SYSTEMATIC REVIEW

Early life adiposity and telomere length across the life course: a systematic review and meta-analysis [version 1; referees: 1 approved with reservations]

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Abstract

Background: The relationship between adiposity at birth and in childhood, and telomere length is yet to be determined. We aimed to systematically review and meta-analyse the results of studies assessing associations between neonatal and childhood adiposity, and telomere length.

Methods: We searched Medline, EMBASE and PubMed for studies reporting associations between adiposity measured in the neonatal period or childhood, and leucocyte telomere length, measured at any age via quantitative polymerase chain reaction, or terminal restriction fragment analysis, either cross-sectionally, or longitudinally. Papers published before April 2017 were included.

Results: Out of 230 abstracts assessed, 23 papers (32 estimates) were retained, from which 19 estimates were meta-analysed (15 cross-sectional, four longitudinal). Of the 15 cross-sectional estimates, seven reported on neonates: four used binary exposures of small-for-gestational-age vs. appropriate-for-gestational age (or appropriate- and large-for-gestational age), and three studied birth weight continuously. Eight estimates reported on childhood measures; five estimates were from studies of binary exposures (overweight/obese vs. non-obese children), and three studies used continuous measures of body mass index. All four longitudinal estimates were of neonatal adiposity, with two estimates for small-for-gestational-age vs. appropriate-for-gestational age neonates, and two estimates of birth weight studied continuously, in relation to adult telomere (49-61 years). There was no strong evidence of an association between neonatal or childhood adiposity, and telomere length. However, between study heterogeneity was high, and there were few combinable studies.

Conclusions: Our systematic review and meta-analysis found no strong evidence of an association between neonatal or childhood adiposity and telomere length.
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Author roles: Guyatt AL: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Rodriguez S: Funding Acquisition, Supervision, Validation, Writing – Review & Editing; Gaunt TR: Supervision, Validation, Writing – Review & Editing; Fraser A: Methodology, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Anderson EL: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction
Telomeres are regions of repetitive (TTAGGG) sequences situated at the ends of chromosomes. They buffer against loss of coding DNA (the ‘end replication problem’), and there is evidence that telomere length is associated with chronological age and longitudinally with diseases of later life, such as cardiovascular disease and cancer.

In addition to disease states, an association has been observed between unhealthy lifestyle factors and a reduction in telomere length. This has led to the suggestion that telomere length may lie on the causal pathway between traditional risk factors and chronic disease. One such studied risk factor is adiposity; there is evidence that greater adiposity in adults is associated with shorter telomere length, in both cross-sectional and longitudinal studies. Given that obesity may result in chronic levels of inflammation and oxidative stress, and that telomeric DNA is vulnerable to damage by oxidative stress, it is plausible that obesity may promote telomere attrition.

Findings from existing studies that have assessed the association between obesity and leucocyte telomere length in children are conflicting, with studies reporting positive, negative and null findings. Two systematic reviews of adiposity and telomere length that primarily focused on adiposity measured in adults have also briefly reported on evidence from studies of adiposity in childhood: Mundstock et al. systematically reviewed and meta-analysed the results of three cross-sectional studies of the association between childhood obesity and telomere length. This review reported greater childhood adiposity to be associated with shorter telomere length. Müezzinler et al. retrieved three studies assessing the association between body mass index (BMI) and telomere length in children, but concluded that none of the studies were suitable for meta-analysis. Additional studies have been published since these reviews. Furthermore, neither study assessed the association of adiposity at birth (as opposed to in childhood) with telomere length. This is of interest for two reasons: firstly, in utero adversity is a predictor of later chronic diseases, for which telomere length may be a risk factor, and secondly, telomere length is a marker of numerous adverse conditions across the life course, yet few studies have examined markers of prenatal adversity (a time of active cell replication) in relation to telomere length. Identifying associations in children (as opposed to adults) may also provide useful information about the ages at which associations between adiposity and telomere length emerge, and whether or not the direction and magnitude of the association between adiposity and telomere length is consistent through infancy, childhood and adulthood.

Here, we report the results of a systematic review and meta-analysis of both cross-sectional and longitudinal studies from the general population (i.e. in non-clinical populations) that have assessed the relationship between measures of neonatal and/or childhood adiposity and telomere length.

Methods
Inclusion criteria
Eligible studies included those with at least one measure of adiposity in the neonatal period or childhood (mean age <19 years). Any measure of adiposity was considered, including (but not restricted to) BMI, weight, waist circumference, waist-to-hip ratio, waist-to-height ratio, skinfold thickness, fat mass, ponderal index, and birth weight. The outcome considered was telomere length measured in peripheral venous or cord blood, by either quantitative polymerase chain reaction (qPCR) or terminal restriction fragment analysis (TRF). We considered both cross-sectional studies in which adiposity and telomere length were measured concurrently and longitudinal studies in which adiposity was measured in the neonatal period/childhood and telomere length was measured after a follow-up period, i.e. in either childhood or adulthood.

Studies were included even if adiposity measures were not the primary exposure (for example, studies in which adiposity measures were measured as covariates) provided that a relationship between adiposity and telomere length was assessed. Papers were only included if adiposity exposures were adjusted for age and sex, or if effect estimates were adjusted for (or stratified by) age and sex. These criteria were relaxed if the estimate was based on a sample in which participants’ ages varied by a range of no more than three years, if exposure groups were matched by age or sex, or if it was shown that age or sex was not associated with telomere length in the population of interest.

Exclusion criteria
Studies examining the effect of an intervention were not included, unless a pre-intervention, cross-sectional estimate of the relationship was provided. Furthermore, studies were excluded if participants were selected into the study on the basis of comorbidities (e.g. sleep apnoea, maternal stress, prematurity). Articles were also excluded if no full text was available from the British Library.

Search strategy
Medline and EMBASE were searched using the Ovid platform. PubMed was also searched. Searches were run until April, 2017. Search terms included thesaurus terms (MeSH/Emtree) for ‘telomere length’, ‘adiposity’, ‘obesity’, ‘weight’ and ‘birth weight’. In addition, thesaurus terms for infants and children were used. Appropriate synonyms were identified for all terms above and entered into the search as keyword searches in the title and abstract. The search strategy is detailed in Supplementary File 1.

Studies were considered eligible for screening regardless of language, provided that a translator could be sourced within the department where the review was performed. Reference lists of pertinent papers were searched in order to identify additional studies that may have been missed by the search strategy.

Only peer-reviewed sources of evidence (journal articles, doctoral theses) were included. If there was evidence of dual publication of a study population, the largest population was used (provided that this was available in full-text form). Conference abstracts were not included, but relevant abstracts were cross-referenced against the search results to ensure that any follow-up peer-reviewed sources resulting from the same data were included.

Study screening and selection
One reviewer (AG) screened all titles and abstracts and excluded those that were clearly ineligible according to the criteria above.
Decisions on remaining titles were made after discussion between two researchers (AG and ELA). Data were extracted from relevant full-text articles by two researchers (AG and ELA), using a standardised extraction form. Study authors were contacted to clarify ambiguous results. Any disagreement between the two researchers performing data extraction was resolved by discussion. Supplementary Figure 1–Supplementary Figure 2 show flowcharts detailing the review and extraction process.

Statistical analyses
There was considerable heterogeneity in the presentation of findings across studies (Table 1 and Table 2). Some studies only presented differences in means in the form of bar charts, in which case data were extracted using plot digitiser software [http://arohatgi.info/WebPlotDigitizer]. Different transformations were used for both the exposures and the outcomes (e.g. normalisation, z-scoring, log-transformation). Thus, to facilitate the pooling of results, all estimates were standardised for the meta-analyses. For studies presenting estimates of average telomere length by adiposity exposure groups (for example, in small-for-gestational-age neonates compared to normal- and large-for-gestational-age neonates), effect sizes were expressed as the difference in telomere length (in SD units) between the two groups. For studies that analysed adiposity and telomere length as continuous variables, effect sizes were expressed as change in telomere length (in SD units) per 1-SD unit increase in the exposure variable. Formulae used for calculating standardised effect estimates and their standard errors are provided in Supplementary File 2.

Estimates and standard errors were meta-analysed in Stata MP Version 13 (StataCorp, TX) with the ‘metan’ command, using random-effects models. Heterogeneity was estimated using the I² statistic, which represents the percentage of the total observed variability that is due to true differences in effect estimates between studies rather than chance variation. Harmonisation of data in preparation for meta-analysis was performed in R (see script in Supplementary File 3). The Stata ‘do’ file for the meta-analysis is available in Supplementary File 4.

Results

Literature search
A total of 427 papers that were published until April 22, 2017 were obtained after searching Medline, EMBASE and PubMed (Supplementary Figure 3). A total of 230 titles remained for assessment. Supplementary Figure 3 shows a PRISMA flow diagram detailing the exclusion process of search results. A completed ‘MOOSE’ (Meta-analyses Of Observational Studies in Epidemiology) checklist is included in Supplementary Figure 4. Supplementary Tables 1-4 give details of all studies assessed, and the reasons for which they were excluded. All titles that passed screening were English language papers. A total of 23 relevant studies (32 estimates) were identified after full-text screening.

Summary of retrieved studies

Estimates not included in meta-analysis. Thirteen estimates were not meta-analysed, either because they reported no estimate, or because the study design was not combinable with any other extracted estimate. The characteristics of these studies, along with the 13 reported effect estimates, are given in Table 1.

Seven of the 13 estimates not included in meta-analysis were of childhood adiposity exposures (waist circumference, fat mass, sum of skinfolds, or BMI). Adiposity measures were recorded either in early childhood (mean age ~5 years) or in adolescence (mean age ~15 years), and were studied as continuous or grouped exposures. Telomere length was measured either cross-sectionally or, after a follow-up period (mean age at telomere measurement in longitudinal studies: 22 and 31 years). Generally, point estimates were negative, but confidence intervals were consistent with no association between measures of childhood adiposity and telomere length. One study reported a weak positive association between BMI at approximately 5 years and telomere length at 31 years, but only in women.

Six of the 13 estimates not included in the meta-analysis studied neonatal adiposity, either as continuous ponderal index, or as continuous or categorical birth weight. Of the six estimates, three were from twin studies, and one estimate was cross-sectional, and five measured telomere length after a degree of follow-up (age range at follow-up: 5–80 years). In both cross-sectional and longitudinal studies, there was no discernible pattern of associations between neonatal adiposity and telomere length.

Estimates included in meta-analysis. The 19 estimates (from 19 studies) that were retained for meta-analysis are described in Table 2. Of these, 15 were cross-sectional and 4 were longitudinal. Of the 15 cross-sectional estimates, 7 reported on neonatal adiposity: 4 used binary exposures of small- vs. appropriate-for-gestational age (or appropriate- and large-for-gestational age), and 3 studied birth weight continuously. Eight papers studied childhood adiposity (age range 2–17 years), of which 5 estimates were from studies of overweight/obese vs. non-obese children, and 3 were studies of body mass index as a continuous measure. Longitudinal studies assessed neonatal adiposity, and telomere length after a follow-up period (range: ~23-69 years): two studied small- versus appropriate-for-gestational age neonates, and two studied birth weight as a continuous exposure.

Meta-analyses

Cross-sectional studies. Figure 1 shows associations of cross-sectional studies of neonatal and childhood adiposity and telomere length. There was no evidence from these meta-analyses that neonatal adiposity or childhood adiposity were associated with concurrently measured telomere length.

Longitudinal studies. All longitudinal studies included in the meta-analysis measured adiposity only in neonates (i.e. no studies measured adiposity in childhood), with telomere length measured as early as 23.8 (SD 0.7) years and as late as 69 years. Pooled estimates are shown in Figure 2. There was no evidence that continuously studied birth weight was associated with prospectively measured telomere length. There was very weak evidence that adults born appropriate-for-gestational age had longer telomeres.
Table 1. Summary of studies included in narrative synthesis only (13 estimates).

<table>
<thead>
<tr>
<th>ID</th>
<th>Adiposity</th>
<th>Exposure</th>
<th>Temporality</th>
<th>Notes</th>
<th>Leanness</th>
<th>Units X</th>
<th>Units Y</th>
<th>Country</th>
<th>DNA</th>
<th>Method</th>
<th>Age Base line</th>
<th>Age Follow-Up</th>
<th>Age Adjustment</th>
<th>Percent Male</th>
<th>Sex Adjustment</th>
<th>Additional Covariates</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strohmaier 2015</td>
<td>BWT</td>
<td>Group</td>
<td>Mixed</td>
<td>Twins</td>
<td>Adipose group</td>
<td>Lean group</td>
<td>.</td>
<td>TS</td>
<td>Various</td>
<td>Multiple sources</td>
<td>dPCR</td>
<td>Neonates</td>
<td>Age range: 0-80 yrs</td>
<td>Twins, plus TL age-adj.</td>
<td>Same-sex twins, TL sex-adj.</td>
<td>.</td>
<td>Twin design, could not combine</td>
</tr>
<tr>
<td>Wojcicki 2016 [Neonatal BMI]</td>
<td>BWT</td>
<td>Group</td>
<td>Long</td>
<td>LGA vs AGA</td>
<td>≥95th C.</td>
<td>&lt;95th C.</td>
<td>.</td>
<td>bp</td>
<td>Central America</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Neonates</td>
<td>Mean (SD): 4.9 (0.5) yrs</td>
<td>Age-adj. Cs, child age at DNA sample</td>
<td>46.8</td>
<td>Sex-adj. Cs</td>
<td>Adj. for repeated telomere-length measures</td>
</tr>
<tr>
<td>Okuda 2002</td>
<td>BWT</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td></td>
<td></td>
<td>g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No estimate</td>
<td>“There was no significant relation of TRF-lengths from blood ... with birthweight, gestational age, and birthweight adjusted for gestational age.” N~165</td>
</tr>
<tr>
<td>Kajantie 2012 [Twin BWT]</td>
<td>BWT</td>
<td>Cont.</td>
<td>Long</td>
<td></td>
<td>kg</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td>Change TL per unit BWT in twin pairs [95%CI]: -0.950 [-3.718, 1.819] p=0.16 N=124 twin pairs</td>
</tr>
<tr>
<td>Kajantie 2012 [Twin PI]</td>
<td>PI</td>
<td>Cont.</td>
<td>Long</td>
<td></td>
<td>kg/m²</td>
<td></td>
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<td></td>
<td>Change TL per unit PI in twin pairs [95%CI]: 0.06 [-0.202, 0.303] p=0.63 N=124 twin pairs</td>
</tr>
<tr>
<td>Kajantie 2012 [PI]</td>
<td>PI</td>
<td>Cont.</td>
<td>Long</td>
<td></td>
<td>kg</td>
<td></td>
<td></td>
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<td></td>
<td>Change TL per unit PI [95%CI]: -0.001 [-0.021, 0.019] p=0.98 N=1894</td>
</tr>
<tr>
<td>ID</td>
<td>Adiposity</td>
<td>Exposure</td>
<td>Temporality</td>
<td>Notes</td>
<td>Adipose Group</td>
<td>Lean Group</td>
<td>Units X</td>
<td>Units Y</td>
<td>Country</td>
<td>DNA</td>
<td>Method</td>
<td>Age Baseline</td>
<td>Age Follow-Up</td>
<td>Age Adjustment</td>
<td>Percent</td>
<td>Sex Adjustment</td>
<td>Additional Covariates</td>
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<tr>
<td>Wojicki 2016</td>
<td>WC Group</td>
<td>XS</td>
<td>Cont.</td>
<td></td>
<td>Obese vs. Nonob</td>
<td></td>
<td>≥90th C.</td>
<td>&lt;90th C.</td>
<td>Central America</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Age: ~4yrs</td>
<td>Age: ~4yrs</td>
<td>Age adj. Cs, child's age at DNA sample</td>
<td>46.8</td>
<td>Sex adj. Cs</td>
<td>Adj. for repeated telomere-length measures</td>
</tr>
<tr>
<td>Buxton 2014</td>
<td>BMI Cont.</td>
<td>Long</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>kg/m²</td>
<td>log TS</td>
<td>Finland</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean(SD): 5.61 (0.99) yrs</td>
<td>Age: 31 yrs</td>
<td>Birth cohort</td>
<td>100</td>
<td>Stratified</td>
<td>Mat. parity, childhood SES, smoking, adult SES, children, batch</td>
</tr>
<tr>
<td>Masi 2012</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td></td>
<td>SD of % FM</td>
<td>TS UK</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 15.1 (0.68) yrs</td>
<td>.</td>
<td>Covariate</td>
<td>Ethnicity, town</td>
<td>Could not combine Change TL per unit FM [95%CI]: -0.013 [-0.030, 0.004] p=0.12 N=1080</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Masi 2012</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td></td>
<td>SDs of log mm</td>
<td>TS UK</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 15.1 (0.68) yrs</td>
<td>.</td>
<td>Covariate</td>
<td>Ethnicity, town</td>
<td>Could not combine Change TL per unit SF [95%CI]: -0.011 [-0.026, 0.005] p=0.21 N=1080</td>
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<tr>
<td>Masi 2012</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td></td>
<td>SDs of log cm</td>
<td>TS UK</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 15.1 (0.68) yrs</td>
<td>.</td>
<td>Covariate</td>
<td>Ethnicity, town</td>
<td>Could not combine Change TL per unit WC [95%CI]: -0.003 [-0.019, 0.012] p=0.664 N=1080</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bethan-court 2014</td>
<td>WC Cont.</td>
<td>Long</td>
<td></td>
<td></td>
<td></td>
<td>TS Philippines</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 14.7 (0.73) yrs</td>
<td>Mean (SD): 21.7 (0.33) yrs</td>
<td>Covariate</td>
<td>Ht. income, WC<em>sex age</em>sex</td>
<td>Could not combine Change TL per unit WCHs [SE]: -0.00059 [-0.0034*, 0.00196*] p=0.647 N=1681</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Abbreviations: adj.=adjusted; cov=covariate(s); Nonob=nonobese; TS=telomere-single gene ratio; qPCR=quantitative polymerase chain reaction; yrs=years; TL=telomere length; BWT=birth weight; 95%CI=95% confidence interval; N=sample size; BMI=body mass index; bp=base pairs; Cs=centile; SD=standard deviation; g=grams; kb=kilobases; TRF=terminal restriction fragment; assoc.=association with; gest.=gestation; wks=weeks; kg= kilograms; z(s)=Z-score(s); Pat./Mat.= paternal/maternal; SES=socioeconomic status; PI=ponderal index; m=meters; WC=waist circumference (adjusted for height); Strat.=stratified; FM=Fat mass; SF=sum of skinfolds; mm=millimeters; cm=centimeters; ht=height. *=estimated from data; 95%CI estimated using formula 95%CI=estimate± (1.96*standard error); standard errors estimated as necessary from published p values, assuming two-tailed tests, degrees of freedom~sample N; P values estimated from t distributions, assuming df~sample N.
### Table 2. Summary of studies included in meta-analysis (19 studies, 19 estimates).

<table>
<thead>
<tr>
<th>ID</th>
<th>Adiposity</th>
<th>Exposure</th>
<th>Temporality</th>
<th>Notes</th>
<th>Adipose Group</th>
<th>Units X</th>
<th>Units Y</th>
<th>Country</th>
<th>DNA</th>
<th>Method</th>
<th>Age Baseline</th>
<th>Age Follow-Up</th>
<th>Age Adjustment</th>
<th>Percent Male</th>
<th>Sex Adjustment</th>
<th>Additional Covariates</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akkad 2006</td>
<td>BWT</td>
<td>Group</td>
<td>XS</td>
<td></td>
<td>AGA vs. SGA</td>
<td>&gt;10th C</td>
<td>&lt;=3rd C</td>
<td>UK</td>
<td>cord</td>
<td>TRF</td>
<td>Mean (SD): 39.1 (1.6) wks</td>
<td>.</td>
<td>Age-adj. Cs</td>
<td>47.2</td>
<td>Sex-adj. Cs</td>
<td>.</td>
<td>A</td>
</tr>
<tr>
<td>Davy 2009</td>
<td>BWT</td>
<td>Group</td>
<td>XS</td>
<td></td>
<td>No FGR vs. FGR</td>
<td>Z=1 to 1</td>
<td>&lt;5th C</td>
<td>b/wt;  &lt;10th C Pl</td>
<td></td>
<td>kib</td>
<td>Philippines</td>
<td>TRF</td>
<td>Gest. 40 wks</td>
<td>.</td>
<td>Age-adj. Cs</td>
<td>.</td>
<td>Sex-adj. Cs</td>
</tr>
<tr>
<td>Tellechea 2015</td>
<td>BWT</td>
<td>Group</td>
<td>XS</td>
<td></td>
<td>AGA vs. SGA</td>
<td>&gt;=10th C</td>
<td>&lt;10th C</td>
<td>Argentina</td>
<td>cord</td>
<td>qPCR</td>
<td>Mean (SD): 38.4 (2.4) wks</td>
<td>.</td>
<td>Age-adj. Cs</td>
<td>.</td>
<td>Sex-adj. Cs</td>
<td>.</td>
<td>A</td>
</tr>
<tr>
<td>De Zeger 2016</td>
<td>BWT</td>
<td>Group</td>
<td>XS</td>
<td></td>
<td>AGA vs. SGA</td>
<td>Z&gt;=-1</td>
<td>Z&lt;-2</td>
<td>Norm. T/S</td>
<td>Spain</td>
<td>cord</td>
<td>qPCR</td>
<td>Mean (SD): 38.4 (1.3) wks</td>
<td>.</td>
<td>Age-adj. Zs</td>
<td>Sex-adj. Zs</td>
<td>Mat. age, BMI, gest. weight, gain and gest. age.</td>
<td>No assoc. sex</td>
</tr>
<tr>
<td>Drury 2015</td>
<td>BWT</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td>g</td>
<td>T/S</td>
<td>USA</td>
<td>cord</td>
<td>qPCR</td>
<td>Mean (SD): 38.9 (1.4) wks</td>
<td>.</td>
<td>No assoc. age</td>
<td>53</td>
<td>Covariate</td>
<td>Race, mat. age at conception, mat. educ., pat. age</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Entringer 2013</td>
<td>BWT</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td>g</td>
<td>T/S</td>
<td>USA</td>
<td>cord</td>
<td>qPCR</td>
<td>Mean (SD): 38.8 (1.4) wks</td>
<td>.</td>
<td>Covariate</td>
<td>48</td>
<td>Covariate</td>
<td>Obstetric complications, preg. specific-stress</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Wojcicki 2015</td>
<td>BWT</td>
<td>Cont.</td>
<td>XS</td>
<td></td>
<td>ptile</td>
<td>bp</td>
<td>USA</td>
<td>cord</td>
<td>qPCR</td>
<td>Tertiles: 24.8&amp;26.8 wks</td>
<td>.</td>
<td>Age-adj. Cs</td>
<td>44.4</td>
<td>Covariate</td>
<td>Mat. BMI, mat. Educ.</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Alegria-Torres 2016</td>
<td>BMI</td>
<td>Group</td>
<td>XS</td>
<td></td>
<td>Obese vs. Nonob.</td>
<td>&gt;85th C</td>
<td>Not stated</td>
<td>T/S</td>
<td>Mexico</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Age 6–12 yrs</td>
<td>.</td>
<td>Age-adj. Cs</td>
<td>43.9</td>
<td>Sex-adj. Cs</td>
<td>.</td>
</tr>
<tr>
<td>ID</td>
<td>Adiposity</td>
<td>Exposure</td>
<td>Temporality</td>
<td>Notes</td>
<td>Adipose Group</td>
<td>Group</td>
<td>Lean Group</td>
<td>Units X</td>
<td>Units Y</td>
<td>Country</td>
<td>DNA</td>
<td>Method</td>
<td>Age Baseline</td>
<td>Age Follow-Up</td>
<td>Age Adjustment</td>
<td>Percent Male</td>
<td>Sex Adjustment</td>
</tr>
<tr>
<td>--------------</td>
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<td>----------</td>
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<td>---------------</td>
<td>---------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Wojcicki 2016</td>
<td>BMI</td>
<td>Group</td>
<td>XS</td>
<td>Obese vs. Nonob.</td>
<td>&gt;=95thC</td>
<td>&lt;95thC</td>
<td>Normal BMI</td>
<td>.</td>
<td>bp</td>
<td>USA</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Approx 4yrs</td>
<td>Mean (SD): 4.9 (0.5) yrs</td>
<td>Age-adj. Cs</td>
<td>46.8</td>
<td>Sex-adj. Cs</td>
</tr>
<tr>
<td>Zannolli 2008</td>
<td>BMI</td>
<td>Group</td>
<td>XS</td>
<td>Obese vs. Nonob.</td>
<td>&gt;=95thC</td>
<td>&lt;95thC</td>
<td>Normal BMI</td>
<td>.</td>
<td>bp</td>
<td>Italy</td>
<td>peripheral</td>
<td>TRF</td>
<td>Mean (SD): 15.1 (0.6) yrs</td>
<td>.</td>
<td>Age-adj. Zs</td>
<td>.</td>
<td>Sex-adj. Zs</td>
</tr>
<tr>
<td>Masi 2012</td>
<td>BMI</td>
<td>Cont.</td>
<td>XS</td>
<td>Obese vs. Nonob.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>T/S</td>
<td>UK</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 9.9 (1.6) yrs</td>
<td>.</td>
<td>Covariate</td>
<td>55.3</td>
<td>Covariate</td>
</tr>
<tr>
<td>Milne 2015</td>
<td>BMI</td>
<td>Cont.</td>
<td>XS</td>
<td>Obese vs. Nonob.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>Z score</td>
<td>Hb</td>
<td>Australia</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Age range: 3-9 yrs</td>
<td>.</td>
<td>Covariate</td>
<td>50</td>
<td>Covariate</td>
</tr>
<tr>
<td>Needham 2012</td>
<td>BMI</td>
<td>Cont.</td>
<td>XS</td>
<td>Obese vs. Nonob.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>T/S</td>
<td>USA</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Mean (SD): 23.8 (0.73) yrs</td>
<td>.</td>
<td>Covariate</td>
<td>48</td>
<td>Covariate</td>
</tr>
<tr>
<td>Shalev 2014</td>
<td>BWT</td>
<td>Group</td>
<td>Long.</td>
<td>AGA vs. SGA</td>
<td>Not stated</td>
<td>Not stated</td>
<td>.</td>
<td>T/S</td>
<td>NZ</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Neonates</td>
<td>Age: 38 yrs</td>
<td>Age-adj. Cs</td>
<td>52</td>
<td>Sex-adj. Cs</td>
<td>No assoc. sex</td>
</tr>
<tr>
<td>De Melo 2017</td>
<td>BWT</td>
<td>Group</td>
<td>Long.</td>
<td>AGA vs. SGA</td>
<td>&gt;=10thC &lt;90thC</td>
<td>&lt;10thC</td>
<td>.</td>
<td>Hb</td>
<td>Brazil</td>
<td>peripheral</td>
<td>TRF</td>
<td>Age range: 37-42 wks</td>
<td>Mean (SD): 61.5 (2.9) yrs</td>
<td>Age-adj. Cs</td>
<td>0</td>
<td>All female</td>
<td>.</td>
</tr>
<tr>
<td>Kajantie 2012</td>
<td>BWT</td>
<td>Cont.</td>
<td>Long.</td>
<td>AGA vs. SGA</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>kg</td>
<td>z</td>
<td>Finland</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Median (IQR): 39.8 (19.1) wks</td>
<td>.</td>
<td>Covariate</td>
<td>46.7</td>
<td>Covariate</td>
</tr>
<tr>
<td>Pearce 2012</td>
<td>BWT</td>
<td>Cont.</td>
<td>Long.</td>
<td>AGA vs. SGA</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>Z score</td>
<td>log bp</td>
<td>UK</td>
<td>peripheral</td>
<td>qPCR</td>
<td>Median (IQR): 40 (40-40) wks</td>
<td>Age range: 49.6-51 yrs</td>
<td>Age-adj. Zs</td>
<td>37.7</td>
<td>Sex-adj. Z+ cov.</td>
</tr>
</tbody>
</table>

Abbreviations: BWT=body mass index; SGA/AGA=small-/appropriate-for-gestational age; FGR=foetal growth restriction; Overwt=overweight; Nonob.=non-obese; Z(s)=Z-score(s); C(s)=centile(s); XS=cross-sectional; Long.=longitudinal; g=grams; p/tile=percentile; z=z-score; kg=kilograms; m=meters; SD=standard deviation; TRF=terminal restriction fragment; qPCR=quantitative polymerase chain reaction; Gest.=gestation; wks=weeks; yrs=years; T/S=telomere-single gene; kb=kilobases; bp=base pairs; adj.=adjusted; Pat.Mat.=paternal/maternal; educ.=education; preg.=pregnancy; circ.=circumference.
### Cross-sectional studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neatatal: AGA vs. SGA (Difference in TL [SD])</td>
<td>0.02 (-0.44, 0.48)</td>
<td>27.45</td>
</tr>
<tr>
<td>Davy 2009</td>
<td>0.24 (-0.75, 1.22)</td>
<td>19.95</td>
</tr>
<tr>
<td>Tellechea 2015</td>
<td>-0.70 (-1.33, -0.07)</td>
<td>25.10</td>
</tr>
<tr>
<td>de Zegher 2016</td>
<td>0.97 (0.51, 1.43)</td>
<td>27.50</td>
</tr>
<tr>
<td>Subtotal (I-squared = 84.2%, p = 0.000)</td>
<td>0.14 (-0.60, 0.89)</td>
<td>100.00</td>
</tr>
<tr>
<td>Childhood: Obese vs. non-obese** (Difference in TL [SD])</td>
<td>-0.26 (-0.60, 0.08)</td>
<td>21.15</td>
</tr>
<tr>
<td>Al-Attas 2010</td>
<td>0.04 (-0.54, 0.62)</td>
<td>17.51</td>
</tr>
<tr>
<td>Buxton 2011</td>
<td>-0.88 (-1.02, -0.73)</td>
<td>23.13</td>
</tr>
<tr>
<td>Wojcicki 2015**</td>
<td>-0.07 (-0.36, 0.23)</td>
<td>21.66</td>
</tr>
<tr>
<td>Subtotal (I-squared = 90.3%, p = 0.000)</td>
<td>-0.22 (-0.70, 0.26)</td>
<td>100.00</td>
</tr>
<tr>
<td>Childhood: Change in TL [SD] per 1-SD birth weight</td>
<td>-0.03 (-0.10, 0.03)</td>
<td>59.84</td>
</tr>
<tr>
<td>Masri 2012</td>
<td>0.05 (-0.05, 0.14)</td>
<td>37.48</td>
</tr>
<tr>
<td>Milne 2015</td>
<td>0.19 (-0.24, 0.61)</td>
<td>2.67</td>
</tr>
<tr>
<td>Needham 2012</td>
<td>0.00 (-0.07, 0.07)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

**Figure 1.** Meta-analyses of cross-sectional studies, separately by birth weight and BMI. Each panel shows a different sub-analysis, which is annotated in the ‘Study ID’ column. Meta-analysis is by random-effects, and 95% confidence intervals (CI) are shown, along with weights for each estimate. Box size is proportional to study weight, and black lines represent 95% CIs. Summary estimates for each panel are shown as diamonds. The scale is in standardised units (see Methods for more information). Specifically, subgroups labelled ‘Neonatal’ focus on studies of neonatal adiposity, and show the pooled estimates for the difference in telomere length (SD units) between small- and appropriate-for-gestational-age babies, and the change in telomere length (SD units), per 1-SD increase in birth weight. Subgroups labelled ‘Childhood’ examine the cross-sectional relationship between childhood or adolescent adiposity with telomere length, and show the difference in telomere length (SD units) for studies comparing groups of overweight/obese to non-overweight/obese children, and the change in telomere length (SD units) per 1-SD increase in BMI. Abbreviations: SGA/AGA=small-/appropriate-and-or-large-for-gestational age; TL=telomere length; SD=standard deviation; BMI=body mass index; ES=effect size. *=For Drury et al. (2015), the standard error was set to 0.00499, instead of 0.00, since a standard error of 0.00 prevented this estimate from being meta-analysed. Given that effect sizes, standard errors and confidence intervals were rounded to 2 decimal places in this paper, this approximates this largest value that this standard error could have taken, and still have been reasonably rounded to 0.00, as reported in the manuscript. **=Wojcicki et al. (2016) same population as Wojcicki et al. (2015) ***=Alegria-Torres et al. (2016) also included overweight children in the risk group (see Table 2).
than those born small-for-gestational age (SMD [95% CI]=0.08 [0.01-0.14]).

**Heterogeneity.** Heterogeneity in meta-analyses of non-continuous adiposity exposures was variable, but generally high (ranging from 0% to 90.3%). This suggests that as much as 90.3% of variation is due to true differences between studies and not due to chance. Heterogeneity was much lower in studies using continuous measures of adiposity (range: 0–26%).

**Discussion**

We undertook a systematic review and meta-analysis of adiposity measured before 19 years of age in relation to longitudinal or cross-sectional estimates of telomere length measured in blood. To our knowledge, this is the first meta-analysis of adiposity and telomere length to synthesise evidence from neonatal measures of adiposity in relation to cross-sectionally or prospectively measured telomere length. We also provide updated estimates of the association of later childhood adiposity with telomere length\(^1\). We found no strong evidence for an association between any adiposity measure of neonatal or childhood adiposity and telomere length. A weak association suggesting that adults born small-for-gestational age had shorter telomeres later in life was based on the meta-analysis of only two studies.

Generally, more heterogeneity was observed among effect estimates from studies assessing categorical adiposity measures (e.g. obese vs non-obese, small-for-gestational age vs. appropriate/large-for-gestational-age); \(I^2\) estimates suggested that much of the between-study variation observed was due to true differences...
between studies and not due to chance. Conversely, very low heterogeneity was observed in the studies using continuous adiposity exposures. We were unable to formally assess possible sources of heterogeneity with meta-regression among studies using categorical adiposity measures, due to the small number of studies. However, heterogeneity is likely to be, at least in part, due to the differing thresholds used to define adiposity categories (e.g. percentiles of BMI).

Mechanisms for the association of adiposity and telomere length

It has been suggested that oxidative stress and inflammation are determinants of telomeric attrition, and it is proposed that as a source of oxidative stress, obesity may accelerate loss of telomeric DNA. When considered as a non-causal biomarker of ageing, the shortening of telomere length as a result of inflammation and oxidative stress is known as the ‘telomeric clock’ model. However, there is evidence that there is a complex ‘axis of ageing’ that exists between telomeres and mitochondrial function: it has therefore been suggested that telomere attrition may impact mitochondrial activity, thus leading to metabolic dysregulation. In animal models, such mitochondrial dysfunction may manifest as increased adiposity and insulin resistance. In this latter case, the causal direction could be reversed, with telomere attrition as a risk factor for disease. However, a Mendelian randomisation analysis (in which genetic variants are used as non-confounded instrumental variables of disease risk factors), of telomere length in relation to BMI found no association in this direction.

Aviv and colleagues challenge the telomere clock hypothesis by suggesting “that individuals who are born with relatively short telomeres tend to enter adulthood with short leucocyte telomere length”. Moreover, this group have observed that the variation in neonatal telomere length is larger than the average amount of attrition that would be expected over a lifetime. This challenges the clock hypothesis, since, if true, individuals should begin life with a ‘clock time’ of zero. Therefore, an alternate hypothesis is that telomere length is largely pre-determined at birth, and that variable rates of attrition in adulthood would not necessarily be enough to alter an individual’s telomere length percentile ranking. Whilst this does not negate the possibility that oxidative stress later in life may still contribute to attrition, this group state that early determinants of telomere length may be more important. Under this assumption, combining estimates of neonatal adiposity in relation to telomere length ascertained at different ages should not alter results appreciably, as each individual would be placed on a set trajectory, altered little by postnatal exposures. In this case, it could be postulated that neonatal adiposity would have a greater association with telomere length than postnatal adiposity measures (including childhood adiposity). However, our results do not provide evidence for this hypothesis, since we found no strong evidence for an association between either neonatal adiposity with telomere length.

Strengths and limitations

Although the relationship between adiposity and telomere length has been studied previously, to our knowledge, this is the first study to systematically review and meta-analyse the evidence concerning neonatal adiposity measures and telomere length. However, there are a number of limitations to this work. Firstly, although we found 19 meta-analysable estimates, the differing study designs meant that estimates were only combinable in small groups. Thus, power to detect associations within each individual category (most of which meta-analysed only 2-3 estimates in each) was limited. The meta-analysis may be subject to non-inclusion bias if the studies included in the meta-analyses are different to those not included. That said, we performed a narrative synthesis of those estimates which we were unable to include in the meta-analyses and conclusions were largely the same. The small number of studies retrieved, combined with their poor combinability, meant that meaningful inference from risk of bias assessments would not have been possible. Not only did studies vary in the measures of adiposity studied (i.e. low birth weight versus small-for-gestational age as measures of neonatal adiposity), and whether they were studied as continuous or binary exposures, but studies also varied by method used to assay telomere length, as well as the transformations performed on exposure and outcome variables, and the age of the children studied. Most studies performed only minimal adjustment for potential confounding variables (or only adjusted exposures), thus we cannot rule out unmeasured or residual confounding. Although we did not find evidence of an effect in this study, a Mendelian randomization framework may prove useful for establishing whether there is a likely causal relationship between adiposity and telomere length. Although Haycock et al. (2017) found no evidence of association between telomere length (exposure) and BMI (outcome), the reverse direction (adiposity→telomere length, as assessed in this review) has not been studied. Utilising the two-sample MR framework in order to assess adiposity as a causal determinant of telomere length would represent a highly powered method of assessing causality using summary-level genetic data.

We harmonised effect estimates into standardised units that would allow comparison of estimates obtained from both qPCR and TRF telomere lengths. However, whilst this allowed comparisons of telomere metrics measured on different scales, it does not address measurement error. Generally, Southern blot estimates (by TRF) may be longer than telomere length measured by qPCR due to inclusion of subtelomeric regions in the measure. Furthermore, there is evidence that different assays have different sensitivity to measuring extremes of telomere lengths, and as such the relationships between the two measures may be non-linear. Quantitative PCR measurements (which relate the relative fluorescence of a telomere amplicon to a single-gene reference) have their own limitations, being more prone to inter and intra-assay variation than the gold standard measurement method of TRF analysis. Whilst the majority of papers using qPCR reported coefficients of variation, suggesting an attempt to minimise batch effects had been made, the single-gene reference for qPCR assays varied between studies, which may have affected assay performance.

Conclusions

We found no strong evidence of a relationship between either neonatal or childhood measures of adiposity and concurrently or prospectively measured telomere length, but there were few combinable studies, and amongst published studies there was
substantial heterogeneity in observed effects. Further work is needed to clarify whether neonatal and childhood adiposity is associated with telomere length.

Abbreviations: BMI=Body Mass Index; WC=Waist Circumference; WHR=Waist-to-hip Ratio; qPCR=quantitative Polymerase Chain Reaction; TRF=Terminal Restriction Fragment; SMD=Standardised Mean Difference; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Competing interests
TRG reports funding from Sanofi, Biogen and GlaxoSmithKline for projects unrelated to the work presented in this manuscript.

Grant information
This work was supported by the Wellcome Trust [102433]; and the MRC Integrative Epidemiology Unit at the University of Bristol [MC_UU_12013/8].

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Acknowledgements
AG is grateful to Andrew Bell (Sheffield Methods Institute, University of Sheffield, Sheffield, UK) and Sean Harrison (Population Health Sciences, University of Bristol, Bristol, UK) for advice, and to the authors of included studies for their help with data collation.

Supplementary material
Supplementary File 1: Search strategy. 
Click here to access the data.

Supplementary File 2: Collation of formulae used in data harmonisation and extraction. 
Click here to access the data.

Supplementary File 3: R script file used for performing harmonisation prior to analysis.
Click here to access the data.

Supplementary File 4: Stata .do file used for performing meta-analysis.
Click here to access the data.

Supplementary Figure 1: Flowchart detailing how abstracts were screened and coded.
Click here to access the data.

Supplementary Figure 2: Flowchart detailing how full texts were screened and coded.
Click here to access the data.

Supplementary Figure 3: PRISMA flowchart. Flowchart detailing the number of papers retrieved at the beginning of the screening process, and reasons for exclusion at each stage.
Click here to access the data.

Supplementary Figure 4: Completed ‘MOOSE’ (Meta-analyses Of Observational Studies in Epidemiology) checklist.
Click here to access the data.

Supplementary Tables 1–3: Summary of papers retrieved, Summary of reasons for exclusion at title/abstract stage and Summary of reasons for exclusion at full text stage.
Click here to access the data.

Supplementary Table 4: Summary of papers assessed.
Click here to access the data.


Open Peer Review

Current Referee Status: ?

Referee Report 08 February 2018

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Authors aimed to systematically review and meta-analyze the results of studies assessing associations between early in life (neonatal/childhood) adiposity and telomere length. Recently (on years 2014, 2015) other authors had reported on evidence from studies of adiposity in childhood, but this is the first meta-analysis of adiposity and telomere length to synthesize evidence from neonatal measures.

This referee thinks that the issue is well prepared and updated. All tables and figures are clear and the references seem appropriate. Supporting material is also suitable enough; authors also presented the “Stata.do” file used for performing meta-analysis.

I believe that this issue will be a contribution to the readers of this journal and I would recommend the paper for indexing after some changes.

The main limitation I find is mentioned by the authors in the Discussion section. Studies on the association between the telomere length and adiposity in the neonatal period are not scarce (n= 11), however the estimates were only combinable in small groups (n= 2, n= 3, n= 4). Studies vary not only in the measures of adiposity studied but also whether they were studied as continuous or binary exposures. Each separate meta-analysis includes small number of studies, and the power of the test in such circumstances is low.

Other major considerations should be taken into account. I would suggest a restructuring of the manuscript (mainly from the Methods section), and perhaps also changing the manuscript Title.

1. Some included studies were aimed to assess the difference in telomere length between small-for-gestational-age and appropriate-for-gestational age (or appropriate- and large-for-gestational age). Even a dataset was extracted from a manuscript on faetal growth retardation (Davy 2009, Table 2):

It has been previously described that maternal complications (and even the low or high birth weight) would be related to complications in adult life. Moreover, the authors in the Discussion section mention that early determinants of telomere length may be important. I would suggest that a meta-analysis based on data on perinatal complications be considered separately, mainly because the underlying mechanisms could be different. According, authors should dedicate a
paragraph in the Discussion section to expand this topic.

Regarding the meta-analysis “AGA vs. SGA (Difference in TL [SD])”, it should be also noted that even if effect sizes were expressed as the difference in telomere length between the two groups, those estimates are not measures of “adiposity”.

2. Authors included both cross-sectional studies (in which adiposity and telomere length were measured concurrently) and longitudinal studies (in which adiposity was measured in the neonatal period/childhood and telomere length was measured later in childhood or adulthood):

Although the authors performed two separate meta-analyzes, it would be convenient to explain in Methods section that two analyzes with different specific objectives will be carried out, because I believe that the interpretation of the results of one or another study may not be the same. For longitudinal studies, the authors do not established an age of telomere length measurement. Therefore, it would be interesting for the reader to have a brief discussion about the aim of this specific study. I believe that the manuscript would be more valuable if data on “shortening” of telomere length is analyzed. Is it possible to add this analysis with the data provided in the manuscripts? Is it possible to request this information from the authors of the longitudinal studies?

3. To facilitate the pooling of results, all estimates were standardized:

Perhaps in order to diminish a possible heterogeneity on datasets, the raw data could have been requested to original authors. Besides, this could have increased the number of included studies.

4. Potential “Publication bias” assessment is missing in the manuscript.

Minor concerns:

1. In the Discussion section, the authors mention that heterogeneity is observed in the meta-analysis of categorical variables, and that this could be due to the cut-off values to define groups. However, at this point the authors should also mention other potential causes of heterogeneity such as the telomere length detection method, ethnicity, etc. Moreover, most studies performed adjustment for potential confounding variables age and sex, but we cannot exclude unmeasured or residual confounding. It is also possible that perinatal factors were involved. For example, data on Entringer 2013 manuscript was corrected for “Obstetric complications, preg. Specific stress” (Table 2), and although in this dataset the estimate was corrected, we cannot assume that other studies were free of perinatal complications.

2. In the Methods section, it is not clearly explained that different meta-analysis will be carried out. I would establish a priori that different studies will be done, and according to this, different types of data will be collected. For example, different measurements of “adiposity” were considered for incorporation into the meta-analysis, including weight and birth weight, but weight or birth weight are not measures of adiposity by themselves. Some studies presented estimates of average telomere length by adiposity exposure groups, for example, in obese vs. non obese, and such studies are eligible indeed.

3. Perhaps the authors should add a brief paragraph on the meaning of the measurement of telomere length in peripheral blood or cord, instead of the adipose tissue itself.
4. Obeying the fact that the telomere length varies by age and gender, the paragraph on adjustment for age and sex in Methods section, should be written aside.

5. Eligible studies included those with at least one measure of adiposity in the neonatal period or childhood (mean age <19 years). Childhood is the age span ranging from birth to adolescence. Perhaps the authors should reconsider the name of the group or the age range.

6. Please add in the Tables the n of the groups (binary exposures).

7. In Table 2, I was not able to find the meaning of the letters (A to F) in the Analysis column.

8. In Table 2, in the column "Sex Adjustment", in row 4 (De Zegher 2016) and also in row 16 (Shalev 2014) there is a question mark of uncertain significance.

9. In Figures 1 and 2 the statistics I² and the p-values are shown. I assumed that the p-value corresponds to the analysis of heterogeneity, but it is actually not clear.

10. In Figures 1 and 2 it would be useful for the reader to find a brief explanation on how to read the Forest plot.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

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

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

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

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