposure (type, timing, duration); child outcome (age, type); exclusion criteria; participant characteristics (cohort size, stage of pregnancy or time after birth, age of offspring); and assessment methods (maternal stress measure, child weight status). This will be done by one reviewer (JC) and all data extraction will be checked by a second reviewer (KMS).

Assessment of risk of bias. The Cochrane Collaboration’s tool for observational studies will be utilised to assess the risk of bias in identified studies (Higgins et al., 2011). This tool considers six domains: selection bias, exposure, outcome measurement, statistical analysis, study attrition and confounding. Each study will be classified as having a high, moderate, low, minimal or unreported risk of bias for each domain, and then rated as having a high, moderate or low overall risk of bias. The risk of bias for each study will be assessed independently by two reviewers. Discrepancies will be resolved by a third reviewer.

Statistical methods

Quantitative data synthesis. Characteristics of the study populations, design, outcomes and results will be summarised. If possible, a meta-analysis will be performed to calculate a quantitative estimate of the relationship between maternal stress during the first 1000 days and the risk of child anthropometric outcomes. This meta-analysis will use random effects models and will be carried out on all studies reporting means, standard deviations, crude and/or adjusted estimates of odds ratios, hazards ratios or relative risks, presented with 95% CIs using the generic inverse variation outcome type in Review Manager (Cochrane Collaboration Software, RevMan) Version 5.3. Statistical analysis will be carried out using RevMan, and a forest plot produced. Potential confounders will be assessed among studies reporting adjusted estimates by examining separate unadjusted and adjusted models, and taking into account the
confounders adjusted for in the original studies. If the data are not sufficiently homogeneous the studies will be summarised and explained in a narrative synthesis.

**Analysis of subgroups or subsets.** If sufficient data are available, the following subgroup analyses will be carried out:

1. Type of stressor (e.g. physiological vs self-report stress; prospective vs retrospective stress);
2. Timing of stressor
3. Age of child at assessment.

**Assessment of reporting biases.** If the number of studies included in the meta-analysis reaches at least 10, a funnel plot and Egger test will be used to assess publication bias. *Comprehensive Meta-Analysis* Version 3 (Borenstein et al., 2013) will be used to carry out Egger’s test.

**Dissemination of findings.** Findings will be submitted to a peer-reviewed journal for publication, and presented at academic conferences.

**Discussion**

The primary aim of this review is to examine associations between prenatal and early life maternal stress and child overweight and obesity. Further to this, and if sufficient data is available, the study aims to determine if the associations are dependent on type of stressor, the timing of the stressor, and the age of the child at the time of weight and growth assessment. The findings of this study will provide important insight into effects and potential pathways of maternal stress effects on child weight outcomes that can have significant implications for both research and practice.

**Current study status**

This systematic review and meta-analysis is currently underway. The review protocol was published on Prospero in June 2018; the literature search and study selection were carried out in July 2018. Data extraction and risk of bias assessment were carried out in July and August 2018, and statistical analysis will be carried out in November and December 2018. The study is expected to be completed in early 2019.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**

The data collection sheet for this study is available from Open Science Framework

OSF: Extended data. Data extraction sheet https://doi.org/10.17605/OSF.IO/Z2T7X (Matvienko-Sikar, 2018)

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**Reporting guidelines**

A completed Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) is available from Open Science Framework

OSF: PRISMA-P checklist for ‘Effects of maternal stress during pregnancy and up to two years after birth on risk of child overweight and obesity’ https://doi.org/10.17605/OSF.IO/Z2T7X (Matvienko-Sikar, 2018)

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**Grant information**

Health Research Board Ireland [HRB-ICE 2015-1026].

This research is supported by an Enterprise Ireland H2020 Co-ordinator Proposal Preparation Support Scheme [Project ID: CS20182080]. KMS is also supported by a Health Research Board Interdisciplinary Capacity Enhancement Award [HRB-ICE 2015-1026]. During this work CF was supported by the Health Research Board, SPHeRE (Structured Population and Health-services Research Education) PhD Programme.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Gillman MW, Rifas-Shiman SL, Kleinman K, et al.: Developmental origins of childhood overweight: potential public health impact. Obesity (Silver Spring), 2008; 16(7): 1651–1656. P B u b l i s h e d A b s t r a c t | P u b l i s h e r F u l l T e x t | F r e e F u l l T e x t

Guhl D, Zhang W, Barsback N, et al.: The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009; 9(1): 88. P B u b l i s h e d A b s t r a c t | P u b l i s h e r F u l l T e x t | F r e e F u l l T e x t

Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 12 March 2019
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Nisreen A. Alwan
Academic Unit of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

A very important question to address. The protocol is clearly described and generally well presented. I have a few issues/queries that I suggest to be considered by the authors:

1. What is the rationale for including cross sectional studies as both exposure and outcome are measured at the same time in this type of study and the question is whether there is a longitudinal relationship with the outcome defined as ‘subsequent child overweight and obesity up to the age of 12 years’?
2. In terms of comparison groups, have you considered whether to include studies that compare one type of stress to another e.g. distress and anxiety?
3. In the outcomes section, all possible outcome measures should be listed. For example, how about skinfold thickness?
4. Under ‘analysis of subgroups or subsets’, the ‘type of stressor’ is not the same as the method of assessment of stress, so point 1 needs to be rephrased as it is confusing in its current form. Point 2 as well needs to be clarified, do you mean timing of exposure assessment?

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: Public health, lifecourse epidemiology

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 21 January 2019

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David P. Laplante
Douglas Mental Health University Institute, Montreal, QC, Canada

While overall I find the manuscript to be well written and easy to follow there are a few issues that I feel need to be addressed.

1. In the Introduction the authors frequently mention ‘inconsistent findings’ without providing any examples of these inconsistencies. A few examples would be helpful.

2. Why include ‘grey literature’? Findings from these non-reviewed manuscripts may be flawed and lead to ‘inconsistent’ findings in the present review.

3. I feel that the 12 year-old cut-off is largely arbitrary. A better rationale is required. If the authors want to avoid the potential influences of puberty, it might be wiser to use a younger age, particularly since boys and girls undergo puberty at different ages.

4. Since stress, distress, and anxiety are to be included as the predictor variables, I suggest that the title of the manuscript be changed to reflect this ‘broader’ definition of ‘stress’.

5. The authors write, ‘Child anthropometrics as measured by, but not limited to:’. What do the authors mean by ‘but not limited to’? This phrase should be removed and all manners in which the authors will accept measurement of child anthropometrics should be clearly indicated.

6. Why were the databases searched limited to Cochrane Library, MEDLINE, PsycINFO, EMBASE, CINAHL, and Maternity and Infant Care. I ask because I am a frequent user of ScienceDirect.

7. In the sixth line of the Discussion the words ‘of the child’ are repeated.

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

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?
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Disaster-related prenatal maternal stress research

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.

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**Comments on this article**

**Version 1**

Author Response 29 Mar 2019

Karen Matvienko-Sikar, University College Cork, Cork, Ireland

**Reviewer 1. David P. Laplante**

While overall I find the manuscript to be well written and easy to follow there are a few issues that I feel need to be addressed.

1. In the Introduction the authors frequently mention ‘inconsistent findings’ without providing any examples of these inconsistencies. A few examples would be helpful.

**Response 1.** The following sentences have been revised on pages X and X to better clarify the reference to inconsistent findings:

> Additionaly, some studies report no associations between maternal stress and childhood obesity (e.g. Kaitz et al., 2015), or reported significant associations for some outcomes or for stress exposures at certain timepoints but not others (e.g. Hohwü et al., 2015). Thus, despite some inconsistencies between studies that do and do not report associations,

> While the research examining the relationship between prenatal and postnatal stress and child obesity appears to indicate a positive association, findings demonstrate inconsistencies between papers...

1. Why include ‘grey literature’? Findings from these non-reviewed manuscripts may be flawed and lead to ‘inconsistent’ findings in the present review.

**Response 2.** While the authors agree that unpublished manuscripts have not undergone the rigour of peer-review, we also feel that excluding un-published manuscripts may contribute to a bias estimate of effect. This is because un-published manuscripts are more likely to include null findings. However, to address potential difference in methodological quality in the papers reviewed, this review will include a quality appraisal of all papers and methodological quality will be considered when evaluating outcomes.
1. I feel that the 12 year-old cut-off is largely arbitrary. A better rationale is required. If the authors want to avoid the potential influences of puberty, it might be wiser to use a younger age, particularly since boys and girls undergo puberty at different ages.

**Response 3.** The authors agree and have changed this to 10 years of age. While a cut-off of 10 years of age could also be suggested to be arbitrary, we feel better avoids potential influences of puberty as suggested.

1. Since stress, distress, and anxiety are to be included as the predictor variables, I suggest that the title of the manuscript be changed to reflect this ‘broader’ definition of ‘stress’.

**Response 4.** The authors have chosen to retain the description in the title as ‘stress’ because stress is typically the broadest and most generic term that is often used to encompass anxiety and distress also (Glover, 2011). It has been made clearer in the introduction however that stress refers to distress and anxiety also: *Maternal stress is highly related to maternal anxiety and distress, and ‘stress’ is often used as a generic term to encompass these factors* (Glover, 2011); *as such the term’ stress is also used herein.*

1. The authors write, ‘Child anthropometrics as measured by, but not limited to:’. What do the authors mean by ‘but not limited to:’. This phrase should be removed and all manners in which the authors will accept measurement of child anthropometrics should be clearly indicated. **Response 5.** The following has been added to more fully outlining child anthropometric measurements: *Child anthropometrics as measured by: Weight, Body Mass Index [BMI]; Waist-Hip Ratio [WHR]; waist circumference; waist to height ratio; weight for length; skinfold thickness; body fat; fat mass index; and body composition.*

1. Why were the databases searched limited to Cochrane Library, MEDLINE, PsycINFO, EMBASE, CINAHL, and Maternity and Infant Care. I ask because I am a frequent user of ScienceDirect.

**Response 6.** Searches and databases used were informed by guidance from a subject librarian. However we will look into whether inclusion of ScienceDirect adds to identification of additional unique articles.

1. In the sixth line of the Discussion the words ‘of the child’ are repeated.

**Response 7.** Thank you, this has been corrected.

**Reviewer 2. Nisreen A. Alwan**

A very important question to address. The protocol is clearly described and generally well presented. I have a few issues/queries that I suggest to be considered by the authors:

1. What is the rationale for including cross sectional studies as both exposure and outcome are measured at the same time in this type of study and the question is whether there is a longitudinal relationship with the outcome defined as ‘subsequent child overweight and obesity up to the age of 12 years’?

**Response 1.** The term ‘subsequent’ has been removed, as this confuses the focus of the review, implying a longitudinal focus, which is not our aim. We do not intend to examine a longitudinal relationship only. Instead, we are interested in associations between stress experienced at anytime point in the first 1000 days and child weight outcome(s). Inclusion of cross sectional enables us to have a broader view of the literature and the findings in relation to effects of stress that can better inform future examinations in the area.
1. In terms of comparison groups, have you considered whether to include studies that compare one type of stress to another e.g. distress and anxiety?

Response 2. For this review we only aim to examine stress in relation to ‘low or no form of stress’. This is because studies that examine different types of stress, including anxiety or distress, will be eligible for inclusion in the current review as they are highly correlated and often comorbid factors. The terms ‘anxiety’ and ‘distress’ are included in our search terms to capture this in terms of exposure. We agree that looking at different types of stress is useful however and have included this as a subgroup analysis: 1. Type of stressor (e.g. stress vs anxiety or general distress)

1. In the outcomes section, all possible outcome measures should be listed. For example, how about skinfold thickness?

Response 3. The following has been added to more fully outlining child anthropometric measurements:
Child anthropometrics as measured by: Weight, Body Mass Index [BMI]; Waist-Hip Ratio [WHR]; waist circumference; waist to height ratio; weight for length; skinfold thickness; body fat; fat mass index; and body composition.

1. Under ‘analysis of subgroups or subsets’, the ‘type of stressor’ is not the same as the method of assessment of stress, so point 1 needs to be rephrased as it is confusing in its current form. Point 2 as well needs to be clarified, do you mean timing of exposure assessment?

Response 4. This section has been clarified as follows:
Analysis of subgroups or subsets. If sufficient data are available, the following subgroup analyses will be carried out:

- Type of stressor (e.g. stress vs anxiety or general distress)
- Approach to stress measurement (e.g. physiological vs self-report stress; prospective vs retrospective stress)
- Timing of stress exposure
- Age of child at assessment

Competing Interests: No competing interests were disclosed.