Adverse Birth Outcomes and Birth Telomere Length: A Systematic Review and Meta-Analysis

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Objectives To synthesize previous findings on the difference in birth telomere length between newborns with and without intrauterine growth restriction (IUGR) or with and without preterm birth.

Study design We systematically searched 3 databases (PubMed, Embase, and Web of Science) for publications that examined the relationships of IUGR or preterm birth with birth telomere length. We conducted meta-analysis to pool the estimated difference in birth telomere length either between IUGR and non-IUGR or between preterm birth and full-term birth. Subgroup analyses were conducted by tissues (newborn blood vs placenta) and techniques used for telomere length measurement (quantitative polymerase chain reaction [qPCR] vs telomere restriction fragment).

Results We included 11 articles on comparing birth telomere length between IUGR (combined n = 227) and non-IUGR (n = 1897) and 7 articles on comparing birth telomere length between preterm birth (n = 182) and full-term birth (n = 1320). We found IUGR was associated with shorter birth telomere length only when birth telomere length was measured in placenta (pooled standardized mean difference [SMD] = −0.85; 95% CI −1.13 to −0.57; IUGR/non-IUGR n = 87/173), but not in newborn blood (pooled SMD = 0.00, 95% CI −0.18 to 0.19; IUGR/non-IUGR n = 148/1733). Birth telomere length was significantly longer in preterm birth than in full-term birth when birth telomere length was measured by qPCR (pooled SMD = 0.40, 95% CI 0.18-0.63; preterm birth/full-term birth n = 137/682) but not by telomere restriction fragment (pooled SMD = 0.05, 95% CI −0.29 to 0.38; preterm birth/full-term birth n = 44/444).

Conclusions IUGR is associated with shorter placental telomere length and preterm birth is associated with longer birth telomere length measured by qPCR. *(J Pediatr 2019;215:64-74)*.

Intrauterine growth restriction (IUGR) and preterm birth are 2 common adverse birth outcomes that have been associated with increased mortality and morbidity during infancy in both developing and developed countries.[1-3] Moreover, there is cumulative evidence indicating that those newborns with IUGR and/or preterm birth face increased risks of obesity, hyperlipidemia, non–insulin-dependent diabetes, and atherosclerosis in later life.[4-8] One possible mechanism underlying these long-term effects of adverse birth profiles is related to abnormal telomere biology, for example, newborns with IUGR and/preterm birth often are characterized by premature aging.[9,10] Telomere length is a well-established biomarker of cellular aging.[11,12] As the protective nucleoprotein structure at the end of chromosomes, telomeres erode every time during cell replication to protect the functional DNA from shortening due to the "end-replication problem."[13,14] Critically shortened telomere length can trigger several signaling pathways such as DNA damage and extracellular stress, a response that causes cellular and organ dysfunctions.[15,16] Telomere length consistently has been found in association with aging-related chronic diseases (ie, cardiometabolic diseases). There are consistent relationships of shortened telomere length with stroke, myocardial infarction, and type 2 diabetes.[17] In addition, longitudinal studies that measured telomere length repeatedly in adults found that baseline telomere length, rather than its attrition rate between baseline and 9-year follow-up, was associated with the risk of atherosclerosis,[18] indicating the importance of baseline telomere length that are determined in earlier life.[19]

Telomere length measured at any cross-section of life is jointly determined by telomere length at birth and telomere length attrition thereafter. Telomere length attrition is rapid before age 5 years (500-1000 base pairs [bp] per year)[20] and then remains relatively stable in the rest of life (25 bp per year).[21,22] Birth telomere

bp	Base pairs
IUGR	Intrauterine growth restriction
LBW	Low birth weight
NOS	Newcastle-Ottawa Scale
qPCR	Quantitative polymerase chain reaction
SGA	Small for gestational age
SMD	Standardized mean difference
TRF	Telomere restriction fragment

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length can vary as much as 3000-5000 bp interindividually, which is greater than the overall telomere length attrition in the whole lifespan.[23] Therefore, birth telomere length determines the interindividual variation of adult telomere length and has been proposed as a biomarker potentially contributing to the development of aging-related chronic diseases.[24,25]

The great interindividual variation in birth telomere length cannot be explained by heritability alone.[26,27] Previous studies found birth telomere length differed by body size and gestational age of the newborn.[13,28] However, these findings were not consistent. For instance, birth telomere length in cord blood of infants with IUGR was found to be longer than those without IUGR when measured with either telomere restriction fragment (TRF)[23,29] or quantitative polymerase chain reaction (qPCR)[30-32] in some studies but also were found shorter with the same measurement technique (TRF[33] and qPCR[34,35]) in others. In addition, comparison of birth telomere length between IUGR and non-IUGR was found to be sensitive to the tissues used for measurement, as previous studies found placental telomere length was relatively longer than cord blood telomere length,[33,36] and the difference in telomere length was greater in placenta than in cord blood when measured in the same population.[33] Similarly for preterm birth, cord blood telomere length has been reported as longer[37] or comparable[10] in newborns with preterm birth than with full-term birth. In addition, the sample size in previous studies was relatively small, which might limit the power to detect moderate difference in birth telomere length between those born with IUGR/preterm birth and their normal counterparts. The small sample size issue also may explain the inconsistent findings from previous studies as reliability in small study could be low. There is a lack of systematic reviews on the associations between birth telomere length and IUGR/preterm birth. Therefore, we conducted a systematic review and meta-analysis to synthesize the previous findings on the associations between birth telomere length and IUGR/preterm birth. We conducted a subgroup analysis based on the tissue used to measure birth, because previous studies found placental telomere length was longer than telomere length in cord blood.[33,36] We also conducted a subgroup analysis based on the technique used for telomere length measurement, because TRF and qPCR are 2 common techniques used in telomere length measurement but their results were considerably inconsistent.[38]

Methods

The review protocol is available in the **Appendix** (www.jpeds.com), which includes the completed MOOSE (Meta-analysis of observational studies in epidemiology) and PRISMA checklists for meta-analysis. The study was registered with PROSPERO (ID: 139447).

Data Sources and Searching Strategies

We searched PubMed, Embase, and Web of Science using a combination of key words. For telomere length, we used a set of terms including telomere length, telomere, telomere shortening, and telomere homeostasis. Then we searched articles for IUGR and preterm birth, respectively. We used IUGR as the conceptual definition of inadequate fetal growth to incorporate 2 common operational definitions including low birth weight (LBW) and small for gestational age (SGA). Although used in different studies, both LBW and SGA indicate insufficient fetal growth, share causes, and have similar short- and long-term outcomes.[39] We used the following terms to search articles for IUGR: intrauterine growth restriction, fetal growth retardation, small for gestational age, low birth weight, extremely low birth weight, and very low birth weight. For preterm birth, we used the following terms: preterm birth, premature birth, infant premature, infant extremely premature, obstetric labor premature, preterm premature rupture of the membranes, and gestational age. A combination of these terms was used to search for the publications on the association of birth telomere length with either IUGR or preterm birth. We did not constrain the time of the article publication. We set English as the publication language. The cited references in the included articles were cross examined. The last search was conducted on March 28, 2018. A full search statement for each database is included in the protocol.

Article Selection

Articles identified in the 3 databases were screened by title and abstract to assess their eligibility for further review. To be included, articles need to be: (1) an empirical article published in an academic journal, (2) full-text published in English, (3) have an abstract available, and (4) be a human study of singleton births. We further excluded articles if they met any of the following exclusion criteria: (1) no quantitative measures of telomere length at birth, (2) no definition of IUGR/preterm birth vs non-IUGR/full-term birth, or (3) no comparison between groups. To maximize the number of eligible articles, we did not exclude any studies with small sample size or low quality.

Data Extraction

Two authors independently extracted the following information: study population (country, race, sample size, and health status), definitions of IUGR and preterm birth, telomere length measurement (tissue and technique), and main results. If any separately extracted data were not matched, the 2 authors would discuss and make a consensus. Where a consensus could not be reached, a third author was available to make the final decision. The Cohen unweighted κ was 0.78, indicating a good agreement between the 2 coders in information extraction. For articles with any missing information for meta-analysis, we requested it from the corresponding authors of original articles via e-mails (up to 3 attempts).

Study Quality Assessment

We assessed study quality according to the adapted version of Newcastle-Ottawa Scale (NOS) quality score for case–control studies.[40] To fit the NOS for case-control studies, we treated IUGR/preterm birth as the case group, non-IUGR/full-term

birth as the control group, and telomere length as exposure. Study quality was scored in 3 separate categories: selection (0-4), comparability (0-2), and exposure (0-3). The total score was calculated as their sum with a maximum score of 9. We considered risk of bias as high, moderate, and low if the total score was 0-2, 3-6, 7-9, respectively. Details of study quality scoring can be found in Table I (available at www.jpeds.com). The intraclass correlation coefficient was 0.996 (95% CI 0.994-0.997) when we repeatedly graded these studies with blinding to previous sores.

Meta-Analysis

We synthesized the comparison of birth telomere length either between IUGR and non-IUGR or between preterm birth and full-term birth from included articles. Standardized mean difference (SMD) of birth telomere length between groups were calculated using the Cohen d (ratio of the mean difference to the pooled standard deviation).[41] SMD from different articles were pooled with weight inversely based on the sample size. Random-effects models were used to assess the heterogeneity across articles, and the Cochran Q test was used to assess the significance of the heterogeneity (type 1 error = 0.05). We used I^2 to measure the portion of heterogeneity of total variation and defined heterogeneity as low (<25%), moderate (25%-50%), and high (>50%).[42] Inverted funnel plots were created to assess publication bias through visually inspecting asymmetry of the plots. Upon observation of evidence indicating potential publication bias, a nonparametric data augmentation (trim and fill analysis) was conducted to assess the influence of publication bias on overall pooled effect estimation.[43] For subgroup analyses, we first stratified articles by the types of tissues (ie, placenta or newborn blood) used in telomere length measurement because telomere length and its regulatory enzyme telomerase have different patterns between these tissues.[44] In addition, we stratified articles by the technique used in telomere length measurement (ie, q-PCR and TRF) because TRF measures the absolute length of telomere length and q-PCR measures its relative length to reference gene (eg, 36B4 gene).[45] In addition, we conducted subgroup analysis by reported race/ethnicity, country, and diagnosis of maternal complication for IUGR. We conducted sensitivity analysis by excluding studies that defined preterm birth differently (eg, restricted to <32 gestational weeks). All data analyses were conducted in Stata software (v12, College Station, Texas).

Results

A total of 2346 records were identified with searching strategies provided in the Methods section. After we removed 615 duplicates, 1731 records were screened by title and abstract (Figure 1; available at www.jpeds.com). There were 1655 records not meeting the inclusion criteria. Among the remaining 76 full-text articles, 61 were excluded due to lack of either birth telomere length measurement or definition of IUGR/preterm birth. Therefore, a total of 15 articles were eventually included in this systematic review: 3 on both IUGR and preterm birth, 8 on IUGR, and 4 on preterm birth only.

Characteristics of Included Studies on IUGR

Table II shows characteristics and quality of the 11 included articles on IUGR. For definitions: 3 articles used SGA defined as <10th percentile or less than the z score of −2 by sex- and gestational age within reference groups[34,46,47]; 1 used FGR defined as birth weight less than 5th percentile of reference group;[33] 3 used either SGA or IUGR defined as birth weight less than 3rd percentile of reference groups;[23,35,48] and 4 used LBW defined as birth weight less than 2500 g.[29-32] A total of 2124 participants (227 IUGR cases and 1897 controls) were included in these articles. Sample size of the included articles ranged from 52 to 752, but the numbers of IUGR cases were all relatively small (2-34). Two articles used placental tissues,[35,48] 8 used newborn's cord blood or heel stick blood,[23,26,30-32,34,46,47] and 1 used both the placenta and cord blood[33] to measure birth telomere length. Eight articles used q-PCR[30-32,34,35,46-48] and 3 used TRF[23,29,33] to measure birth telomere length. Study quality score of included studies ranged from 6-9 (maximum 9) with a median of 7 (Table II). The overall risk of bias was low to moderate in the included studies. For the selection criterion, 8 of 11 studies were scored 4 (maximum 4) with a median of 4 (Table I). For the comparability criterion, 6 of 11 studies were scored 0 (maximum 2) with a median of 0. All studies were scored 3 (maximum 3) on the exposure criterion. The overall NOS score was not correlated with effect size (r = −0.49, P = .13).

Meta-Analysis on IUGR

Heterogeneity among the included articles was large and statistically significant (I^2 = 75.9%; P < .001). As shown in Figure 2, birth telomere length was significantly shorter in IUGR cases compared with non-IUGR controls (pooled SMD −0.26, 95% CI −0.41 to −0.10). There was moderate evidence suggesting publication bias in the meta-analysis on IUGR, with more studies being scattered on the right side of the pooled SMD (Figure 3, A; available at www.jpeds.com). To assess the potential influence of publication bias, we conducted a trim and fill analysis.[43] The 2 filled studies, which were potentially unidentified publication, were estimated to report shorter telomere length in IUGR than non-IUGR (Figure 4; available at www.jpeds.com). The filled pooled SMD was −0.35 (95% CI −0.68 to −0.01), indicating a possible underestimation of the effect due to lack of publications reporting shorter telomere length in IUGR group than in non-IUGR group.

In subgroup analysis by the types of tissues in measurement of birth telomere length, placental telomere length (3 articles) remained significantly shorter in IUGR cases (pooled SMD −0.85, 95% CI −1.13 to −0.57; I^2 = 71.5%, P = .030) than non-IUGR controls (Figure 2, A). However, newborn blood telomere length (9 articles) was similar between IUGR cases and non-IUGR controls (pooled SMD 0.00, 95%CI −0.18 to 0.19; I^2 = 42.2%, P = .086).

Table II. Characteristics of included studies on IUGR

Authors	Year	Countries	Race	Health status	Sample size	Definitions of IUGR and non-IUGR	Tissue used for telomere length measure	Method of telomere length measure	Birth telomere length of IUGR case, mean ± SD	Birth telomere length of non-IUGR control, mean ± SD	Study quality score (out of 9)
Akkad et al[23]	2006	United Kingdom	White	Healthy	34 SGA; 38 AGA	SGA <3%, control >10% percentile	Cord blood	TRF	Absolute length (kb): 10.33 ± 1.3	Absolute length (kb): 8.41 ± 0.9	8
Davy et al[33]	2009	US	Filipino	Healthy	32 FGR; 36 gestational age–matched control	FGR <5th percentile; control: mean BW ± 1 SD	Fetal side placenta and cord blood	TRF	Absolute length (kb): 11.94 ± 2.54, n = 32, placenta; 11.57 ± 1.73, n = 8, cord	Absolute length (kb): 14.81 ± 2.28, n = 36, placenta; 11.76 ± 2.31, n = 9, cord	6
Toutain et al[35]	2013	US	Not specified	With prenatal complications*	24 severe IUGR; 28 controls	IUGR <3%, control >10% percentile	Chorionic villus (placenta)	qPCR	T/S ratio (%): 0.78 ± 0.26	T/S ratio (%): 1.19 ± 0.40	6
Tellechea et al[46]	2015	Argentina	Not specified	Some with hypertension	12 SGA, 45 AGA	SGA <10th, AGA: 10th-90th percentile	Cord blood	qPCR	T/S ratio (%): 1.73 ± 0.19	T/S ratio (%): 1.73 ± 0.19	8
Wojcicki et al[32]	2015	US	Latino	Some with complications†	2 LBW, 52 non-LBW	LBW <2500 g; non-LBW >2500 g	Cord blood	qPCR	Convert length (bp): 8282.2 ± 110.9	Convert length (bp): 7564.7 ± 684.2	7
de Zegher et al[34]	2016	Belgium	Not specified	Uncomplicated term singleton	27 SGA, 42 AGA	SGA <2, AGA: −1 to 1 z score	Cord blood	qPCR	T/S ratio (%): 0.75 ± 0.31	T/S ratio (%): 1.00 ± 0.39	9
Wilson et al[48,‡]	2016	Canada	Not specified	Malformation newborns excluded	31 IUGR, 109 normal control	IUGR <3th percentiles; normal control not specified	Fetal-side placenta	qPCR	T/S ratio (%): 2.23 ± 0.64	T/S ratio (%): 2.51 ± 0.60	8
Factor-Litvak et al[29]	2016	US	Multirace	Singleton	20 LBW, 470 non-LBW	LBW <2500 g non-LBW ≥2500 g	Cord blood	TFR	Absolute length (kb): 9.56 ± 0.71	Absolute length (kb): 9.50 ± 0.70	7
Lee et al[47]	2017	Singapore	Chinese	Health status unknown	20 SGA, 155 AGA	SGA <10th, AGA: 10th-90th percentile	Cord blood	qPCR	T/S ratio (%): 0.79 ± 0.26	T/S ratio (%): 0.83 ± 0.28	6
Liu et al[30]	2017	China	Chinese	Singleton, some with complications†	23 LBW, 729 non-LBW	LBW <2500 g non-LBW ≥2500 g	Cord blood	qPCR	T/S ratio (%): 0.935 ± 0.061	T/S ratio (%): 0.922 ± 0.057	7
Needham et al[31]	2017	US	Multirace	Singleton, some with complications†	2 LBW, 193 non-LBW	LBW <2500 g Non LBW ≥2500 g	Dried blood spot	qPCR	T/S ratio (%): 2.35 ± 0.14	T/S ratio (%): 2.24 ± 0.33	8

AGA, appropriate for gestational age; *BW*, birth weight; *FGR*, fetal growth restriction; *kb*, kilobase; *T/S*, relative telomere to single-copy gene.
*Amenorrhea for FGR, other prenatal diagnosis for controls; all preterm.
†Complications included preeclampsia, hypertension, gestational diabetes.
‡Telomere length measures in the assigned groups were requested from authors as data were not reported in the original article.

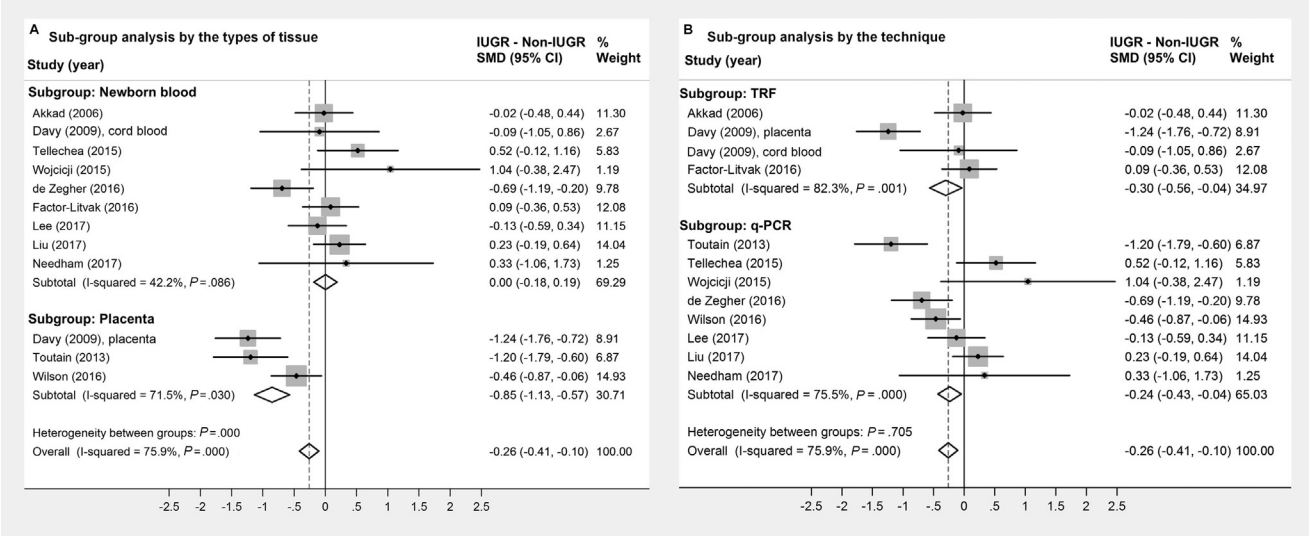

Figure 2. Forest plot of differences in birth telomere length between IUGR and Non-IUGR. **A,** Subgroup analysis by the types of tissues used in telomere length measurement; **B,** subgroup analysis by the technique used in telomere length measurement.

Heterogeneity between the 2 subgroups of studies by tissue types was significant ($P < .001$). In subgroup analysis by the technique used in measurement of birth telomere length (Figure 2, B), both qPCR-measured telomere length (8 studies, pooled SMD −0.24, 95%CI −0.43 to −0.04; $I^2 = 75.5\%$, $P < .001$) and TRF-measured telomere length (3 studies, pooled SMD −0.30, 95% CI −0.56 to −0.04; $I^2 = 39.4\%$, $P = .175$) remained significantly shorter in the IUGR cases than non-IUGR controls. Heterogeneity between the 2 subgroups of studies by measurement techniques was not significant ($P = .705$).

We conducted additional senstivity analysis based on race, country, and maternal complication diagnosis. First, we stratified the analyses by reported race/ethnicity (Figure 5; available at www.jpeds.com). Heterogeneity was significant among groups ($P < .001$). Most of the studies (6/11) reported racial groups as multiple (eg, inclusive of white, black, and Hispanic) or did not specify the racial groups. As one combined subgroup for these studies, the pooled SMD was −0.42 (95% CI −0.65 to −0.19). Two studies reported racial group as Chinese (subgroup SMD 0.07; 95% CI −0.24 to 0.38). Second, we stratified the analyses by country (US or non-US, Figure 6 [available at www.jpeds.com.]). Heterogeneity was significant between groups ($P = .03$). Five studies were conducted in the US with subgroup SMD being −0.51 (95% CI −0.78 to −0.24). Six studies were conducted in countries other than the US with subgroup SMD being −0.14 (95% CI −0.33 to 0.05). Third, we stratified the analyses by maternal health conditions (Figure 7; available at www.jpeds.com). There are 3 studies that specifically included only healthy pregnant women and the subgroup SMD was −0.56 (95% CI −0.83 to −0.29). Of the 6 studies that included pregnant women with complications (eg, gestation-induced-hypertension), the subgroup SMD was −0.16 (95% CI −0.40 to 0.07). Two studies did not report on health status of participants with SMD being −0.02 (−0.34 to 0.31).

Characteristics of Included Studies on Preterm Birth

Table III shows the characteristics and quality of the 7 included articles on preterm birth. Six articles[29-31,50-52] enrolled preterm birth cases born before 37 weeks of gestational age, and 1 study[10] only enrolled preterm birth cases born before 32 weeks of gestational age. A total of 1502 participants (182 preterm birth cases and 1320 controls) were included in these articles. Sample size of the included articles ranged from 26 to 606, but the numbers of preterm birth cases were relatively small, ranging from 1 to 97. Six articles used cord blood or venous blood[10,29-31,37,50] and 1 used placental tissue[51] to measure birth telomere length. Two articles used TRF,[29,50] and 5 used qPCR to measure telomere length.[10,30,31,37,51] Study quality score of included studies ranged from 5 to 8 (maximum 8) with a median of 7 (Table III). The overall risk of bias was low to moderate in the included studies. For the selection criterion, 5 of 7 were scored 4 (maximum 4) with a median of 4 (Table I). For the comparability criterion, 6 of 7 studies were scored 0 (maximum 1) with a median of 0. All studies were scored 3 (maximum 3) on the exposure criterion. The overall NOS score was not correlated with effect size ($r = −0.18$, $P = .89$).

Meta-Analysis on Preterm Birth

One article[31] was excluded from the meta-analysis because it included only 1 case of preterm birth. The heterogeneity among the articles was small and nonsignificant ($I^2 = 7.8\%$, $P = .368$). As shown in Figure 8, birth telomere length was significantly longer in preterm birth cases compared to

Table III. Characteristics of included studies for meta-analysis on preterm birth

Authors	Year	Country, race	Health status	Sample size	Definition of preterm birth	Tissue used for telomere length measure	Method of telomere length measure	Birth telomere length of preterm birth case, mean ± SD	Birth telomere length of full-term birth control, mean ± SD	Study quality score (out of 8)
Friedrich et al[50]	2002	Germany, race unspecified	Health status unspecified	11 term, 15 preterm	<37 wk	Cord blood	TRF	Absolute length (bp): 8512 ± 523	Absolute length (bp): 8323 ± 503	5
Menon et al[37]	2012	US, black and white	pPROM, intact membrane preterm birth, some are smokers	69 preterm birth, 35 term	<37 wk	Cord blood	qPCR	Absolute length (bp): 11 679.6 ± 4348.2	Absolute length (bp): 9011.1 ± 2497.3	7
Ferrari et al[51]	2015	Italy, race unspecified	Health status unspecified	43 term, 15 preterm birth (including pPROM)	<37 wk	Fetal side of placenta	qPCR	T/S ratio (%): 6.38 ± 5.53	T/S ratio (%): 5.18 ± 3.84	7
Factor-Litvak et al[29]	2016	US, multirace	Singleton	29 preterm birth, 433 term birth	<37 wk	Cord blood	TFR	Absolute length (kb): 9.48 ± 0.72	Absolute length (kb): 9.50 ± 0.70	7
Liu et al[30]	2017	Shanghai China; race Han	Singleton, some with complications	31 preterm birth, 575 term birth	<37 wk	Cord blood	qPCR	T/S ratio (%): 0.94 ± 0.06	T/S ratio (%): 0.92 ± 0.06	7
Needham et al[31,*]	2017	US; multirace	Singleton, some with complications	1 preterm birth, 194 term birth	<37 wk	Dried blood spot	qPCR	T/S ratio (%): 2.45	T/S ratio (%): 2.24 ± 0.33	8
Vasu et al[10]	2017	United Kingdom, race not specified	Newborns with malformation were excluded	22 preterm birth at birth, 31 term	<32 wk (very preterm)	Venous blood	qPCR	T/S ratio (%): 1.22 ± 1.62, n = 14, male; 1.32 ± 0.72, n = 8, female	T/S ratio (%): 1.13 ± 0.76, n = 18, male; 1.00 ± 0.51, n = 11, female	6

pPROM, preterm premature rupture of the membranes.
*Study excluded from meta-analysis because it included only 1 preterm birth case.

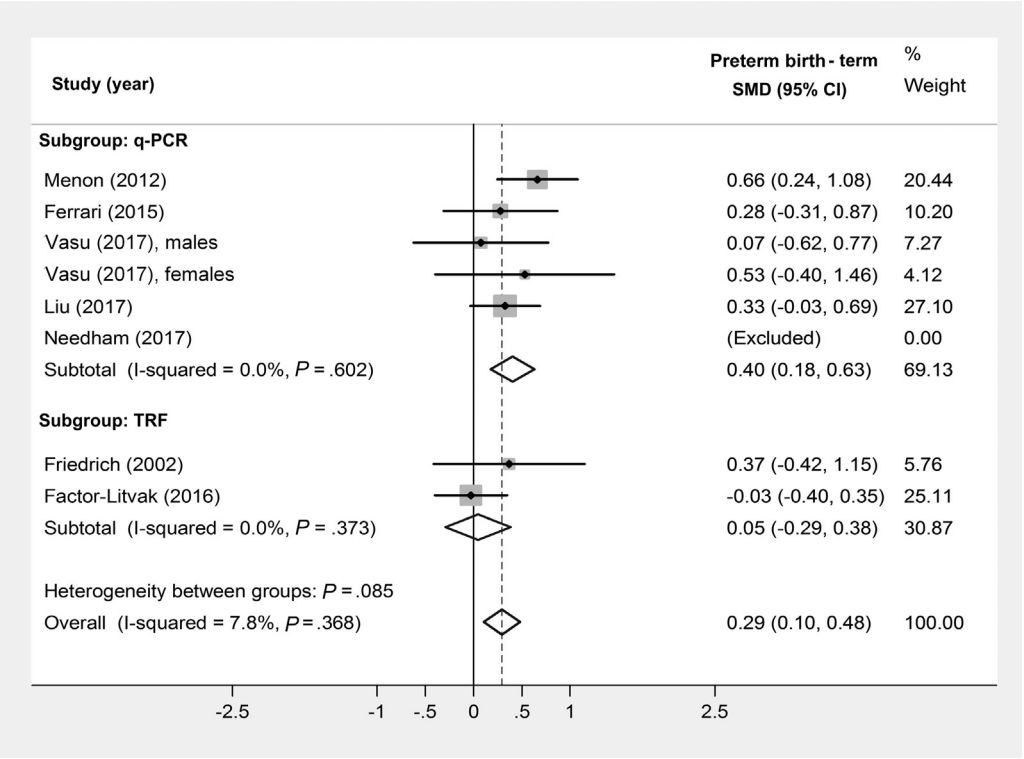

Figure 8. Forest plot of differences in birth telomere length between preterm birth and term birth.

full-term birth controls (pooled SMD 0.29, 95% CI 0.10-0.48). There was little evidence suggesting potential publication bias (**Figure 3**, B), and thus we did not perform a trim and fill analysis.

We did not conduct a subgroup analysis by the types of tissues in measurement of birth telomere length, because there is only 1 study that used placenta to measure telomere length and the other 5 used newborn blood. In subgroup analysis by the technique used in measurement of birth telomere length, qPCR measured telomere length (4 articles) remained significantly longer in preterm birth cases compared with full-term birth controls (pooled SMD 0.40, 95% CI 0.18-0.63; I^2 = 0.0% P = .602). However, TRF-measured telomere length (2 articles) was similar between preterm birth cases and full-term birth controls (pooled SMD 0.05, 95% CI −0.29 to 0.38; I^2 = 0.0%, P = .373). As a sensitivity analysis, we first excluded 1 study[10] that restricted preterm birth to <32 weeks of gestational age (**Figure 9**; available at www.jpeds.com) and the pooled SMD was 0.30 (95% CI 0.10-0.50). This is only slightly different from the pooled effect before exclusion (0.29; 95% CI 0.10-0.48), indicating a negligible influence of this study on the summary effect estimation. Second, we further excluded another study[37] that included preterm premature rupture of the membranes in the definition of preterm birth (**Figure 10**; available at www.jpeds.com). The pooled SMD was 0.19 (95% CI −0.04 to 0.42). Comparing this with the pooled SMD before exclusion, we found that the effect estimation decreased by 36.7%, indicating this study may moderately affect the effect estimation. The attenuation is driven by the strong effect from this particular study (SMD 0.66, 95% CI 0.24-1.08) and its relatively high weight (20.4%) in study pooling.

Discussion

This systematic review and meta-analysis compared birth telomere length between IUGR/preterm birth cases and their normal counterparts. We identified 11 journal articles on IUGR and 7 on preterm birth. We found IUGR was associated with shorter and preterm birth was associated with longer birth telomere length. Furthermore, in the subgroup analyses on IUGR, the difference was significant only when birth telomere length was measured in placenta but not in newborn blood. In the subgroup analyses on preterm birth, the difference was significant only when birth telomere length was measured by qPCR but not by TRF.

As a general outcome of cumulative adverse intrauterine exposures, IUGR is commonly used in studying developmental origins of aging-related diseases (eg, cardiovascular diseases, diabetes).[53,54] Telomere length, often measured in later life, is linked to aging-related diseases.[55,56] Because of the critical role of birth telomere length in determining telomere length in later life,[28,57,58] it is intriguing to explore the potential mediation role of telomere length biology underlying the relationship between intrauterine exposures and

aging-related diseases by first comparing telomere length at birth between IUGR and non-IUGR.[59,60] In this meta-analysis, we found significantly shorter placental telomere length in IUGR cases compared with in non-IUGR controls. There are 2 possible explanations. First, short placental telomere length may serve as a biomarker of accelerated placental aging that has been consistently associated with IUGR.[33,59,61] Moreover, this notion was supported by the previous finding that telomere-induced senescence biomarkers (eg, p21 protein, p16 protein, and elongation factor-1a) were substantially greater and telomere length was significantly lower in IUGR placenta.[19] Therefore, shortened placenta telomere length may cause IUGR through telomeric induced senescence.[62] In particular, shortened placental telomere length may undermine the function of placenta by triggering p53 and nuclear factor kappa-light-chain-enhancer of activated B pathways, which subsequently induce proinflammatory cytokines and oxidative stress.[12,63] Undermined placental function may limit the nutrition and oxygen transportation to the fetus and thus increase the risk of IUGR.

Second, oxidative stress also might play a role underlying the association between shorter placental telomere length and IUGR.[64] Specifically, telomere is rich of guanine that is sensitive to oxidative stress. Shortened placental telomere length may therefore reflect cumulative oxidative stress burden over intrauterine life.[65] Increased placental oxidative stress has been associated with IUGR.[66,67] As a mosaic tissue, the placental tissues can be different according to sampling sites (eg, maternal vs fetal face, near vs far from cord insertion). However, previous studies found telomere length measured from different sampling tissues of the placenta was moderately to highly correlated without detectable difference.[36,68,69] Nevertheless, further research is warranted to answer whether shortened placental telomere length could be an underlying mechanism of the association between intrauterine exposures and aging-related diseases later in life. Future studies should examine the association of placental telomere length with aging-related diseases occurrence, and the mediating role of placental telomere length in the association between intrauterine exposures and disease occurrence later in life.

Unlike placental telomere length, we did not find a significant difference in telomere length in newborn blood between IUGR cases and non-IUGR controls. One possible reason is that telomerase activity is expressed differently between the placenta and the fetus in the case of IUGR. Previous studies found placental telomerase activity decreased throughout gestation,[44] and that the telomerase activity was lower in the placenta of IUGR than of non-IUGR.[70,71] However, telomerase activity in the fetal hematopoietic system maintains at a relatively high level,[72] and IUGR fetuses may develop an adaptive responses including increased telomerase activity as response to adverse intrauterine environment (eg, high oxidative stress),[73,74] so that their blood telomere length is not substantially shorter than non-IUGR. Nevertheless, we cannot rule out the possibility of false-negative results due to the small pooled sample size for telomere length measured in newborn blood. Further studies with larger sample size are warranted to elucidate the true relationship between IUGR and birth telomere length in newborn blood. In addition, more research on postnatal telomere attrition especially in early life (eg, first 5 years)[20] can help to comprehensively evaluate the role of telomere length biology in the theory of developmental origins of health and disease.

We combined studies that used different types of newborn blood (ie, cord blood, venous blood, dried blood spot). Methodologic studies found high correlation ($r = 0.81$, $P < .001$) between telomere length measured from samples of fresh peripheral blood and of dried blood spot from the same healthy adults,[75] and moderate correlations ($r = 0.57$, $P = .001$) between telomere length measured from samples of venous blood and cord blood from the same newborn.[76] In our sensitivity analysis, exclusion of studies that used dried blood spot (for IUGR)[31] or venous blood (for preterm birth)[10] did not meaningfully change the pooled SMD, indicating the influence of the types of newborn blood may be negligible.

In this meta-analysis, we found birth telomere length was significantly longer in preterm birth compared with full-term birth. This seems contradicting with the evidence that preterm birth was associated with early aging phenotypes (eg, activation of p38 mitogen kinase).[37] Relatively longer telomere length in preterm birth may be explained by fewer cell replications and DNA turnover in the final several weeks of gestation that are missed in preterm birth.[50] In a twin study, log-transformed placental telomere length gradually decreased with gestational age, with an estimation of 13.98 kb at 28 weeks, 11.67 kb at 37 weeks, and 10.56 kb at 42 weeks of gestation.[52] One of our reviewed studies (ie, Vasu et al[10]) measured preterm birth's telomere repeatedly after birth at term equivalent age (ie, 40 weeks from conception, $n = 5$) and found preterm birth's postnatal telomere length was actually shorter than full-term birth's telomere length at birth (born at 40 weeks from conception, $n = 29$). These findings together indicated the critical role of last few weeks of gestation in determining birth telomere length in preterm birth. Future studies should consider adjusting for gestational age when comparing telomere length measured at birth and during early infancy between different groups (eg, exposed vs nonexposed). An analogy is adjusting for gestational age at birth when one examines the association between birth characteristics (eg, birth weight) and early infancy weight z score.[77]

TRF and qPCR are 2 most commonly used techniques in telomere length measurement, but previous validation studies only found modest correlation (eg, $R^2 = 0.27$[38]) between TRF and qPCR results. Our subgroup analysis by techniques found that telomere length was significantly different only when it was measured by qPCR but not by TRF between preterm birth cases and full-term birth controls. A possible reason for this inconsistency was that the total number of combined samples across studies was still small in TRF subgroup (combined $n = 65$ for preterm birth cases), which might limit the power to detect a statistically significant

difference. Another possible reason is that the restricted enzyme of TRF cleaves other genome segment identical to telomere length (ie, TTAGGG) from subtelomere and chromosomal areas than those in the telomere area. Therefore, TRF over counts telomere length and this non-differential misclassification may lead to underestimation of the difference in telomere length between comparison groups.

The comparison of different telomere length measurement techniques has recently been reviewed in detail elsewhere.[38,78,79] For a specific study, the selection of telomere length measurement technique should consider relative or absolute length of telomere, available DNA sample, processing time requirement, and cost. In particular, TRF allows counting base pairs of telomeres. But TRF is subject to overcounting nontelomeric sequences, because it heavily relies on restriction enzyme recognition sites of the telomeric region and may detect some similar but out-of-region sequences. TRF requires more DNA sample (micrograms), and thus may prohibit analyses of some banked samples with limited DNA quantity (eg, newborn's dried blood spots). TRF is labor intensive and costly. In contrast, qPCR can only measure relative telomere length, which makes direct comparison and synthesizing results from different studies challenging. The advantages of qPCR include high throughput and requirement of a small amount of DNA,[80] which make qPCR a preferred tool in large-scale epidemiologic studies, especially those with limited quantity of banked biological samples. The cost of qPCR is relatively low, although it requires specific instruments to run assays.

This study is limited in several ways. First, results for IUGR might be subject to publication bias, given the asymmetric distribution of SMD in the funnel plot. The true difference in birth telomere length between IUGR cases and non-IUGR controls was likely to be underestimated, which is supported by the results from the trim and fill analysis Second, we searched articles only in 3 electronic databases and did not include relevant unpublished studies or articles such as meeting abstracts and dissertations, which might have introduced biases. Third, we only included articles published in English, which might miss articles published in other languages. Fourth, we could not adjust for sex and race/ethnicity, as they were not adjusted in most articles. Future studies using individual participant data meta-analysis with adjustment for sex, race/ethnicity, and other potential confounders are warranted. In addition, all of these studies were conducted cross-sectionally, by defining IUGR/preterm birth and measuring telomere length at the same time (birth). Intrinsically, causality cannot be inferred from a cross-sectional study because of the unclear temporality between the exposure and outcome. Intrauterine growth and gestational age can affect fetal cell turnover and proliferation, both of which are determinants of birth telomere length.[50] Meanwhile, telomere length also may affect fetal growth and gestational age through modulation of several pathways including senescence and inflammation.[49] Therefore, interpretation of causality from our meta-analysis needs additional cautions. We also noticed the relatively small sample size (ie, 2-34 for IUGR cases and 1 to 97 for preterm birth cases) in the reviewed papers. Although meta-analysis is a useful tool to increase sample size by pooling studies, false negative results (eg, similar telomere length when measured by TRF) could not be ruled out.

In this systematic review, we found that IUGR is associated with shorter placental telomere length and preterm birth is associated with longer birth telomere length measured by qPCR. Future research should conduct mediation analyses on birth telomere length in the relationship of IUGR, preterm birth, and other intrauterine exposures with health outcomes in later life. We suggest that gestational age should be controlled for in research on determinants or outcomes of telomere length, especially for studies with preterm birth subjects. It is also important to extend the follow-up period to early childhood (another critical period for telomere attrition), and examine the influences of IUGR and preterm birth on childhood telomere length trajectories. ■

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References

1. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151-61.
2. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. Lancet 2013;382:417-25.
3. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth 2010;10(suppl 1):S1.
4. Barnes SK, Ozanne SE. Pathways linking the early environment to long-term health and lifespan. Prog Biophys Mol Biol 2010;106:323-36.
5. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ 1990;301:259-62.
6. Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, et al. Developmental plasticity and human health. Nature 2004;430:419-21.
7. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019-22.
8. Martyn CN, Barker DJ, Osmond C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. Lancet 1996;348:1264-8.
9. Paules C, Dantas AP, Miranda J, Crovetto F, Eixarch E, Rodriguez-Sureda V, et al. Premature placental aging in term small-for-gestational-age and fetal-growth-restricted fetuses. Ultrasound Obstet Gynecol 2019;53:615-22.
10. Vasu V, Turner KJ, George S, Greenall J, Slijepcevic P, Griffin DK. Preterm infants have significantly longer telomeres than their term born counterparts. PLoS One 2017;12:e0180082.
11. Duque-Guimaraes D, Ozanne S. Early nutrition and ageing: can we intervene? Biogerontology 2017;18:893-900.
12. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. J Mol Cell Cardiol 2015;89:122-35.

13. Blackburn EH. Structure and function of telomeres. Nature 1991;350:569-73.
14. Olovnikov AM. Telomeres, telomerase, and aging: origin of the theory. Exp Gerontol 1996;31:443-8.
15. Harley CB, Villeponteau B. Telomeres and telomerase in aging and cancer. Curr Opin Genet Dev 1995;5:249-55.
16. Ye J, Renault VM, Jamet K, Gilson E. Transcriptional outcome of telomere signalling. Nat Rev Genet 2014;15:491-503.
17. D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H, Pare G. Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. Circ Cardiovasc Genet 2015;8:82-90.
18. Toupance S, Labat C, Temmar M, Rossignol P, Kimura M, Aviv A, et al. Short telomeres, but not telomere attrition rates, are associated with carotid atherosclerosis. Hypertension 2017;70:420-5.
19. Aviv A, Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, et al. Leukocyte telomere dynamics: longitudinal findings among young adults in the Bogalusa Heart Study. Am J Epidemiol 2009;169:323-9.
20. Zeichner SL, Palumbo P, Feng Y, Xiao X, Gee D, Sleasman J, et al. Rapid telomere shortening in children. Blood 1999;93:2824-30.
21. Frenck RW Jr, Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci U S A 1998;95:5607-10.
22. Daniali L, Benetos A, Susser E, Kark JD, Labat C, Kimura M, et al. Telomeres shorten at equivalent rates in somatic tissues of adults. Nat Commun 2013;4:1597.
23. Akkad A, Hastings R, Konje JC, Bell SC, Thurston H, Williams B. Telomere length in small-for-gestational-age babies. BJOG 2006;113:318-23.
24. Sabharwal S, Verhulst S, Guirguis G, Kark JD, Labat C, Roche NE, et al. Telomere length dynamics in early life: the blood-and-muscle model. FASEB J 2018;32:529-34.
25. Factor-Litvak P, Susser E. The importance of early life studies of telomere attrition. Paediatr Perinat Epidemiol 2015;29:144-5.
26. Entringer S, de Punder K, Verner G, Wadhwa PD. Fetal programming of telomere biology: Role of maternal nutrition, obstetric risk factors, and suboptimal birth outcomes. diet, nutrition, and fetal programming. New York (NY): Humana Press; 2017. p. 569-93.
27. Dugdale HL, Richardson DS. Heritability of telomere variation: it is all about the environment!. Philos Trans R Soc Lond B Biol Sci 2018;373:20160450.
28. Demerath EW, Cameron N, Gillman MW, Towne B, Siervogel RM. Telomeres and telomerase in the fetal origins of cardiovascular disease: a review. Hum Biol 2004;76:127-46.
29. Factor-Litvak P, Susser E, Kezios K, McKeague I, Kark JD, Hoffman M, et al. Leukocyte telomere length in newborns: implications for the role of telomeres in human disease. Pediatrics 2016;137.
30. Liu H, Zhou G, Chen Q, Ouyang F, Little J, Zhang J, et al. Impact of dehydroepiandrosterone sulfate on newborn leukocyte telomere length. Sci Rep 2017;7:42160.
31. Needham BL, Hicken MT, Govia IO, Mitchell C, Abdou CM. Maternal social disadvantage and newborn telomere length in archived dried blood spots from the michigan neonatal biobank. Biodemography Soc Biol 2017;63:221-35.
32. Wojcicki JM, Olveda R, Heyman MB, Elwan D, Lin J, Blackburn E, et al. Cord blood telomere length in Latino infants: relation with maternal education and infant sex. J Perinatol 2016;36:235-41.
33. Davy P, Nagata M, Bullard P, Fogelson NS, Allsopp R. Fetal growth restriction is associated with accelerated telomere shortening and increased expression of cell senescence markers in the placenta. Placenta 2009;30:539-42.
34. de Zegher F, Diaz M, Lopez-Bermejo A, Ibanez L. Recognition of a sequence: more growth before birth, longer telomeres at birth, more lean mass after birth. Pediatr Obes 2017;12:274-9.
35. Toutain J, Prochazkova-Carlotti M, Cappellen D, Jarne A, Chevret E, Ferrer J, et al. Reduced placental telomere length during pregnancies complicated by intrauterine growth restriction. PLoS One 2013;8:e54013.
36. Allsopp R, Shimoda J, Easa D, Ward K. Long telomeres in the mature human placenta. Placenta 2007;28:324-7.
37. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. Front Immunol 2014;5:567.
38. Elbers CC, Garcia ME, Kimura M, Cummings SR, Nalls MA, Newman AB, et al. Comparison between southern blots and qPCR analysis of leukocyte telomere length in the health ABC study. J Gerontol A Biol Sci Med Sci 2014;69:527-31.
39. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound Obstet Gynecol 2013;41:136-45.
40. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. 2004. http://www.ohri.ca/programs/clinical_epidemiology.oxford.htm. Accessed November 1, 2018.
41. Sterne JA. Meta-analysis in Stata: An updated collection from the Stata Journal. College Station (TX): StataCorp Press LP; 2009.
42. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
43. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
44. Chen RJ, Chu CT, Huang SC, Chow SN, Hsieh CY. Telomerase activity in gestational trophoblastic disease and placental tissue from early and late human pregnancies. Hum Reprod 2002;17:463-8.
45. Cawthon RM. Telomere measurement by quantitative PCR. Nucleic Acids Res 2002;30:e47.
46. Tellechea M, Gianotti TF, Alvarinas J, Gonzalez CD, Sookoian S, Pirola CJ. Telomere length in the two extremes of abnormal fetal growth and the programming effect of maternal arterial hypertension. Sci Rep 2015;5:7869.
47. Lee SP, Hande P, Yeo GS, Tan EC. Correlation of cord blood telomere length with birth weight. BMC Res Notes 2017;10:469.
48. Wilson SL, Liu Y, Robinson WP. Placental telomere length decline with gestational age differs by sex and TERT, DNMT1, and DNMT3A DNA methylation. Placenta 2016;48:26-33.
49. Lin S, Huo X, Zhang Q, Fan X, Du L, Xu X, et al. Short placental telomere was associated with cadmium pollution in an electronic waste recycling town in China. PLoS One 2013;8:e60815.
50. Friedrich U, Schwab M, Griese EU, Fritz P, Klotz U. Telomeres in neonates: new insights in fetal hematopoiesis. Pediatr Res 2001;49:252-6.
51. Ferrari F, Facchinetti F, Saade G, Menon R. Placental telomere shortening in stillbirth: a sign of premature senescence? J Matern Fetal Neonatal Med 2016;29:1283-8.
52. Gielen M, Hageman G, Pachen D, Derom C, Vlietinck R, Zeegers MP. Placental telomere length decreases with gestational age and is influenced by parity: a study of third trimester live-born twins. Placenta 2014;35:791-6.
53. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev 2017;75:951-70.
54. Gillman MW. Developmental Origins of Health and Disease. N Engl J Med 2005;353:1848-50.
55. Entringer S, Buss C, Wadhwa PD. Prenatal stress, development, health and disease risk: A psychobiological perspective—2015 Curt Richter Award Paper. Psychoneuroendocrinology 2015;62:366-75.
56. Aviv A, Kark JD, Susser E. Telomeres, atherosclerosis, and human longevity: a causal hypothesis. Epidemiology 2015;26:295-9.
57. Benetos A, Kark JD, Susser E, Kimura M, Sinnreich R, Chen W, et al. Tracking and fixed ranking of leukocyte telomere length across the adult life course. Aging Cell 2013;12:615-21.
58. Rewak M, Buka S, Prescott J, De Vivo I, Loucks EB, Kawachi I, et al. Race-related health disparities and biological aging: does rate of telomere shortening differ across blacks and whites? Biol Psychol 2014;99:92-9.
59. Biron-Shental T, Sukenik-Halevy R, Sharon Y, Laish I, Fejgin MD, Amiel A. Telomere shortening in intra uterine growth restriction placentas. Early Hum Dev 2014;90:465-9.
60. Sampson MJ, Hughes DA. Chromosomal telomere attrition as a mechanism for the increased risk of epithelial cancers and senescent phenotypes in type 2 diabetes. Diabetologia 2006;49:1726-31.

61. Cox LS, Redman C. The role of cellular senescence in ageing of the placenta. Placenta 2017;52:139-45.
62. Sultana Z, Maiti K, Dedman L, Smith R. Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction? Am J Obstet Gynecol 2018;218:S762-73.
63. Zhang J, Rane G, Dai X, Shanmugam MK, Arfuso F, Samy RP, et al. Ageing and the telomere connection: an intimate relationship with inflammation. Ageing Res Rev 2016;25:55-69.
64. Kawanishi S, Oikawa S. Mechanism of telomere shortening by oxidative stress. Ann N Y Acad Sci 2004;1019:278-84.
65. Bijnens E, Zeegers MP, Gielen M, Kicinski M, Hageman GJ, Pachen D, et al. Lower placental telomere length may be attributed to maternal residential traffic exposure; a twin study. Environ Int 2015;79:1-7.
66. Min J, Park B, Kim YJ, Lee H, Ha E, Park H. Effect of oxidative stress on birth sizes: consideration of window from mid pregnancy to delivery. Placenta 2009;30:418-23.
67. Kim YJ, Hong YC, Lee KH, Park HJ, Park EA, Moon HS, et al. Oxidative stress in pregnant women and birth weight reduction. Reprod Toxicol 2005;19:487-92.
68. Jones CW, Gambala C, Esteves KC, Wallace M, Schlesinger R, O'Quinn M, et al. Differences in placental telomere length suggest a link between racial disparities in birth outcomes and cellular aging. Am J Obstet Gynecol 2017;216:294.e1-8.
69. Garcia-Martin I, Janssen AB, Jones RE, Grimstead JW, Penketh RJA, Baird DM, et al. Telomere length heterogeneity in placenta revealed with high-resolution telomere length analysis. Placenta 2017;59:61-8.
70. Kudo T, Izutsu T, Sato T. Telomerase activity and apoptosis as indicators of ageing in placenta with and without intrauterine growth retardation. Placenta 2000;21:493-500.
71. Izutsu T, Izutsu N, Iwane A, Takada A, Nagasawa T, Kanasugi T, et al. Expression of human telomerase reverse transcriptase and correlation with telomerase activity in placentas with and without intrauterine growth retardation. Acta Obstet Gynecol Scand 2006;85:3-11.
72. Lansdorp PM, Dragowska W, Mayani H. Ontogeny-related changes in proliferative potential of human hematopoietic cells. J Exp Med 1993;178:787-91.
73. Cross JA, Temple RC, Hughes JC, Dozio NC, Brennan C, Stanley K, et al. Cord blood telomere length, telomerase activity and inflammatory markers in pregnancies in women with diabetes or gestational diabetes. Diabet Med 2010;27:1264-70.
74. Li P, Tong Y, Yang H, Zhou S, Xiong F, Huo T, et al. Mitochondrial translocation of human telomerase reverse transcriptase in cord blood mononuclear cells of newborns with gestational diabetes mellitus mothers. Diabetes Res Clin Pract 2014;103:310-8.
75. Zanet DL, Saberi S, Oliveira L, Sattha B, Gadawski I, Cote HC. Blood and dried blood spot telomere length measurement by qPCR: assay considerations. PLoS One 2013;8:e57787.
76. Imam T, Jitratkosol MH, Soudeyns H, Sattha B, Gadawski I, Maan E, et al. Leukocyte telomere length in HIV-infected pregnant women treated with antiretroviral drugs during pregnancy and their uninfected infants. J Acquir Immune Defic Syndr 2012;60:495-502.
77. Centers for Disease Control and Prevention. Guidelines for growth charts and gestational age adjustment for premature infants and children up to the age of 24 months. Atlanta (GA): Centers for Disease Control and Prevention; 2005.
78. Eisenberg DT. Telomere length measurement validity: the coefficient of variation is invalid and cannot be used to compare quantitative polymerase chain reaction and Southern blot telomere length measurement techniques. Int J Epidemiol 2016;45:1295-8.
79. Lai TP, Wright WE, Shay JW. Comparison of telomere length measurement methods. Philos Trans R Soc Lond B Biol Sci 2018;373:20160451.
80. Turner KJ, Vasu V, Greenall J, Griffin DK. Telomere length analysis and preterm infant health: the importance of assay design in the search for novel biomarkers. Biomark Med 2014;8:485-98.

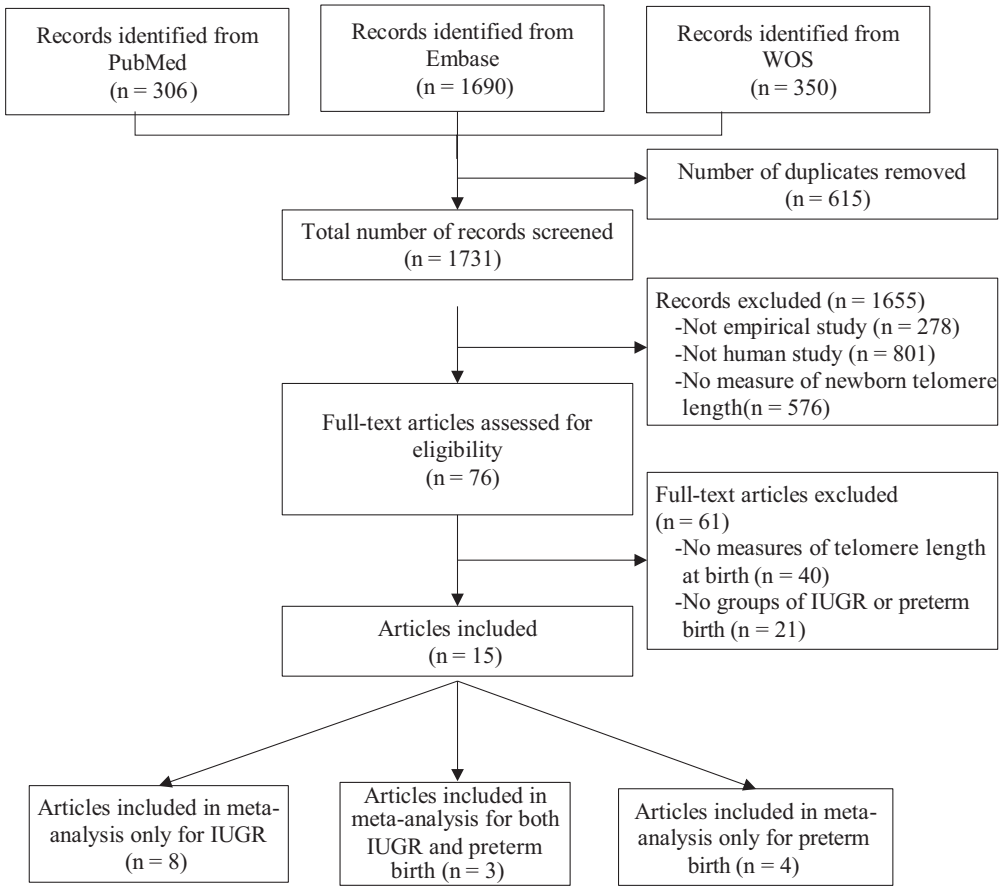

Figure 1. Flow chart for articles selected for the systematic review and meta-analysis. *WOS*, Web of Science.

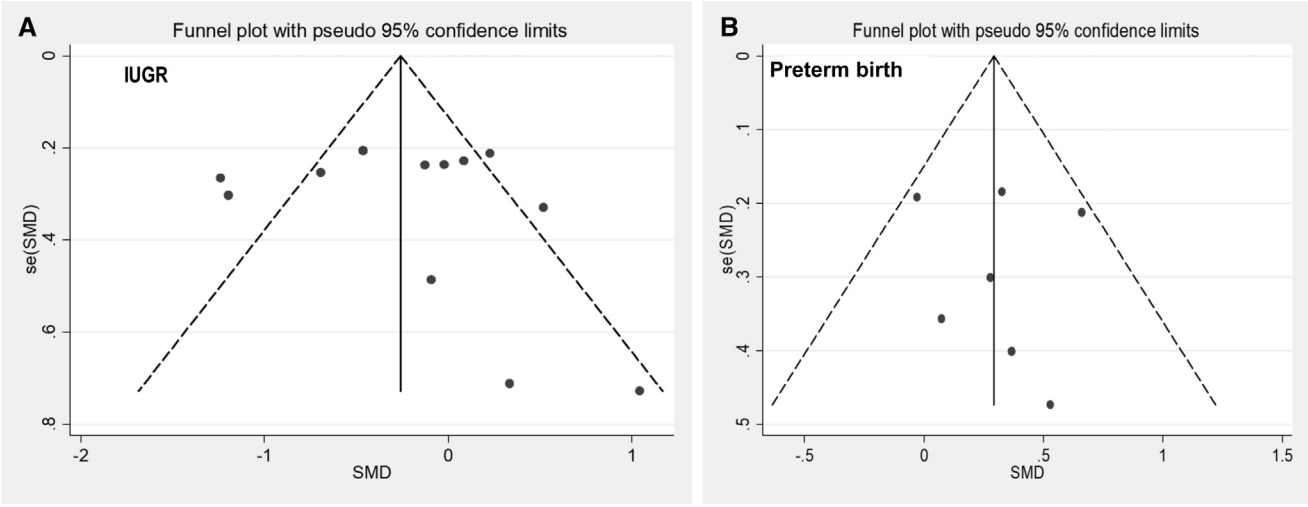

Figure 3. Funnel plots depicting the level of publication bias within the **A,** IUGR and **B,** preterm birth meta-analysis.

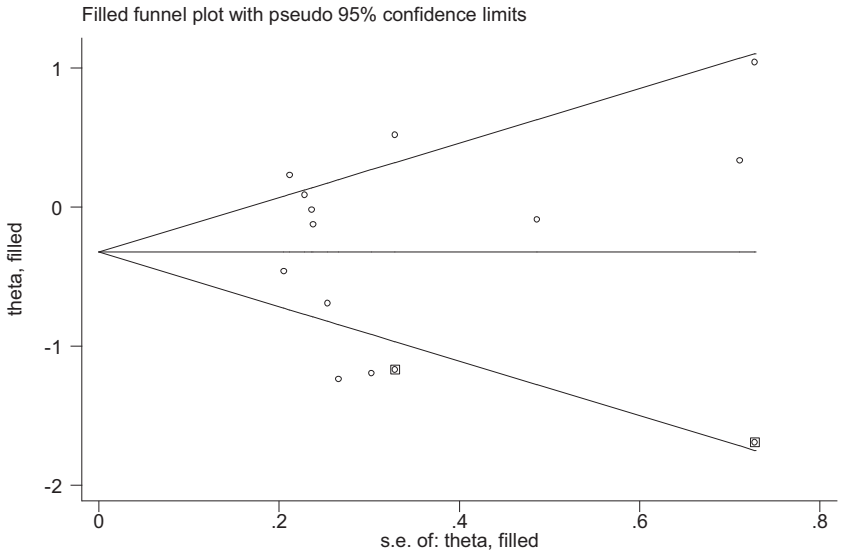

Figure 4. Funnel plots with filled studies for IUGR meta-analysis. *Round dots* indicate included studies; *square dots* indicate potentially unidentified studies that may alleviate publication biases.

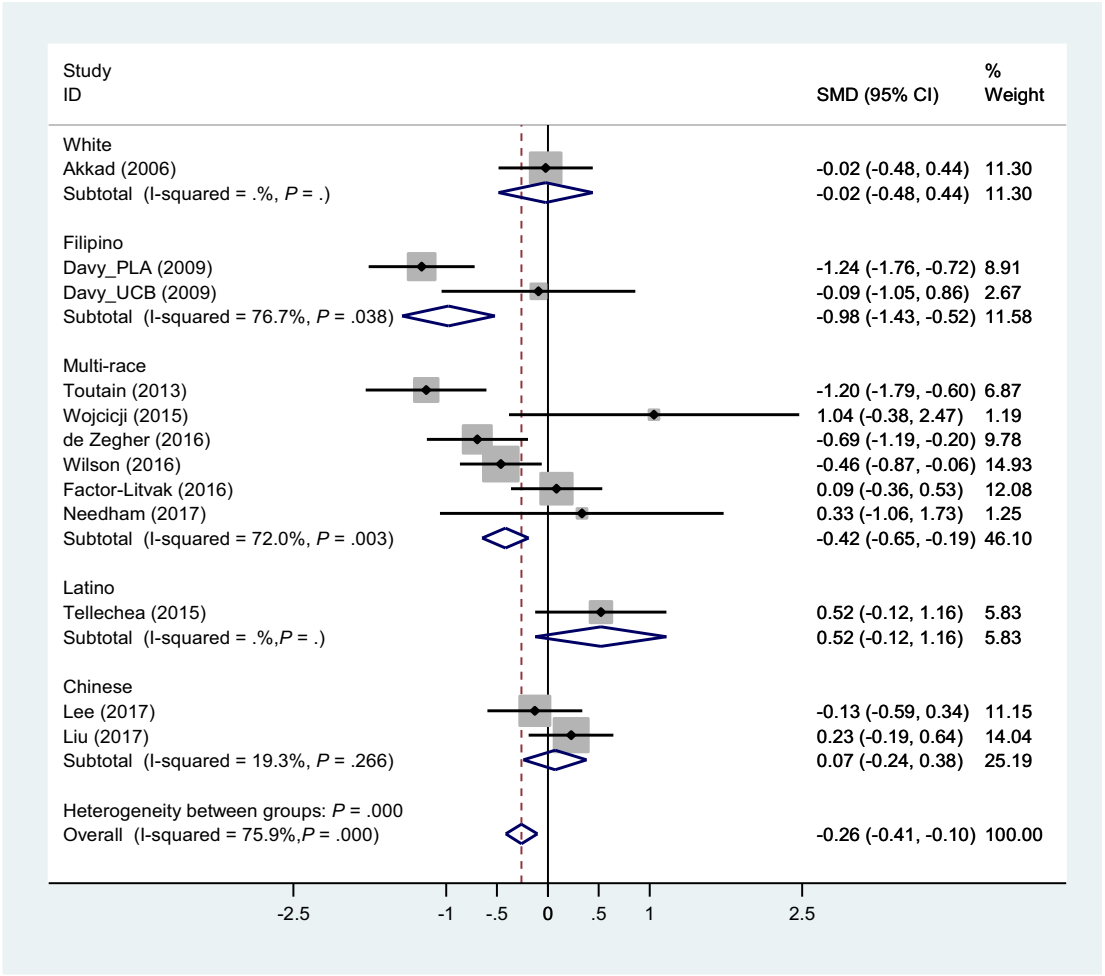

Figure 5. Forest plot of differences in birth telomere length between IUGR and non-IUGR according to reported race/ethnicity.

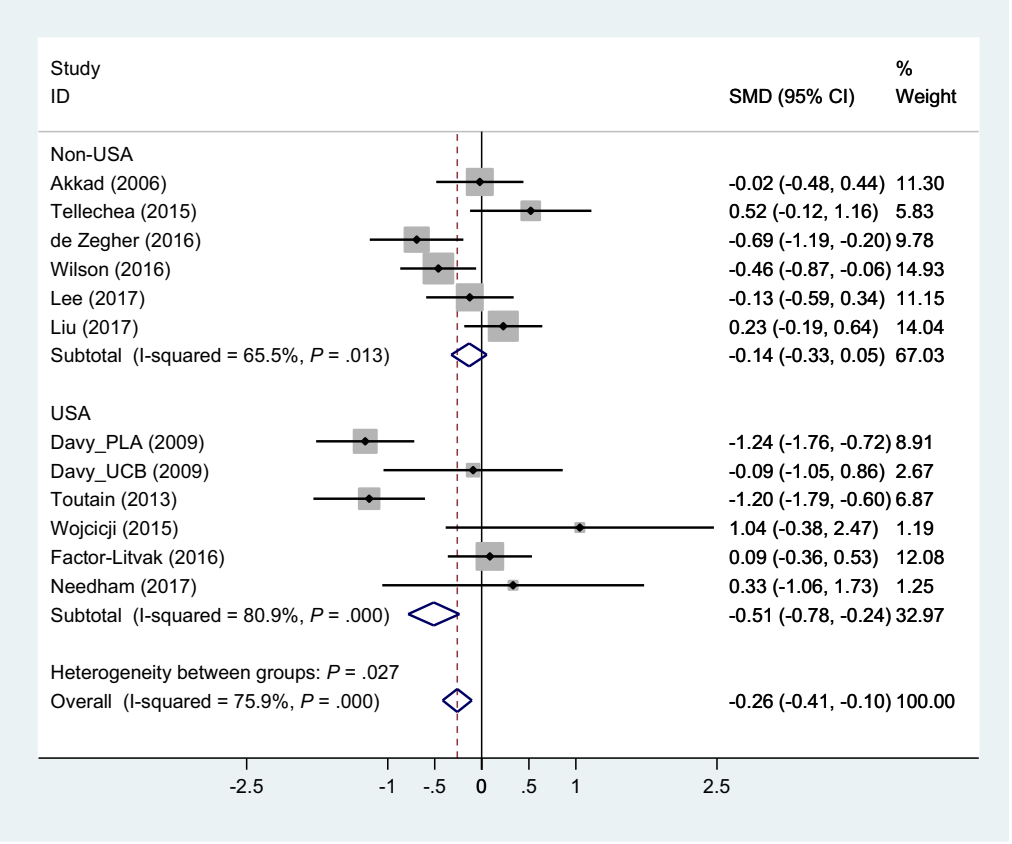

Figure 6. Forest plot of differences in birth telomere length between IUGR and non-IUGR according to country.

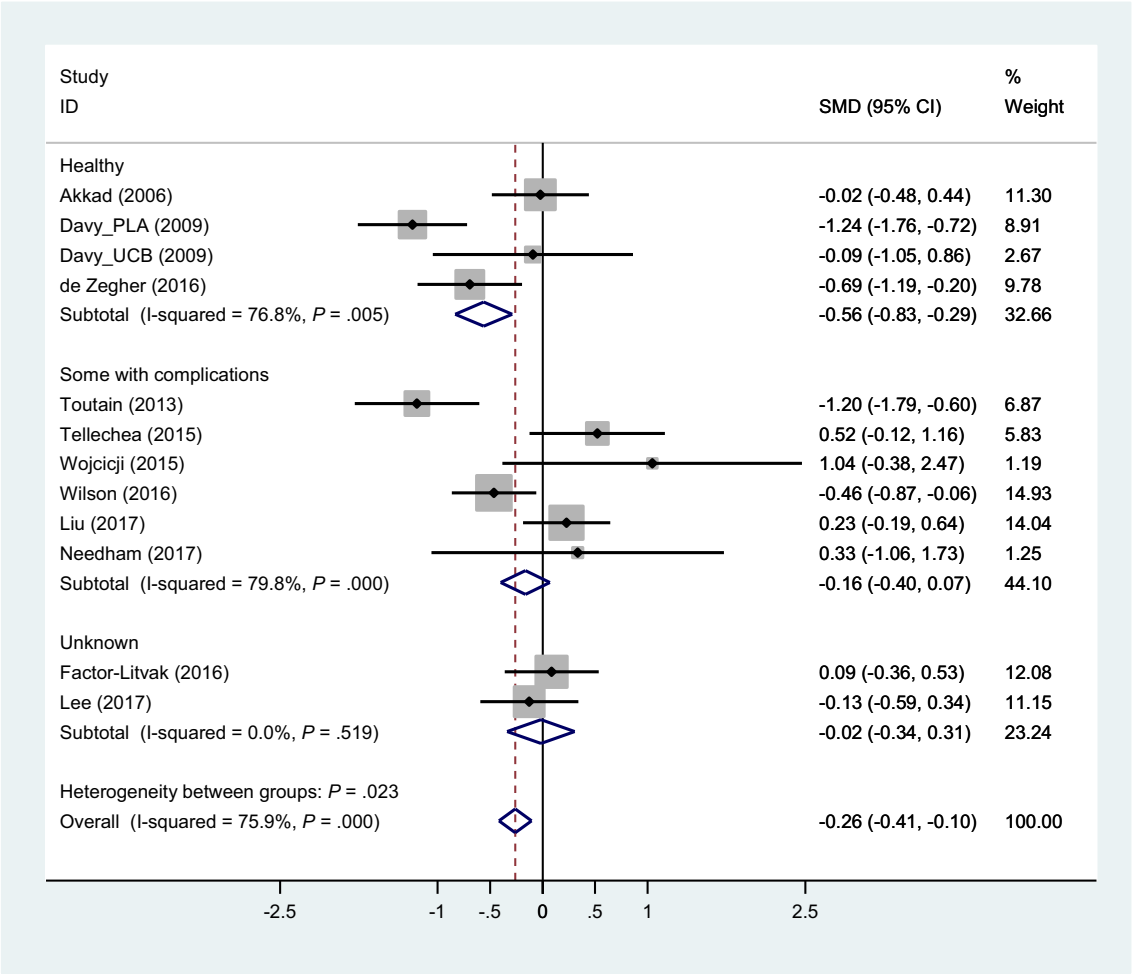

Figure 7. Forest plot of differences in birth telomere length between IUGR and non-IUGR according to prevalence of maternal complications.

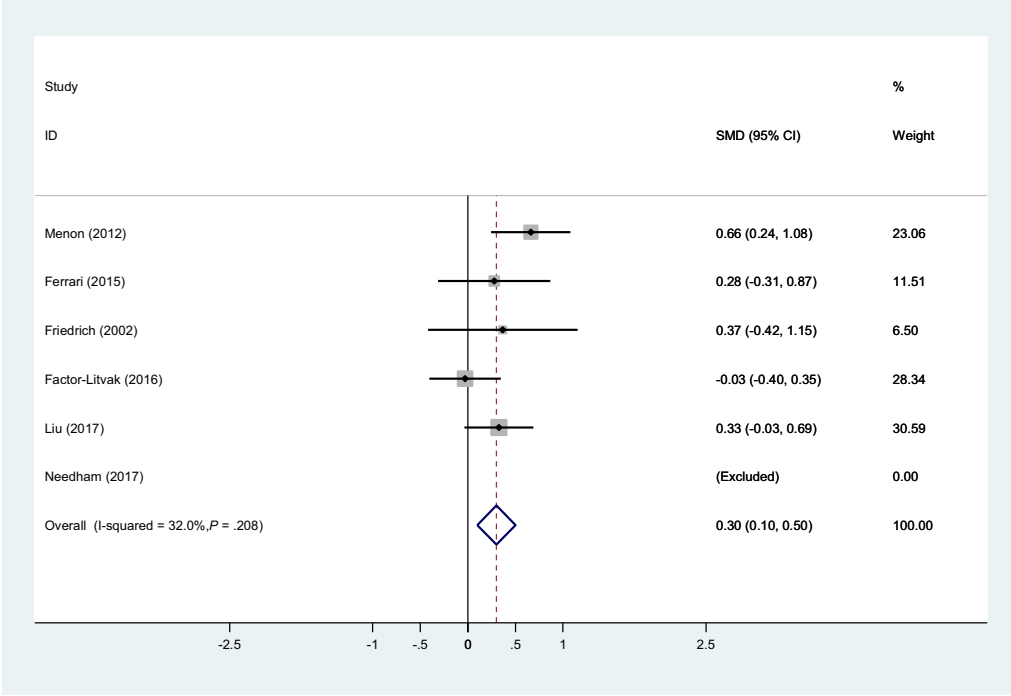

Figure 9. Forest plot of differences in birth telomere length between preterm birth and term birth excluding studies defined preterm birth <32 weeks.

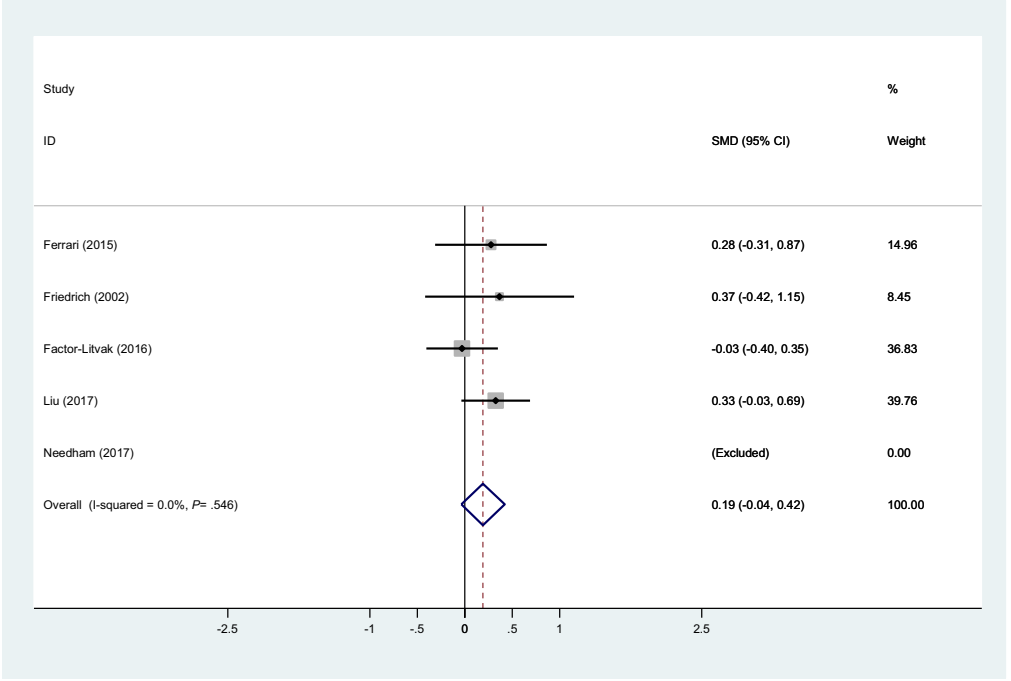

Figure 10. Forest plot of differences in birth telomere length between preterm birth and term birth excluding studies defined preterm birth <32 weeks and with preterm premature rupture of the membranes cases.

Table I. NOS quality score for included studies

		Selection				Comparability*		Exposure			Sum			
Authors	Year	Case definition	Case representativeness	Control selection	Control definition	Sex standardization	Further adjustment	Ascertainment	Consistency	Nonresponse rate	Selection	Comparability	Exposure	Overall
IUGR														
Akkad et al[23]	2006	1	1	1	1	1	0	1	1	1	4	1	3	8
Davy et al[33]	2009	1	0	1	1	0	0	1	1	1	3	0	3	6
Toutain et al[35]	2013	1	0	1	1	0	0	1	1	1	3	0	3	6
Tellechea et al[46]	2015	1	1	1	1	1	0	1	1	1	4	1	3	8
Wojcicki et al[32]	2015	1	1	1	1	0	0	1	1	1	4	0	3	7
de Zegher et al[18]	2016	1	1	1	1	1	1	1	1	1	4	2	3	9
Wilson et al[48]	2016	1	1	1	1	1	0	1	1	1	4	1	3	8
Factor-Litvak et al[29]	2016	1	1	1	1	0	0	1	1	1	4	0	3	7
Lee et al[47]	2017	1	0	1	1	0	0	1	1	1	3	0	3	6
Liu et al[30]	2017	1	1	1	1	0	0	1	1	1	4	0	3	7
Needham et al[31]	2017	1	1	1	1	0	1	1	1	1	4	1	3	8
Median		1	1	1	1	0	0	1	1	1	4	0	3	7
Preterm birth														
Friedrich et al[50]	2002	1	0	0	1	N/A	0	1	1	1	2	0	3	5
Menon[37]	2012	1	1	1	1	N/A	0	1	1	1	4	0	3	7
Factor-Litvak et al[29]	2016	1	1	1	1	N/A	0	1	1	1	4	0	3	7
Lee et al[47]	2017	1	1	1	1	N/A	0	1	1	1	4	0	3	7
Liu et al[30]	2017	1	1	1	1	N/A	0	1	1	1	4	0	3	7
Needham et al[31]	2017	1	1	1	1	N/A	1	1	1	1	4	1	3	8
Vasu et al[10]	2017	1	1	0	1	N/A	0	1	1	1	3	0	3	6
Median		1	1	1	1	N/A	0	1	1	1	4	0	3	7

N/A, not available.
*A study earns 1 point if the case and control definition include adjustment for sex and gestational age, and earns another point if sex and other factors were adjusted for in analysis.