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Etiology and Pathophysiology

Body mass index and leukocyte telomere length in adults: a systematic review and meta-analysis

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Summary

The objective of this study was to provide a systematic review and meta-analysis of studies on the relationship between body mass index (BMI) and leukocyte telomere length (LTL). Relevant studies were identified by a systematic search of MEDLINE, Embase and Web of Knowledge databases. Pooled correlation and regression coefficients were calculated using meta-analysis methods for both cross-sectional and longitudinal studies. Studies without suitable data for meta-analysis were summarized separately. Overall, 29 studies were included, of which 16 were eligible for meta-analysis, including two longitudinal studies. The majority of studies reported an inverse relationship between BMI and telomere length. For cross-sectional studies, the pooled estimates for correlation and regression coefficients were –0.057 (95% confidence interval [CI]: –0.102 to –0.012) and –0.008 kBP kg m^{-2} (95% CI: –0.016 to 0.000), respectively. The two longitudinal studies were small (70 and 311 subjects), covered different age ranges and yielded inconsistent results. No evidence of any gender difference was observed. Despite some variation between studies and very limited data from longitudinal studies, the results of this meta-analysis suggest a biologically plausible inverse association between BMI and LTL in adults. However, the associations require clarification, in particular by large longitudinal studies with careful control for possible confounding factors in overall, age- and sex-specific analyses.

Keywords: BMI, leukocyte telomere length, obesity, review.

Abbreviations: BMI, body mass index; kBP, kilobase pairs; LTL, leukocyte telomere length; PCR, polymerase chain reaction; QS, quality score; TL, telomere length; TRF, terminal restriction fragment.

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Introduction

Telomeres are hexameric (TTAGGG) nucleotide sequences at the ends of chromosomes that are repeated hundreds to thousands times (1). These gene-poor regions are bound by specific proteins, forming a complex. This complex protects ('caps') the ends of chromosomes, preventing their degradation and fusions. Telomeres shorten with each cell division as a result of the 'end-replication problem', i.e. incomplete replication of linear chromosomes by DNA polymerases (2–4). When telomeres are critically short their associated proteins can no longer be recruited, leaving the chromosome ends 'uncapped'. Short telomere length (TL) has been associated with increased all-cause mortality and several diseases including cardiovascular diseases, diabetes mellitus, dementia and osteoporosis (5–8).

TL has high inter-individual variability. It is both highly heritable and affected by exposure to environmental and

lifestyle factors throughout life (9,10). These factors are thought to alter TL by their effects on oxidative stress and systematic inflammation (11). Oxidative stress is caused by accumulation of reactive oxygen species (ROS) within cells. ROS are oxygen containing highly reactive molecules. Elevated ROS levels damage cell constituents, leading to cellular dysfunction (12). The G triplets in telomeres are particularly vulnerable to attack by ROS (13). As DNA repair machinery is deficient in telomeres, this attack and cleavage results in telomere shortening (14). Because of its effects on immune cell turnover and oxidative stress, inflammation also causes accelerated telomere loss (15).

Obesity is defined according to the ranges of body mass index (BMI = weight [kg]/height $[m]^2$) by the World Health Organization. A BMI value within the range of 18.5–24.9 is categorized as normal, 25.0–29.9 as overweight and ≥30 as obese. Obesity is now considered as a global epidemic and a leading cause of death as a result of metabolic imbalances caused by excessive adiposity (16,17). Obesity is a state of high-systematic oxidative stress and inflammation (18), characterized by activation of oxidative stress processes and release of inflammatory cytokines. Because of the negative effects of oxidative stress on TL, it is hypothesized that obesity accelerates telomere shortening. There are studies confirming this hypothesis whereas others have not found any association. Moreover, the majority of associations found so far included adult individuals in middle ages only. It is furthermore unclear if and to what extent BMI across the whole range of values might affect TL.

A recent review by Tzanetakou *et al*. (19) provided some evidence linking obesity and accelerated ageing process via regulation of telomeres. However, their review was narrative (non-systematic) in nature, was not restricted to studies in humans and addressed a broad range of adiposity measures. Moreover, no meta-analysis was carried out.

We therefore conducted a systematic review and meta-analysis of epidemiological studies, specifically focusing on studies reporting on the association of BMI and leukocyte TL (LTL) in the general population, paying particular attention to study design and gender differences.

Methods

A systematic search of the literature was performed and is reported in adherence to the standards of reporting of meta-analyses of observational studies in epidemiology (20).

Search strategy

PubMed Online (Ovid Technologies, New York, NY, USA), Embase (Elsevier, Amsterdam, The Netherlands) and Web of Knowledge (Thomson Scientific Technical Support, New York, NY, USA) databases were used for the search from the inception until 16 January 2013. Search terms 'telomere', 'weight' and 'obes/*' were used in all three databases. The Reference Manager 12 software (Thomson Reuters, New York, NY, USA) was used for searching. Duplicates were removed. Two reviewers (AM and AKZ) performed independent searches and compared results, until consensus on the optimal research strategy was reached.

Eligibility criteria

Articles that were not human-based epidemiological studies (i.e. methodological and laboratory-based studies using cell lines or other organisms), irrelevant to the research question (did not report on the association between BMI and LTL) and not primary literature were excluded. Studies that measured TL in cells other than leukocytes were also excluded, as LTL is the most commonly used proxy of TL in tissues that are affected by ageing (21). No exclusion criteria based on age were set. Only studies that reported on the relationship between BMI and LTL were included in meta-analyses. From case-control studies, only data from controls were used.

Studies that reported on the association between BMI and LTL without providing suitable data for meta-analysis were summarized in a separate table.

Study selection

In an initial step, titles and abstracts were screened for potentially eligible studies, which subsequently underwent full-text review. Cross referencing of selected studies was employed to complete identification of eligible studies.

Data extraction

Data were extracted from eligible studies independently by two reviewers (AM and AKZ) in a standardized manner, and any disagreement was resolved by consensus. Extracted items included study design, author(s), year of publication, study population, country, number of subjects, mean age, age range, mean BMI, LTL measurement method, correlation coefficient of BMI, and LTL and regression coefficient for BMI when regressed against LTL where available.

Data presentation and meta-analyses

Data are presented separately for studies presenting correlation and/or regression coefficients (which were included in the meta-analyses) and other studies not reporting any correlation or regression coefficients.

In order to assess the quality of studies to be included in the meta-analyses, separate study quality scores (QS),

ranging from 0 to 4, for correlation and regression coefficients were developed. The scores were built by taking into consideration the quality of the predictor variable (self-reported vs. measured BMI), quality of the outcome variable (reporting on the coefficients of variation for LTL measurements), quality of the calculated estimates (adjustments for age and sex) and the width of the age range of the cohort (two or more decades vs. less than two decades[1]). Studies with QS equal to or greater than 3 were classified as high-quality studies. Subgroup analyses for high- and low-quality studies were carried out.

Meta-analyses were conducted separately for cross-sectional and longitudinal studies. Separate meta-analyses were performed for correlation and regression coefficients. The analyses for regression coefficients were stratified by LTL measurement method. Summary statistics are reported separately for studies that reported their coefficients for women and men together, women only and men only. The random effects estimates, which allow for variation of true effects across studies, were taken as main results. Comprehensive Meta-Analysis software version 2.2.048 (Biostat, Englewood, NJ, USA) was used for the analyses. Forest plots were created for graphical display of the results. The *Q*-statistic, which reflects the percentage of total variability in effect size because of heterogeneity between studies, and Kendall's tau, which helps to identify a potential publication bias, were also calculated.

Sensitivity analyses were performed to determine the robustness of the estimates across subgroups of studies defined by study population and study design and quality characteristics.

Results

The literature search process is illustrated in Supplementary Fig. 1. After exclusion of duplicates, the remaining 652 articles were screened for abstracts and titles. One hundred forty-five articles went through full-text review after exclusion of articles that were not human-based epidemiological studies or not relevant to the research question (did not report on the association between BMI and LTL). Twenty-nine eligible studies were identified. However, 13 of them were not suitable to be included in meta-analysis, as no correlation or regression coefficients were reported. Those studies and their main findings are summarized separately in Table 1.

Three studies (23,26,30) included children and adolescent participants with an age range of 2–18 years. However, none of these studies were suitable for meta-analysis. Hence, the association between BMI and LTL could only be investigated in adults.

Two of the studies included in meta-analysis are longitudinal. One case-control study was included in this review (35). The study had a nested case-control study design. Only data from the control group were used in the analyses. The study by Kiefer *et al.* (36) includes two different study populations.

Figure 1 shows the information provided by the cross-sectional studies included in meta-analyses. Correlation coefficients were provided for both sexes, women and men, by six, seven and three studies, respectively. Regression coefficients were reported by seven terminal restriction fragment (TRF)-based studies and three polymerase chain reaction (PCR)-based studies. Among the former, three, two and two studies reported regression coefficients for men and women, women and men only, respectively. The unit of regression coefficients from TRF-based studies was kBP kg m^{-2}. Regression coefficients in PCR-based studies represent one unit change in relative LTL (T/S ratio) per unit of BMI (kg m^{-2}).

Study QS (0–4) for studies included in meta-analyses averaged 2.7 and 3.1 for correlation and regression coefficients, respectively. The proportion of high-quality studies (QS ≥ 3) was 50 and 56% for studies reporting correlation and regression coefficients, respectively.

Table 2 and Supplementary Table 1 shows authors, country, sample size, mean age, age range, mean BMI, gender of study participants, LTL measurement method, correlation and regression coefficients between BMI and LTL with their *P*-values, and list of factors they were adjusted for cross-sectional and longitudinal studies, respectively. The summary statistics, their *P*-values and 95% confidence intervals calculated by the meta-analyses are presented for correlation and regression coefficients separately in Table 3 for cross-sectional studies.

In summary, the majority of the studies were from the United States. The age range of studies included in meta-analyses is 18–93 years. The mean BMI of study populations ranges 24.5–30.4. The majority of the correlation coefficients reported were not adjusted for covariates; by contrast, all regression coefficients were adjusted for multiple possible confounding factors including age.

Cross-sectional studies

Correlation between body mass index and leukocyte telomere length

A total of six studies from the United States, Saudi Arabia and Finland reported the correlation coefficient between BMI and LTL for both sexes together in their study population. The coefficients ranged from 0.05 to –0.27. The inverse correlations found by Lee *et al.* (40), Al-Attas *et al.* (43), Nordfjäll *et al.* (44) and Hunt *et al.* (46) were statistically significant, whereas others did not detect statistically significant correlations. One of the coefficients (40) was only adjusted for age, and another one (44) was adjusted for age, sex and recruitment centre. The other coefficients

[1]An indicator of external validity/generalizability.

Table 1 Summary of main findings of the studies that could not be included in meta-analysis

Authors, year	Country	Sample size	Study design	Age range (mean)	Sex	BMI–TL association	*P*-value	Other adiposity–TL association	Measurement method	Nature of association of adiposity with TL
Tiainen *et al.*, 2012 (22)	Finland	1,942	Cross-sectional	57–70	M, W	Data not given		WHR	PCR (T/S ratio)	No association
Buxton *et al.*, 2011 (23)	France	793	Cross-sectional	2–17	Boys and girls	Unpaired *t*-test for obese vs. non-obese children	$P < 0.0001$	Weight, BMI *z*-score	PCR (T/S ratio)	Inverse (both overall and gender-specific)
Entringer *et al.*, 2011 (24)	Germany	94	Cross-sectional	(24.5)	M, W	(Pre-natal stress adj.) â = –0.001 (unadj.) â = 0.000 (fully adj.)	*P*-value not given but no statistical significance	None	PCR (converted to kBP)	No association
Strandberg *et al.*, 2011 (25)	Finland	622	Cross-sectional	(75.7)	M	TL differences across BMI classes	*P* (unadj.) = 0.14 *P* (age adj.) = 0.10 *P* (multiple adj.) = 0.07	Weight gain between 1960 and 2003	TRF analysis (kBP)	Weak inverse association with no statistical significance
Zhu *et al.*, 2011 (26)	USA	667	Cross-sectional	14–18	Boys and girls	Data not given		WC, %BF, VAT, SAAT	PCR (T/S ratio)	No association with any adiposity variables
Farzaneh-Far *et al.*, 2010 (27)	USA	608*	Longitudinal	(66.1)	M, W	Cross sectionally no association; waist-to-hip ratio longitudinally and telomere loss rate per year â (adj.) = –86; $P = 0.02$		Adiponectin, leptin, CRP, IL-6, TNF-á WHR â (adj.) = –120 (BP per year) $P = 0.003$	PCR (converted to kBP)	Inverse for WHR but not BMI for rate of yearly telomere loss
Prescott *et al.*, 2010 (28)	USA	Control: 1,181	Nested case-control study	(~59)	W	BMI vs. RTL quartile in controls; *P* for trend = 0.003		Weight gain from 18 until blood collection	PCR (T/S ratio converted to *z*-scores)	Inverse
Kim *et al.*, 2009 (29)	USA	644	Cross-sectional	35–74	W	*P* for trend	0.003	BMI in 30 s, weight change since 30 s, frequency of weight cycling	PCR (T/S ratio)	Inverse
Zannolli *et al.*, 2008 (30)	Italy	76 (53 children, 23 adults)	Cross-sectional	2.5–15.2; 28.0–67.3	M, W	*t*-Test for difference of means for obese and normal	Children: 0.402 Adults: 0.041	None	TRF analysis (kBP)	No association in children; inverse association in adults
McGrath *et al.*, 2007 (31)	USA	Control: 192 Cases: 184	Case-control	(64.1)	M, W	Not given	$P > 0.8$	None	PCR (T/S ratio)	No association
Cherkas *et al.*, 2006 (32)	UK	1,552	Cross-sectional	32–68	W	*P* for trend (age adj.)	$P < 0.045$	None	TRF analysis (kBP)	Inverse
Epel *et al.*, 2006 (33)	USA	62	Cross-sectional	20–50	W	Data not given		Sagittal diameter	PCR	No association
Bischoff *et al.*, 2006 (34)	Denmark	812	Cross-sectional	73–101	M, W	Data not given		None	TRF analysis (kBP)	No association

*All with stable coronary artery disease.
%BF, percentage body fat; adj., adjusted for; BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; kBP, kilobase pairs; M, men; PCR, polymerase chain reaction; RTL, relative telomere length; SAAT, subcutaneous abdominal adipose tissue; TL, telomere length; TNF-á, tumour necrosis factor á; TRF, terminal restriction fragment; unadj., unadjusted for; VAT, visceral adipose tissue; W, women; WC, waist circumference; WHR, waist-to-hip ratio.

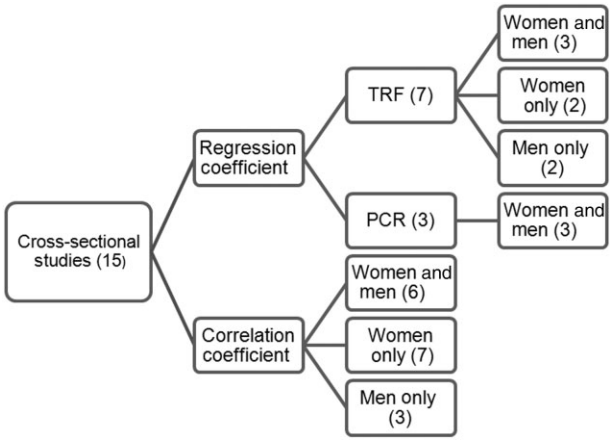

Figure 1 Information provided by cross-sectional studies involved in meta-analysis. The number of studies in each group is indicated in parenthesis. PCR, polymerase chain reaction; TRF, terminal restriction fragment.

were not adjusted. Meta-analysis of these coefficients supported the inverse relationship between BMI and LTL with statistical significance (pooled $r = -0.092$ [95% CI: –0.163 to –0.019], $P = 0.013$).

Women-specific correlation coefficients between BMI and LTL were reported by six studies. The study participants were from the United States, United Kingdom and Sweden, with an age range of 18–79 years. The coefficients ranged from 0.18 to –0.29. Except for two studies, all coefficients showed an inverse relationship with statistical significance. The pooled coefficient calculated by the meta-analysis also indicated an inverse relationship. However, the estimate failed to reach statistical significance (pooled $r = -0.045$ [95% CI: –0.101 to 0.012], $P = 0.119$). Only three men-specific correlation coefficients were reported. Two of them were statistically significant, showing an inverse relationship. Although the pooled estimate from the meta-analysis also indicated an inverse correlation, the estimate was not statistically significant (pooled $r = -0.055$ [95% CI: –0.159 to 0.050], $P = 0.303$). When all correlation coefficients were pooled together without using overlapping data, the pooled coefficient indicated an inverse association with statistical significance ($r = -0.057$ [95% CI: –0.102 to –0.012], $P = 0.013$) (Fig. 2). Subgroup analysis including only age-adjusted correlation coefficients yielded similar results ($r = -0.059$ [95% CI: –0.127 to 0.010], $P = 0.092$). The estimate did not reach statistical significance, which is probably due to the small number of studies included. The pooled estimate for the not age-adjusted coefficients was greater than the overall estimate and reached statistical significance ($r = -0.096$ [95% CI: –0.172 to –0.018], $P = 0.016$) (Supporting Information Table S2).

A statistically significant heterogeneity was detected among studies ($Q = 56.93$; $P = 3.4 \times 10^{-8}$). After exclusion of studies by Sun *et al.* (39), Kiefer *et al.* (36), Al-Attas *et al.* (43) and Lee *et al.* (40), the heterogeneity was dissolved ($Q = 11.45$; $P = 0.076$). The pooled estimate from the remaining studies was calculated as –0.045 (95% CI: –0.077 to –0.014).

The funnel plots (Supporting Information Fig. S2) and Kendall's tau statistics did not show evidence of publication bias for any meta-analysis.

Regression coefficient of body mass index against leukocyte telomere length

Regression coefficients of BMI with absolute LTL for men and women were reported by three studies (43,45,47). The age of study participants ranged from 18 to 92 years, and coefficients ranged from –0.15 to –0.01 BP kg m^{-2}. Two of the coefficients showed statistical significance (43,45). There were only two studies providing sex-specific regression coefficients (45,48). Although the pooled coefficients were not statistically significant, they all showed an inverse association. When all the regression coefficients from mutually exclusive study populations were pooled together without taking gender stratification into account, a marginally statistically significant summary estimate was calculated ($\beta = -0.008$ [95% CI: –0.016 to 0.000], $P = 0.058$). Although heterogeneity was also detected among these studies, excluding the outlier study (43) did not alter the summary statistic to a relevant extent ($\beta = -0.008$ [95% CI: –0.012 to –0.004], $P < 0.0001$).

Three studies reported regression coefficients for BMI with relative LTL for men and women together (37,40,41). The pooled coefficient suggested an inverse relationship, although it was not statistically significant ($\beta = -0.014$ [95% CI: –0.037 to 0.010], $P = 0.249$).

The funnel plots and Kendall's tau statistics did not show evidence of publication bias for any meta-analysis (Supporting Information Fig. S3).

Longitudinal studies

Two relatively small-sized longitudinal studies were identified (number of study subjects: 70 and 311, respectively). Both studies reported a correlation coefficient between change in BMI and rate of yearly telomere loss. Hovatta *et al.* (38) also assessed the correlation between baseline BMI and LTL; this study was therefore also included in the meta-analysis of cross-sectional studies. Although both coefficients were statistically significant, they were in opposite directions. The study with an age range of 40–64 years found a positive relationship (38), whereas Gardner *et al.* (50) with an age range of 21.0–43.5 years found an inverse relationship. Nevertheless, the multiple factor-adjusted regression coefficients from both studies suggested an inverse relationship, which was statistically significant in the study of Hovatta *et al.* (38) As these studies used

Table 2 Details of cross-sectional studies

Authors, year	Country	Sample size	Age range (mean age)	Mean BMI	Sex	BMI and TL association				Measurement method
						Correlation coefficient		Regression coefficient*		
						Correlation coefficient (*P*-value)	Covariates adjusted for	Regression coefficient (*P*-value)	Covariates adjusted for	
Njajou *et al.*, 2012 (37)	USA	2,721	70–79 (73.6)	27.4	M, W	–	–	–0.12 (>0.05)	Age, sex, race, smoking, physical activity, T2DM	PCR (T/S ratio)
Hovatta *et al.*, 2012 (38)	Finland	311	40–64 (56.9)	30.4	M, W	0.01 (0.83)	None	–	–	PCR (T/S ratio)
Sun *et al.*, 2012 (39)	USA	5,862	(58.7)	25.2	W	0.02 (0.15)	Age	–	–	PCR (T/S ratio converted to *z*-scores)
Lee *et al.*, 2011 (40)	USA	309	18–80 (39.7)	26.4	M, W	1 = –0.315 2 = –0.227 (<0.0001)	1: None 2: Age	–0.021 (0.001)	Age and other significantly associated factors†	PCR (T/S ratio)
Diaz *et al.*, 2010 (41)	USA	317	40–64 (50)	29.2	M, W	0.05 (0.37)	None	2.98×10^{-4} (0.92)	Age, sex, race	PCR (T/S ratio)
Cassidy *et al.*, 2010 (42)	USA	2,284	(58.9)	25.5	W	–0.06 (0.009)	None	BMI ≥35 vs. normal BMI –0.14 (0.03)	Age and other significantly associated factors‡	PCR (T/S ratio converted to *z*-scores)
Al-Attas *et al.*, 2010 (43)	Saudi Arabia	193	18–66 (40.6)	28.3	M, W	–0.27 (all) –0.26 (women) –0.25 (men) (all $P < 0.05$)	None	–0.15 (0.004)	Age and other significantly associated factors§	PCR (converted to kBP)
Kiefer *et al.*, 2008 (36)	USA	Study 1: 36 Study 2: 20	Study 1: 20–50 (38.9) Study 2: 52–79 (59.7)	Study 1: 25.0 Study 2: 27.9	W	S1: 0.18 ($P > 0.5$) S2: –0.29 ($P > 0.5$)	None	S1: –0.12 (0.36) S2: –0.29 (0.22) Combined: –0.12 ($P > 1$)	S1: age, smoking S2: age Combined: age, smoking	PCR (T/S ratio)
Nordfjäll *et al.*, 2008 (44)	Sweden	989	26–75 (52.6)	26.4	M, W	All: –0.08 (0.013) Men: –0.041 (0.35) Women: –0.106 (0.021)	Age, sex, centre	–	–	PCR (T/S ratio)
O'Donnell *et al.*, 2008 (45)	USA	1,062	33–86 (59.1)	27.7	M, W	–	–	All: –0.01 (0.01) Men: –0.005 (0.35) Women: –0.015 (0.01)	Age, sex, smoking status, pulse pressure, ICA–IMT¶	TRF analysis (kBP)
Hunt *et al.*, 2008 (46)	USA	2,453	19–93 (51.5)	29.5	M, W	–0.071 (0.002)	None	–	–	TRF analysis (kBP)
Fitzpatrick *et al.*, 2007 (47)	USA	419	65–92 (74.2)	–	M, W	–	–	–0.01 (0.13)	Age, sex, race	TRF analysis (kBP)
Bekaert *et al.*, 2007 (48)	Belgium	2,509	35–55 (46)	25.8	M, W	–	–	Men: –4.494 (0.41) Women: –4.122 (0.35)	Age	TRF analysis (kBP)
Brouilette *et al.*, 2007 (35)	UK	Controls: 1,058	45–64 (56.7)	25.6	M	0.013 (0.700)	Age	–	–	PCR (T/S ratio)
Valdes *et al.*, 2005 (49)	UK	1,122	18–76 (47.8)	25.1	W	–0.077 (0.019)	Age	–	–	TRF analysis (kBP)

*Unit of regression coefficients for TRF-based studies is kBP kg m^{-2}, for PCR-based studies is (T/S ratio) kg m^{-2}.
†Adjusted for age, total cholesterol/HDL-C ratio, HDL-C, log-triglycerides, apolipoprotein B, systolic blood pressure and a categorized variable for glucose level.
‡Adjusted for age, smoking, post-menopausal hormone use, physical activity, intakes of polyunsaturated FA, saturated FA, trans-FA, monounsaturated FA, energy, cereal fibre and protein.
§Adjusted for age, systolic and diastolic blood pressure, WHR, glucose, insulin, HOMA–IR, HDL, LDL, total cholesterol, triglycerides, leptin, adiponectin, resistin, TNF-á, aPAI-1, ANG-II and CRP.
¶Internal carotid artery intima–media thickness.
ANG-II, angiotensin II; aPAI-1, active plasminogen activator inhibitor-1; BMI, body mass index; CRP, C-reactive protein; FA, fatty acid; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model of assessment–insulin resistance; ICA–IMT, internal carotid artery–intima-media thickness; kBP, kilobase pairs; LDL, low-density lipoprotein; M, men; PCR, polymerase chain reaction; T2DM, type 2 diabetes mellitus; TL, telomere length; TNF-á, tumour necrosis factor á; TRF, terminal restriction fragment; W, women; WHR, waist-to-hip ratio.

Table 3 Results from the meta-analyses of cross-sectional studies

		Summary statistic	*P*-value	95% confidence interval		Number of studies	Total population size
				Lower limit	Upper limit		
Meta-analysis of correlation coefficients between BMI and telomere length	Men and women	–0.092	0.013	–0.163	–0.019	6	4,572
	Women only	–0.063	0.053	–0.125	0.001	7	9,839
	Men only	–0.055	0.303	–0.159	0.050	3	1,669
	All combined	–0.057	0.013	–0.102	–0.012	12	12,501
Meta-analysis of adjusted regression coefficients* of BMI with telomere length			Absolute telomere length				
	Men and women	–0.014	0.125	–0.032	0.004	3	1,674
	Women only	–0.009	0.100	–0.019	0.002	2	1,913
	Men only	–0.005	0.214	–0.012	0.003	2	1,714
	All combined	–0.008	0.058	–0.016	0.000	5	4,183
			Relative telomere length				
	Men and women	–0.014	0.249	–0.037	0.010	3	3,347

*Unit of regression coefficients for TRF-based studies (measure absolute telomere length) is kBP kg m^{-2}, for PCR-based studies (measure relative telomere length) is (T/S ratio) kg m^{-2}.
BMI, body mass index; PCR, polymerase chain reaction; TRF, terminal restriction fragment.

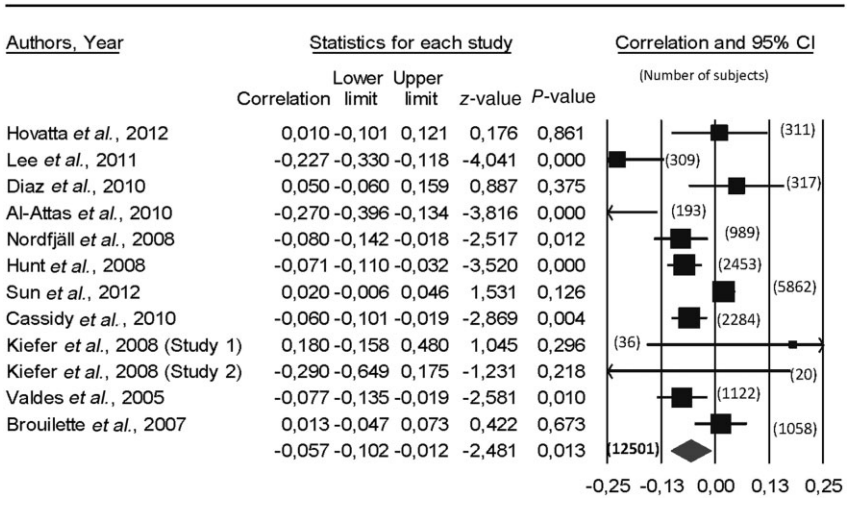

Figure 2 Meta-analysis of correlation coefficients of body mass index and leukocyte telomere length.

different LTL measurement methods, calculation of a pooled regression coefficient was not meaningful.

Studies not included in meta-analysis

Except for two studies (27,28), all identified studies not included in the meta-analysis (as they did not report any correlation or regression coefficients) had a cross-sectional design (Table 1). Three studies (23,26,30) investigated the relationship in children and adolescents, with ages ranging from 2 to 18 years. Comparison between these studies was particularly limited because of the high heterogeneity in the reported data. Overall, these studies either reported no statistically significant association between BMI and LTL or an inverse association. There was no evidence of a positive relationship.

Discussion

To our knowledge, this is the first systematic review and meta-analysis on the relationship between LTL and BMI. Overall, 29 studies were identified, 16 of which reported correlation and/or regression coefficients between BMI and LTL and could be included in the meta-analyses. Two out of 16 studies had a longitudinal design and reported correlation and regression coefficients between change in BMI and rate of yearly telomere loss. Thirteen studies that had information about the relationship between BMI and LTL but did not report correlation or regression coefficients were summarized on a separate table.

The majority of published studies found statistically significant inverse associations between BMI and LTL. Although a few positive associations were also reported,

none of them reached statistical significance. The pooled correlation and regression coefficients of cross-sectional studies showed a consistent inverse association between BMI and LTL. When all of the regression and correlation coefficients for mutually exclusive study populations were pooled together ignoring gender stratification, the summary estimate for the correlation coefficient was statistically significant and for the regression coefficient showed marginal statistical significance. Significant heterogeneity among studies was detected. After exclusion of the outlier studies, the pooled estimates did not alter considerably and the heterogeneity was dissolved. There was no indication of publication bias. A distinctive difference between gender-specific estimates was not observed.

The inconsistencies observed in the associations between BMI and LTL may be due to several reasons. Variations in study size and age structure of study population can both contribute to the heterogeneity. Several previous studies have suggested that the relationship between LTL and adiposity is stronger in younger adults than in older adults (40,44,47). We also observed a similar trend in the studies included in our meta-analysis. However, scarcity of data limited more in-depth analysis of potential variation by age. The study of Nordfjäll *et al*. (44) also suggests that the BMI–LTL association may further be modified by gender. They found the adiposity and LTL association to be stronger in women and this difference to be more pronounced at younger ages (44).

Additionally, the quality of BMI as an indicator of adiposity may vary during life course. In young and middle ages, BMI highly correlates with fat mass as weight changes during these ages primarily depend on fat mass gain or loss (51). In older ages (65 years and older) BMI is a less reliable marker of adiposity because of differential loss of muscle and bone mass, and height (52–54). Hence, BMI of those individuals may seem to be maintained or even decreased, although adiposity in the body might be increased. Therefore, more precise and detailed measures of fat mass and distribution, such as percentage body fat, visceral and abdominal subcutaneous adipose tissue, are needed to further elucidate the nature and strength of the obesity–LTL association. Alternatively, other fat distribution measures such as waist circumference and waist-to-hip ratio might also be used, which are easier to obtain for large-scale studies.

The size of the relationship between BMI and LTL can be further underestimated by presence of a subclinical disease, which shifts the individual to a lower weight category (55). Different adjustments for confounders, especially for regression coefficients, might be an additional reason for inconsistent results in the literature. Finally, the possibility of residual confounding always has to be kept in mind in observational studies.

Only two eligible longitudinal studies were identified for meta-analysis. They were both small-scale studies with different, non-overlapping age ranges and they provided unadjusted correlation coefficients that were in opposite directions. LTL was measured with different methods. Thus, their results have very limited comparability. Nonetheless regression coefficients, which were adjusted for multiple factors including age, indicated an inverse association in both studies. This review clearly revealed the necessity of more and larger longitudinal studies investigating telomere dynamics with respect to changes in weight status, with sufficiently long follow-up times in different age groups spanning different phases of life course.

Study limitations and strengths

Our review has specific strengths and limitations. Although a large number of studies were identified via searches performed on three databases, i.e. PubMed MEDLINE, Embase and Web of Knowledge, and extensive checks for completeness by cross referencing were performed, it cannot be guaranteed that all relevant studies were found. For practical reasons unpublished and non-English data could not be considered. As some heterogeneity among studies was detected, the results should be interpreted with caution. The majority of the correlation coefficients were not adjusted for age, which is inversely associated with LTL (21) and positively correlated with BMI in most adult populations (56). Therefore, the true (age-independent) correlation between BMI and LTL is expected to be lower than the estimate calculated in this meta-analysis. Another limitation of the meta-analysis concerns the restriction to studies that have reported either a correlation or regression coefficient for BMI and LTL. Hence, studies that used different adiposity measures were excluded. Conversely, this strict and focused systematic approach ensured a more standardized summary of the literature. All of the regression coefficients included in the analyses were adjusted for age. Additionally, the majority of them were also adjusted for smoking and physical activity, which both affect oxidative stress level in the body (57).

As stratification of studies by gender reduced the number of studies in each meta-analysis, the power of detecting a statistically significant relationship and the precision of calculated estimates were limited. Moreover, because of limited data reliable gender-specific interpretations cannot be done. Additionally, it should be also kept in mind that current LTL measurement methods have their own limitations, and comparing LTL from different measurement methods introduces additional heterogeneity, limiting the comparability of the studies.

Conclusion

The results of this meta-analysis are consistent with the proposed biological mechanism that increased adiposity

leads to telomere shortening, which can hasten the ageing process. However, the available data are still sparse and some individual studies reported associations in opposite directions. Furthermore, pooled correlation coefficients were generally rather small (<0.1), which indicates that only a very small proportion of LTL is statistically explained by BMI. Although all summary estimates from meta-analyses suggest an inverse relationship, they do not all reach statistical significance, which could also result from the scarcity of comparable studies. Overall, the heterogeneity in study characteristics, along with the small numbers of studies, limits clinical inference based on internal and external validity. In order to enhance the evidence for the association between obesity and LTL, large-scale epidemiological studies, which would analyse this association in different age groups and sexes both cross-sectionally and longitudinally, are greatly needed. Ideally, such studies would also include additional measures of adiposity, such as waist circumference, waist-to-hip ration and percentage body fat. Further studies are highly desirable to enable more precise estimates, as well as thorough analyses of dose–response relationship between measure of adiposity and LTL, which should finally contribute to better understanding of the role of adiposity and oxidative stress in telomere dynamics.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12126

Figure S1 Flow diagram of the systematic literature search process.
Figure S2 Meta-analysis of correlation coefficients of BMI and LTL.
Figure S3 Meta-analysis of regression coefficients of BMI with absolute LTL.
Table S1 Details of longitudinal studies.
Table S2 Sensitivity analyses of the meta-analysis of correlation coefficients.
Table S3 Sensitivity analyses of the meta-analysis of regression coefficients from studies.

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