TITLE:

BMI is negatively associated with telomere length; a collaborative cross-sectional meta-analysis of 87 observational studies

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RUNNING HEAD:

BMI and telomere length: a meta-analysis

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ABBREVIATIONS

BMI= body-mass index

TL= Telomere length

BP= base pairs

T/S ratio= Telomere to Single Copy Gene ratio

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ABSTRACT

Background

Even before the onset of age-related diseases obesity might be a contributing factor to the cumulative burden of oxidative stress and chronic inflammation throughout the life course and obesity may therefore contribute to accelerated shortening of telomeres.

Obese persons are expected to have shorter telomeres, but the association between body-mass index (BMI) and leucocyte telomere length (TL) might differ across the lifespan, ethnicities and sexes.

Objective

A collaborative cross-sectional meta-analysis of observational studies was conducted to investigate the associations between BMI and TL across life span.

Design

Eighty-seven distinct study samples were included in the meta-analysis capturing data from 146,114 individuals. Study-specific age and sex adjusted regression coefficients were combined using a random-effects model in which absolute (base pairs [bp]) and relative (T/S ratio) TLs were regressed against BMI. Stratified analysis was performed by three age categories ("young" ≥18 and ≤ 60 years, "middle" > 60 and ≤ 75, "old" > 75 years), sex, and ethnicity.

Results

Each unit increase in BMI corresponded to a -3.99 bp (95%C.I. -5.17, -2.81) difference in TL in the total pooled sample; among young adults each unit increase in BMI corresponded to a -7.67 bp (95%C.I. -10.03, -5.31). Each unit increase in BMI corresponded to a $-1.58*10^{-3}$ units T/S ratio (-0.16%) (95%C.I. $-2.14*10^{-3}$, $-1.01*10^{-3}$) difference in age and sex adjusted relative telomere length in the total pooled sample; among young adults each unit increase in BMI corresponded to a $-2.58*10^{-3}$ units T/S ratio (-0.26%) (95%C.I. $-3.92*10^{-3}$, $-1.25*10^{-3}$). The

associations were predominantly for the white pooled population. No sex differences were observed.

Conclusions

Higher BMI is associated with shorter telomeres, especially in younger individuals. The presently observed difference is not negligible. Meta-analyses of longitudinal studies evaluating change in body weight alongside change in TL are warranted.

KEY WORDS:

BMI, telomere length, obesity, low grade inflammation, meta-analysis, observational studies

INTRODUCTION

Telomeres, the nucleoprotein structures at the ends of chromosomes, shorten with each cell division in somatic cells (1). When telomere length reaches a critical value, cells either enter a state of senescence or undergo apoptosis (2). Oxidative stress and chronic inflammation are suggested to play a role in accelerated telomere attrition (3-5). Even before the onset of age-related diseases obesity might be a contributing factor to the cumulative burden of oxidative stress and chronic inflammation throughout the life course and obesity may therefore contribute to accelerated shortening of telomeres.

Obesity is a growing health problem and worldwide its prevalence has more than doubled since 1980 (6). In addition, the burden of diabetes and cardiovascular disease is partly attributable to being overweight and obese (6). Tackling obesity might be a starting point to delay telomere shortening and the onset of age-related diseases. Although obesity is associated with shorter telomeres (7), studies in the elderly found no relation between telomere length and obesity and no relation between telomere length and mortality (8, 9). We hypothesize that obese persons will have shorter telomeres, compared to those of normal weight of the same chronological age, but that the association between obesity and telomere length will differ across the lifespan.

Sex and ethnicity may influence the association between BMI and telomere length. On average, women have longer telomeres than men (10-12). However, published results on sex differences in association between BMI and telomere length are inconsistent (13-15). African Americans and Native Americans have higher rates of obesity (16), and also racial differences in telomere length have frequently been reported with adult African Americans having longer telomeres than white individuals (17-21), but evidence is lacking whether the association between BMI and telomere length differs between ethnicities.

Two recent meta-analyses reported the negative association between BMI and telomere length on reported summary statistics in the literature, but could not examine sex differences nor the influence of age and ethnicity (7, 22). To further evaluate whether BMI is associated with telomere length, a large-scale collaborative cross-sectional meta-analysis was conducted across observational studies that collected information on BMI and telomere length of adult individuals. To avoid publication bias and maximize the data in the analyses, a consistent standardized analysis plan across studies was used and principal investigators (PIs) of published studies were contacted and asked to participate in the TELOMAAS group. As the relationship between telomere length and BMI could be moderated by age, sex, and ethnicity we completed additional analyses stratifying by these factors.

METHODS

Search strategy

We performed a broad literature search up till the end of November 10th 2017 using PUBMED, EMBASE and the Cochrane database without restrictions. Numerous studies have measured BMI and telomere length for purposes other than the association between telomere length and BMI as an outcome. Therefore, the search was rather broad and not narrowed to telomere length or BMI. Based on the existing relation between obesity, diabetes and cardiovascular diseases, and because telomere length is related to aging we completed a search in which terms related to these conditions were entered. Additionally, search items related to study design were entered. The complete search criteria are listed in Supplemental Methods. Citation and reference tracking were performed until no new studies were found. One author (MG) performed the literature search and

selected potentially relevant publications. Titles and abstracts of potentially relevant studies were screened. In addition, when the abstract indicated that the article was reporting a study of diabetes and/or cardiovascular disease, the full text was screened. No restrictions for study design or language were applied.

Eligibility criteria

Studies were included if height and weight or BMI was collected. The corresponding author was invited to participate in the meta-analysis and identified additional unpublished studies. PIs of these unpublished studies were also invited to participate. Cohort studies with healthy individuals at baseline were included and if the study design was a case-control study, only controls were included in the meta-analysis. In compiling the database care was taken to exclude overlapping study cohorts. The study sample (abbreviated as study) was taken as the unit for this meta-analysis.

Data extraction

The detailed study protocol can be found in Supplemental Material: Study Protocol for Participating PIs. The PI of each study completed a questionnaire and additional information was extracted from the manuscript. The following data were collected: study name, study design (cohort or case-control), sample size (cohort size or control group size), presence of the variables age, sex, ethnicity (when at least 70% of the individuals of a sample was of a single ethnicity (e.g. white, African American, Native American, Asian, Hispanic) the sample was classified as a sample of a particular ethnicity, when no ethnicity constitutes 70% of the sample, the sample was classified as a mixed sample), leucocyte telomere length, and BMI (kg/m^2), whether BMI was measured or self-reported, white blood cell types from which DNA was extracted for telomere

measurements, method of telomere length measurement, and of DNA storage (Supplemental Material: Study Protocol for Participating PIs). Absolute telomere length in base pairs (bp) was distinguished from relative telomere length based on Telomere to Single Copy Gene ratio (T/S ratio) (23). For example, a T/S ratio of 0.8 indicates a relative telomere length which is 80% of the reference used (100%).

The PI was free to provide the de-identified raw data or to perform analyses and provide summary statistics. If the PI provided raw data, MG conducted the linear regression analyses to obtain the summary statistics The linear regression analyses were a combination of one of the following sex and age groups: men and women analyzed together and separately; all age groups together and analyzed in three a priori chosen subgroups ("young" ≥18 and ≤ 60 years, "middle" > 60 and ≤ 75, "old" > 75 years). When appropriate, i.e. men and women analyzed together and/or all age groups together, the analyses were corrected for sex and/or for age. If the T/S ratio was used to estimate absolute telomere length, the PI was asked to provide new analyses with the T/S ratio as the outcome. If the PI did not respond to this request absolute telomere length based on the T/S ratio was used for analyses and included in the analysis. The regression coefficients (beta estimates) and standard errors (SE) were then used in the meta-analyses. In the case of longitudinal data one randomly selected telomere length measurement along with the corresponding measurements (e.g. BMI, age) for that time point was used in the analysis. The summary statistics thus included the results of twelve linear regression analyses with telomere length (bp or T/S ratio) as the outcome and BMI as the independent variable.

Assessment of small study effects

To examine the potential presence of publication bias, visual inspection of funnel plots for asymmetry was performed, followed by the Egger and Begg's linear regression test for small study effects (24) and the Duval and Tweedie nonparametric "trim and fill" method (25).

Statistical analysis

Statistical pooling

The primary outcome of the meta-analysis was a pooled estimation of the difference in absolute telomere length in bp or relative telomere length (T/S ratio) per unit increase in BMI. Study specific regression coefficients (beta estimates) and standard errors (SE) were combined using random-effects pooling in twelve meta-analyses. The assumption of a linear association between BMI and telomere length was verified using the raw data provided by the PIs (Supplemental Methods and Results).

Assessment of heterogeneity

Details are given in Supplemental Methods.

Statistical heterogeneity was estimated by Q and I^2 statistics (26, 27) for each of the twelve meta-analyses. Low heterogeneity was indicated by I^2 up to 25%, medium heterogeneity by 25-50%, and high heterogeneity by > 50% (27). To confirm the expected differences in association for age and sex, meta-regression analysis was performed with age and sex as sources of heterogeneity. Age was therefore categorized into three age categories ("young" ≥18 and ≤ 60 years, "middle" > 60 and ≤ 75, "old" > 75 years) and also in two ("young" ≥18 and ≤ 60 years vs. "middle and old" > 60 years) age categories. Also other potential sources of heterogeneity at study level were investigated by meta-regression analysis (Supplemental Methods).

Sensitivity analyses

The following sensitivity analyses were performed: (1) outlier analyses by omitting one study at a time, (2) omitting studies that used the relative telomere length to estimate the absolute telomere

length, (3) stratification by method of measurement of telomere length (Southern blot vs. q-PCR), (4) using a cut off value of 90% for defining ethnicity. Details are given in Supplemental Methods.

Statistical analyses were performed using Stata software version 12.0 (StataCorp, College Station, TX, USA). All statistical tests were two-sided; p values < 0.05 were considered statistically significant, except where otherwise specified.

RESULTS

Search

The search (PUBMED, EMBASE, and Cochrane) yielded 5,021 publications, from which 173 potentially relevant publications were identified. Some authors contributed to more than one publication. As a result, 153 corresponding authors were identified and contacted. Sixty one corresponding authors responded positively, 56 authors did not respond, six declined to participate, and three authors did not have the requested data. Since one publication could include multiple studies, the PIs (if not the same as corresponding authors) of the studies were contacted. Eight additional studies were identified by the corresponding authors and the PIs of these additional studies were contacted. We decided to exclude nine studies using techniques other than Southern blots and q-PCR, because the regression coefficients (beta estimates) may not be directly comparable.

In total, 87 unique studies were included in the meta-analyses. Twenty-nine studies measured absolute telomere length and 58 studies used the T/S ratio. A flow chart of the inclusion procedure is presented Figure 1.

Description of studies

The characteristics of the 87 studies included in this meta-analysis are provided in Table 1. Absolute telomere lengths were obtained from 29 studies (3, 5, 13, 14, 17, 28-61) (and the unpublished data of the HyperGEN study), of which four studies estimated absolute telomere length based on the T/S ratio (19, 22, 62-68). In 17 studies Southern blots were used (3, 5, 13, 14, 17, 28-40, 44, 45, 48-52, 55, 56, 59, 61). Fifty-eight studies presented the relative telomere length (T/S ratio) (4, 15, 69-133) (and the unpublished data of Utah Pedigree study). One PI provided the data stratified by cell type (104). One PI provided longitudinal data (55).

The total pooled sample of this meta-analysis consisted of 146,114 adults (40% men), the young pooled sample (≥18 and ≤ 60 years) consisted of 81,446 adults (51% men), the middle aged pooled sample (> 60 and ≤ 75 years) consisted of 42,991 adults (41% men), and the old pooled sample (> 75 years) consisted of 8,495 adults (65% men). Overall, the majority of the adults were white (including Arab; 83%), followed by Asian (7%), African American (4%), Hispanic, and Native Americans (both 3%). Six studies provided data of mixed study populations stratified by ethnicity (17, 71, 72, 101, 132, 133) (and the unpublished data of the HyperGEN study). Sixty-five studies consisted of > 70% white individuals (of which 60 had at least 90% white individuals) (3, 5, 13-15, 17, 22, 28-34, 36-45, 48-59, 63-65, 68, 71-95, 98, 100-103, 105, 108-114, 116-118, 120-129, 131) (and unpublished data of the HyperGEN, and Utah Pedigree studies). Four studies consisted only of African Americans (17, 71, 72, 101) (and the unpublished data of the HyperGEN study); five only of Asians (35, 61, 100, 115, 130), one study only of Native Americans (96, 97, 106, 107), and four studies comprised only Hispanics (60, 71, 72, 83, 84, 101). One study could not provide information about ethnicity (119).

Assessment of small study effects

Visual inspection of the funnel plots for absolute telomere length and for relative telomere length yielded symmetric plots (Supplemental Figure 1 Funnel Plots). No publication bias was detected using Egger's test or Begg's test. The "trim and fill" method added one hypothetical study to the meta-analysis for absolute telomere length. However, the recalculated summary estimate did not change and was still significant with their inclusion (beta= -3.99 (95%C.I. -5.16, -2.84); $p < 0.001$).

Meta-analyses

A summary of the beta estimates of the meta-analysis is shown in Table 2. An overall overview of the meta-analysis is shown Supplemental Tables 2 and 3 in which the beta estimates of all meta-analyses for absolute telomere length as the outcome (Supplemental Table 2) and of all meta-analyses for relative telomere length as the outcome (Supplemental Table 3) are presented. The accompanying forest plots are presented in the Supplemental Figures 2 and 3: Forest Plots.

Overall meta-analysis

Overall, sex- and age-adjusted absolute telomere length was significantly associated with BMI. Each unit increase in BMI corresponded to a -3.99 bp (95%C.I. -5.17, -2.81; I^2= 0.6%) difference in absolute telomere length (Table 2 and Figure 2 Forest plot). For example, an estimated difference in telomere length between a normal weight individual with a BMI of 25 kg/m^2 and an obese individual with a BMI > 30 kg/m^2 is (rounded) 20.0 bp, and, if a larger difference is used (BMI 20 kg/m^2 vs. BMI > 30 kg/m^2), 39.9 bp. The estimated difference between normal weight and morbid obesity (BMI > 40 kg/m^2) is at least 59.9 bp. Each unit increase in BMI corresponded to a $-1.58*10^{-3}$ units T/S ratio (-0.16%) (95%C.I. $-2.14*10^{-3}$, $-1.01*10^{-3}$; I^2= 41.1%) difference in age- and sex-adjusted relative telomere length. An estimated difference in relative telomere length between normal weight and obesity is at least $7.9*10^{-3}$ units

(0.79%) T/S ratio (Table 2 and Figure 3 Forest plot) and between normal weight and morbid obesity at least $23.7*10^{-3}$ units T/S ratio (2.37%). The associations between BMI and telomere length did not differ significantly between men and women (see below).

Age

Analysis stratified by age category revealed that in young adults (≥18 and ≤ 60 years) a unit increase of BMI corresponded to a -7.67 bp (95%C.I. -10.03, -5.31; I^2=31.2%) difference in absolute telomere length (Table 2 and Figure 4).

In middle age adults (> 60 and ≤ 75) the overall association between BMI and telomere length was -1.65 bp (95%C.I. -4.41, 1.11; I^2= 19.7) per unit increase in BMI.

In old adults (> 75 years) the overall association between BMI and telomere length was -5.89 bp (95%C.I. -10.41, -1.37; I^2= 5.3) per unit increase in BMI.

For relative telomere length, each unit increase in BMI corresponded to a $-2.58*10^{-3}$ units T/S ratio (-0.26%) (95%C.I. $-3.92*10^{-3}$, $-1.25*10^{-3}$; I^2= 80.0%) difference in relative telomere in young adults (Table 2 and Figure 5).

In middle age adults, the overall association between BMI and relative telomere length was found ($-1.08*10^{-3}$ units T/S ratio (-0.1%) (95%C.I. $-1.76*10^{-3}$, $-0.39*10^{-3}$; I^2= 0.0)) per unit increase in BMI. For old adults no statistically significant association ($0.20*10^{-3}$ units T/S ratio (0.02%) (95%C.I. $-1.40*10^{-3}$, $1.80*10^{-3}$; I^2= 0.0)) was found between BMI and relative telomere length.

<u>Meta-regression and sources of heterogeneity</u>

Age and ethnicity were a source of heterogeneity at study level in the meta-regression analyses. Sex was never a source of heterogeneity (Supplemental Results). Therefore, all analyses were stratified by ethnicity in addition to the originally planned analyses.

With absolute telomere length as the outcome, stratified analyses revealed that all estimates were statistically significant for the white pooled sample, whereas none of the other were statistically significant.

With relative telomere length as the outcome, stratified analyses revealed that the estimates (except one estimate for the "old" pooled sample) were statistically significant for the white pooled sample. In addition, the estimates of the overall and young pooled sample for the Native Americans and the estimate of the young pooled Asian were statistically significant. None of the estimates for the African American and Hispanic were statistically significant.

Sensitivity analysis

None of the sensitivity analyses resulted in substantial change of the summary estimate (Supplemental Results).

DISCUSSION

This cross-sectional meta-analysis of 87 observational studies of adult pooled population confirmed previous observations that BMI is negatively associated with telomere length. After stratification for age and ethnicity the negative association between BMI and telomere length appeared to be stronger in the "young adult" pooled population (age < 60 years) and in the white pooled population. Differences between men and women could not be confirmed.

Based on our estimates for absolute telomere length, a ~5-unit increase in BMI appears to be equivalent to a difference in telomere length of ~20-38 bp or ~$7.9*10^{-3}$ -$13*10^{-3}$ units T/S ratio (0.79-1.3%). Compared to an estimated average yearly decrease (i.e., ~25 bp/year or ~0.01 T/S

ratio/per year) of leucocyte telomere length in adults based on cross-sectional data (3, 32, 134-136), the association is not negligible. In addition, compared to accelerated attrition (i.e. 3-5 bp/year) due to smoking one pack of cigarettes daily (94, 137) the association reported in this meta-analysis appears relevant and could exceed or at least be in line with the effect of smoking. A major disadvantage of cross-sectional analysis is the impossibility to infer causation. However, the robust association between higher BMI and lower telomere length found in this meta-analysis highlights another potential area of concern for the obesity epidemic.

Since obesity, and more specifically an increase in leptin and a decrease in adiponectin have been associated with low-grade inflammation and oxidative stress (138), the observed negative association between BMI and leucocyte telomere length may be due in part to the chronic inflammatory state associated with higher leptin. Recently, a negative association was observed between age-related relative telomere length and serum leptin in seven cohorts of 11,448 participants, which remained significant after adjustment for BMI (103). These data suggest that beyond a high BMI, inflammatory conditions, mediated via increase in leptin, likely contribute to telomere shortening. Since a longitudinal study found a tendency for a higher reduction in BMI over a 5 year period in participants who initially had the longest telomeres (98), it is also suggested that a common factor, such as chronic inflammation, is associated both with leptin resistance and with telomere length.

The negative association between BMI and telomere length was most apparent in the younger pooled population, in which a stronger association was found for absolute and relative telomere length compared to the other age groups, which highlights the urgency to address the obesity epidemic. Three possible explanations could explain this observation. First, BMI could be a better marker for adiposity in younger individuals aged less than 60 years compared to older individuals (22). Above 65 years of age BMI may less consistently reflect obesity because of

potential loss of muscle and bone mass and height (22). The fact that older men weigh less than the middle-aged men at a given height is attributed to older men having less lean tissue, and a lower BMI can actually reflect a higher fat mass (139). Second, selective survival might be one of the causes for the stronger association found in the younger age category. As Manson et al. state “obesity in one’s 40s contributes to the onset of type 2 diabetes in one’s 50s, which leads to myocardial infarction (MI) in one’s 60s, heart failure and weight loss due to debilitation and muscle wasting at age 70, and death at age 75” (140). People who suffered from age-related diseases may have died and those who survived may therefore differ from those who died (141). Third, older people are more likely to have chronic diseases that lead to weight loss and people with chronic diseases are probably less likely to participate in studies (140).

The magnitude of the negative association between BMI and leucocyte telomere length was found largest in the white pooled population. One possible explanation could be that telomere length differs between different cell types (142) and that leucocyte cell subpopulations (143) differ between whites and African Americans. However, since only four samples consisted of African Americans, more research is required to resolve whether this observation explains the racial differences in association between telomere length and BMI for white and African Americans. Second, it was recently reported that the estimation of visceral adipose tissue, the most relevant tissue that determines the risk to develop chronic metabolic diseases, was different in white and African American adults (144). At higher BMI or increased waist circumference (WC), white adults had higher levels of visceral adipose tissue than African American adults (138). Since the presence of leptin resistance or markers of inflammation were not included in these studies, it remains to be determined whether the relation between BMI, leptin resistance, inflammation and telomere attrition is different for African Americans from whites. In addition, the one study sample consisting of 3,256 mostly “young” Native Americans showed similar

results as found for the white study population (107). The majority of this study sample was centrally obese, and leucocyte telomere length was negatively correlated with C-reactive protein.

One of the main strengths of this study is that we did not rely on publications. Instead we contacted PIs, which in turn have pointed us towards important studies we may have missed, to obtain the data used in the meta-analysis. Also we incorporated several potential confounders (age and sex) and sources of heterogeneity (ethnicity and study design). The response rate of the originally contacted PIs was 55% with a final count of 87 unique studies and over 140,000 individuals. Although it is impossible to make a direct comparison with the unpublished beta estimates of the non-responders, we assume, also based on the absence of significant publication bias, that the studies in this meta-analysis are a random selection of all studies conducted and that we present a valid representation of the association between BMI and telomere length. Because of the large variation in adult telomere length, as well as biological and measurement variation (q-PCR), large sample sizes are needed, especially in cross-sectional studies, to detect modest effects (30). In this meta-analysis we were able to detect a statistically significant association of -3.99 bp or $-1.58*10^{-3}$ units T/S ratio (0.16%) per unit increase BMI.

Two recently meta-analyses, which relied on published data, also reported negative associations between BMI and telomere length. The first smaller scale meta-analysis reported negative regression coefficients on the association between telomere length and BMI (22), of which five studies were also included in this meta-analysis (13, 14, 19, 82, 145). The larger scale meta-analysis reported a weak negative correlation, a standardized mean differences of 0.84 (95%C.I. 0.22, 1.46) between obese individuals and normal weight individuals and an odds ratio of 1.39 (95%C.I. 1.15, 1.69) (7). Of the 45 samples that met our inclusion criteria 33 collaborated in our analysis. This shows that the results between the meta-analyses are consistent and very robust. Although age and ethnicity were taken into account, it should be mentioned that the older

study sample was relatively small (~ 8,400 individuals), and that the majority of the individuals were white (83%). Unfortunately, we did not include smoking in the meta-analysis. Smoking is generally associated with a lower BMI and shorter telomere length (3, 137, 140), which may have caused an underestimation of the inverse association between BMI and telomere length. Also inflammation was not directly measured. We were also not able to measure telomere attrition as we did not incorporate longitudinal data and reverse causation cannot be excluded. However, there are very few large scale studies with repeated measures of telomere length.

The lengths of telomeres at different ages are highly correlated, and it has been suggested that most of the variation in leucocyte telomere length in adults is a result of telomere length at birth and that therefore the impact of environmental and lifestyle factors is rather small (137, 146). Benetos et al. described that ranking of individuals into deciles according to their telomere length barely changes across adult life. They showed that around half of the individuals stay in the same decile, whereas 17.9% showed a downwards shift and 20.7% showed an upward shift of one decile (137). Our meta-analysis shows that five units increase in BMI corresponds to ~20 bp or even ~38 bp change in the young pooled population, which is equivalent to at least a yearly decrease irrespective of ranking. This could be an additional argument to tackle the obesity epidemic.

In summary, a higher BMI is associated with shorter telomeres, especially in the younger pooled population. Although no causal inference can be drawn and residual confounding is always a possibility, the results were robust across a variety of potential confounders. Given this, we could possibly infer that tackling the obesity epidemic might be a starting point to delay telomere shortening and the onset of age-related diseases, thereby contributing to a decreased biological aging of the population. However, meta-analyses of longitudinal studies that can evaluate change in body weight alongside change in telomere length are warranted.

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AUTHOR CONTRIBUTIONS

M.G. wrote the manuscript, researched data and contributed to design and discussion had responsibility for final content.

G.H. contributed to design and discussion and reviewed/edited manuscript.

E.A. contributed to design and reviewed/edited manuscript

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Allsopp RC, Harley CB. Evidence for a critical telomere length in senescent human fibroblasts. Exp Cell Res. 1995;219:130-6.
2. Hayflick L. Mortality and immortality at the cellular level. A review. Biochemistry Biokhimiia. 1997;62:1180-90.
3. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD. Obesity, cigarette smoking, and telomere length in women. Lancet. 2005;366:662-4.
4. Sampson MJ, Winterbone MS, Hughes JC, Dozio N, Hughes DA. Monocyte telomere shortening and oxidative DNA damage in type 2 diabetes. Diabetes Care. 2006;29:283-9.
5. Demissie S, Levy D, Benjamin EJ, Cupples LA, Gardner JP, Herbert A, Kimura M, Larson MG, Meigs JB, Keaney JF, et al. Insulin resistance, oxidative stress, hypertension, and leukocyte telomere length in men from the Framingham Heart Study. Aging Cell. 2006;5:325-30.
6. WHO; fact sheet 311 m. obesity and overweight http://www.who.int/mediacentre/factsheets/fs311/en/index.htm2012 [
7. Mundstock E, Sarria EE, Zatti H, Mattos Louzada F, Kich Grun L, Herbert Jones M, Guma FT, Mazzola In Memoriam J, Epifanio M, Stein RT, et al. Effect of obesity on telomere length: Systematic review and meta-analysis. Obesity (Silver Spring). 2015;23:2165-74.
8. Njajou OT, Cawthon RM, Blackburn EH, Harris TB, Li R, Sanders JL, Newman AB, Nalls M, Cummings SR, Hsueh WC. Shorter telomeres are associated with obesity and weight gain in the elderly. International journal of obesity. 2012;36:1176-9.
9. Martin-Ruiz CM, Gussekloo J, van Heemst D, von Zglinicki T, Westendorp RG. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. Aging Cell. 2005;4:287-90.
10. Benetos A, Okuda K, Lajemi M, Kimura M, Thomas F, Skurnick J, Labat C, Bean K, Aviv A. Telomere length as an indicator of biological aging: the gender effect and relation with pulse pressure and pulse wave velocity. Hypertension. 2001;37:381-5.
11. Gardner M, Bann D, Wiley L, Cooper R, Hardy R, Nitsch D, Martin-Ruiz C, Shiels P, Sayer AA, Barbieri M, et al. Gender and telomere length: systematic review and meta-analysis. Experimental gerontology. 2014;51:15-27.
12. McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiol Biomarkers Prev. 2007;16:815-9.
13. O'Donnell CJ, Demissie S, Kimura M, Levy D, Gardner JP, White C, D'Agostino RB, Wolf PA, Polak J, Cupples LA, et al. Leukocyte telomere length and carotid artery intimal medial thickness: the Framingham Heart Study. Arterioscler Thromb Vasc Biol. 2008;28:1165-71.
14. Bekaert S, De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Langlois M, Segers P, Cooman L, Van Damme P, Cassiman P, et al. Telomere length and cardiovascular risk factors in a middle-aged population free of overt cardiovascular disease. Aging Cell. 2007;6:639-47.
15. Nordfjall K, Eliasson M, Stegmayr B, Melander O, Nilsson P, Roos G. Telomere length is associated with obesity parameters but with a gender difference. Obesity (Silver Spring). 2008;16:2682-9.
16. Story M, Evans M, Fabsitz RR, Clay TE, Holy Rock B, Broussard B. The epidemic of obesity in American Indian communities and the need for childhood obesity-prevention programs. Am J Clin Nutr. 1999;69:747S-54S.

17. Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A. Leukocyte telomeres are longer in African Americans than in whites: the National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. Aging Cell. 2008;7:451-8.
18. Chen W, Kimura M, Kim S, Cao X, Srinivasan SR, Berenson GS, Kark JD, Aviv A. Longitudinal versus cross-sectional evaluations of leukocyte telomere length dynamics: age-dependent telomere shortening is the rule. J Gerontol A Biol Sci Med Sci. 2011;66:312-9.
19. Diaz VA, Mainous AG, Player MS, Everett CJ. Telomere length and adiposity in a racially diverse sample. International journal of obesity. 2010;34:261-5.
20. Zhu H, Wang X, Gutin B, Davis CL, Keeton D, Thomas J, Stallmann-Jorgensen I, Mooken G, Bundy V, Snieder H, et al. Leukocyte telomere length in healthy Caucasian and African-American adolescents: relationships with race, sex, adiposity, adipokines, and physical activity. The Journal of pediatrics. 2011;158:215-20.
21. Fitzpatrick AL, Kronmal RA, Kimura M, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Hardikar S, Aviv A. Leukocyte telomere length and mortality in the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci. 2011;66:421-9.
22. Muezzinler A, Zaineddin AK, Brenner H. Body mass index and leukocyte telomere length in adults: a systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2014;15:192-201.
23. Cawthon RM. Telomere measurement by quantitative PCR. Nucleic Acids Res. 2002;30:e47.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
25. 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.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21:1539-58.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
28. Aviv A, Valdes A, Gardner JP, Swaminathan R, Kimura M, Spector TD. Menopause modifies the association of leukocyte telomere length with insulin resistance and inflammation. J Clin Endocrinol Metab. 2006;91:635-40.
29. Valdes AM, Richards JB, Gardner JP, Swaminathan R, Kimura M, Xiaobin L, Aviv A, Spector TD. Telomere length in leukocytes correlates with bone mineral density and is shorter in women with osteoporosis. Osteoporos Int. 2007;18:1203-10.
30. Richards JB, Valdes AM, Gardner JP, Kato BS, Siva A, Kimura M, Lu X, Brown MJ, Aviv A, Spector TD. Homocysteine levels and leukocyte telomere length. Atherosclerosis. 2008;200:271-7.
31. Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, Kimura M, Lu X, Spector TD, Aviv A. The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med. 2008;168:154-8.
32. Gardner JP, Li S, Srinivasan SR, Chen W, Kimura M, Lu X, Berenson GS, Aviv A. Rise in insulin resistance is associated with escalated telomere attrition. Circulation. 2005;111:2171-7.
33. Aviv A, Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, Srinivasan SR, Berenson GS. Leukocyte telomere dynamics: longitudinal findings among young adults in the Bogalusa Heart Study. Am J Epidemiol. 2009;169:323-9.

34. Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, Srinivasan SR, Berenson GS, Aviv A. Leukocyte telomere length is associated with HDL cholesterol levels: The Bogalusa heart study. Atherosclerosis. 2009;205:620-5.
35. Adaikalakoteswari A, Balasubramanyam M, Ravikumar R, Deepa R, Mohan V. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. Atherosclerosis. 2007;195:83-9.
36. Barbieri M, Paolisso G, Kimura M, Gardner JP, Boccardi V, Papa M, Hjelmborg JV, Christensen K, Brimacombe M, Nawrot TS, et al. Higher circulating levels of IGF-1 are associated with longer leukocyte telomere length in healthy subjects. Mech Ageing Dev. 2009;130:771-6.
37. De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Criekinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S. Paternal age at birth is an important determinant of offspring telomere length. Hum Mol Genet. 2007;16:3097-102.
38. De Meyer T, Rietzschel ER, De Buyzere ML, Langlois MR, De Bacquer D, Segers P, Van Damme P, De Backer GG, Van Oostveldt P, Van Criekinge W, et al. Systemic telomere length and preclinical atherosclerosis: the Asklepios Study. Eur Heart J. 2009;30:3074-81.
39. Rietzschel ER, De Buyzere ML, Bekaert S, Segers P, De Bacquer D, Cooman L, Van Damme P, Cassiman P, Langlois M, van Oostveldt P, et al. Rationale, design, methods and baseline characteristics of the Asklepios Study. Eur J Cardiovasc Prev Rehabil. 2007;14:179-91.
40. Vasan RS, Demissie S, Kimura M, Cupples LA, White C, Gardner JP, Cao X, Levy D, Benjamin EJ, Aviv A. Association of leukocyte telomere length with echocardiographic left ventricular mass: the Framingham heart study. Circulation. 2009;120:1195-202.
41. Houben JM, Giltay EJ, Rius-Ottenheim N, Hageman GJ, Kromhout D. Telomere length and mortality in elderly men: the Zutphen Elderly Study. J Gerontol A Biol Sci Med Sci. 2011;66:38-44.
42. Houben JM, Mercken EM, Ketelslegers HB, Bast A, Wouters EF, Hageman GJ, Schols AM. Telomere shortening in chronic obstructive pulmonary disease. Respir Med. 2009;103:230-6.
43. Rius-Ottenheim N, Houben JM, Kromhout D, Kafatos A, van der Mast RC, Zitman FG, Geleijnse JM, Hageman GJ, Giltay EJ. Telomere length and mental well-being in elderly men from the Netherlands and Greece. Behav Genet. 2012;42:278-86.
44. Jeanclos E, Schork NJ, Kyvik KO, Kimura M, Skurnick JH, Aviv A. Telomere length inversely correlates with pulse pressure and is highly familial. Hypertension. 2000;36:195-200.
45. Hjelmborg JV, Nzietchueng R, Kimura M, Gardner JP, Bladbjerg EM, Christensen K, Aviv A, Benetos A. Leukocyte telomere length is inversely correlated with plasma Von Willebrand factor. Thromb Res. 2010;125:e339-42.
46. Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere length trajectory and its determinants in persons with coronary artery disease: longitudinal findings from the heart and soul study. PLoS One. 2010;5:e8612.
47. Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. JAMA. 2010;303:250-7.
48. Huda N, Tanaka H, Herbert BS, Reed T, Gilley D. Shared environmental factors associated with telomere length maintenance in elderly male twins. Aging Cell. 2007;6:709-13.
49. Fitzpatrick AL, Reed T, Goldberg J, Buchwald D. The association between prolonged fatigue and cardiovascular disease in World War II veteran twins. Twin Res. 2004;7:571-7.

50. Strandberg TE, Kovanen PT, Eklund KK. Is the "lipid paradox" in rheumatoid arthritis really a paradox? Comment on the article by Bartels et al. Arthritis Rheum. 2011;63:3644-5; author's reply 5-6.
51. Strandberg TE, Saijonmaa O, Fyhrquist F, Tilvis RS, Strandberg AY, Miettinen TA, Pitkala KH, Salomaa V. Telomere length in old age and cholesterol across the life course. J Am Geriatr Soc. 2011;59:1979-81.
52. Strandberg TE, Saijonmaa O, Tilvis RS, Pitkala KH, Strandberg AY, Miettinen TA, Fyhrquist F. Association of telomere length in older men with mortality and midlife body mass index and smoking. J Gerontol A Biol Sci Med Sci. 2011;66:815-20.
53. Rode L, Nordestgaard BG, Weischer M, Bojesen SE. Increased body mass index, elevated C-reactive protein, and short telomere length. J Clin Endocrinol Metab. 2014:jc20141161.
54. Skamra C, Romero-Diaz J, Sandhu A, Huang Q, Lee J, Pearce W, McPherson DD, Sutton-Tyrrell K, Pope R, Ramsey-Goldman R. Telomere length in patients with systemic lupus erythematosus and its associations with carotid plaque. Rheumatology. 2013;52:1101-8.
55. Kark JD, Goldberger N, Kimura M, Sinnreich R, Aviv A. Energy intake and leukocyte telomere length in young adults. Am J Clin Nutr. 2012;95:479-87.
56. Kark JD, Nassar H, Shaham D, Sinnreich R, Goldberger N, Aboudi V, Bogot NR, Kimura M, Aviv A. Leukocyte telomere length and coronary artery calcification in Palestinians. Atherosclerosis. 2013;229:363-8.
57. Harris SE, Martin-Ruiz C, von Zglinicki T, Starr JM, Deary IJ. Telomere length and aging biomarkers in 70-year-olds: the Lothian Birth Cohort 1936. Neurobiol Aging. 2012;33:1486 e3-8.
58. Deary IJ, Gow AJ, Taylor MD, Corley J, Brett C, Wilson V, Campbell H, Whalley LJ, Visscher PM, Porteous DJ, et al. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC Geriatr. 2007;7:28.
59. Zannolli R, Mohn A, Buoni S, Pietrobelli A, Messina M, Chiarelli F, Miracco C. Telomere length and obesity. Acta Paediatr. 2008;97:952-4.
60. Iglesias Molli AE, Panero J, Dos Santos PC, Gonzalez CD, Vilarino J, Sereday M, Cerrone GE, Slavutsky I, Frechtel GD. Metabolically healthy obese women have longer telomere length than obese women with metabolic syndrome. PLoS One. 2017;12:e0174945.
61. Xue HM, Liu QQ, Tian G, Quan LM, Zhao Y, Cheng G. Television Watching and Telomere Length Among Adults in Southwest China. Am J Public Health. 2017;107:1425-32.
62. Diaz VA, Mainous AG, 3rd, Everett CJ, Schoepf UJ, Codd V, Samani NJ. Effect of healthy lifestyle behaviors on the association between leukocyte telomere length and coronary artery calcium. Am J Cardiol. 2010;106:659-63.
63. Willeit P, Willeit J, Brandstatter A, Ehrlenbach S, Mayr A, Gasperi A, Weger S, Oberhollenzer F, Reindl M, Kronenberg F, et al. Cellular aging reflected by leukocyte telomere length predicts advanced atherosclerosis and cardiovascular disease risk. Arterioscler Thromb Vasc Biol. 2010;30:1649-56.
64. Willeit P, Willeit J, Mayr A, Weger S, Oberhollenzer F, Brandstatter A, Kronenberg F, Kiechl S. Telomere length and risk of incident cancer and cancer mortality. JAMA. 2010;304:69-75.
65. Zheng YL, Ambrosone C, Byrne C, Davis W, Nesline M, McCann SE. Telomere length in blood cells and breast cancer risk: investigations in two case-control studies. Breast Cancer Res Treat. 2010;120:769-75.
66. Mainous AG, 3rd, Codd V, Diaz VA, Schoepf UJ, Everett CJ, Player MS, Samani NJ. Leukocyte telomere length and coronary artery calcification. Atherosclerosis. 2010;210:262-7.

67. Mainous AG, 3rd, Everett CJ, Diaz VA, Baker R, Mangino M, Codd V, Samani NJ. Leukocyte telomere length and marital status among middle-aged adults. Age and ageing. 2011;40:73-8.
68. Ehrlenbach S, Willeit P, Kiechl S, Willeit J, Reindl M, Schanda K, Kronenberg F, Brandstatter A. Influences on the reduction of relative telomere length over 10 years in the population-based Bruneck Study: introduction of a well-controlled high-throughput assay. Int J Epidemiol. 2009;38:1725-34.
69. Bull CF, O'Callaghan NJ, Mayrhofer G, Fenech MF. Telomere length in lymphocytes of older South Australian men may be inversely associated with plasma homocysteine. Rejuvenation Res. 2009;12:341-9.
70. Cross JA, Brennan C, Gray T, Temple RC, Dozio N, Hughes JC, Levell NJ, Murphy H, Fowler D, Hughes DA, et al. Absence of telomere shortening and oxidative DNA damage in the young adult offspring of women with pre-gestational type 1 diabetes. Diabetologia. 2009;52:226-34.
71. Nettleton JA, Diez-Roux A, Jenny NS, Fitzpatrick AL, Jacobs DR, Jr. Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2008;88:1405-12.
72. Roux AV, Ranjit N, Jenny NS, Shea S, Cushman M, Fitzpatrick A, Seeman T. Race/ethnicity and telomere length in the Multi-Ethnic Study of Atherosclerosis. Aging Cell. 2009;8:251-7.
73. Salpea KD, Nicaud V, Tiret L, Talmud PJ, Humphries SE. The association of telomere length with paternal history of premature myocardial infarction in the European Atherosclerosis Research Study II. J Mol Med (Berl). 2008;86:815-24.
74. Puterman E, Lin J, Blackburn E, O'Donovan A, Adler N, Epel E. The power of exercise: buffering the effect of chronic stress on telomere length. PLoS One. 2010;5:e10837.
75. Atzmon G, Cho M, Cawthon RM, Budagov T, Katz M, Yang X, Siegel G, Bergman A, Huffman DM, Schechter CB, et al. Evolution in health and medicine Sackler colloquium: Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. Proc Natl Acad Sci U S A. 2010;107 Suppl 1:1710-7.
76. Hou L, Savage SA, Blaser MJ, Perez-Perez G, Hoxha M, Dioni L, Pegoraro V, Dong LM, Zatonski W, Lissowska J, et al. Telomere length in peripheral leukocyte DNA and gastric cancer risk. Cancer Epidemiol Biomarkers Prev. 2009;18:3103-9.
77. Kananen L, Surakka I, Pirkola S, Suvisaari J, Lonnqvist J, Peltonen L, Ripatti S, Hovatta I. Childhood adversities are associated with shorter telomere length at adult age both in individuals with an anxiety disorder and controls. PLoS One. 2010;5:e10826.
78. Kim S, Parks CG, DeRoo LA, Chen H, Taylor JA, Cawthon RM, Sandler DP. Obesity and weight gain in adulthood and telomere length. Cancer Epidemiol Biomarkers Prev. 2009;18:816-20.
79. Kurz DJ, Kloeckener-Gruissem B, Akhmedov A, Eberli FR, Buhler I, Berger W, Bertel O, Luscher TF. Degenerative aortic valve stenosis, but not coronary disease, is associated with shorter telomere length in the elderly. Arterioscler Thromb Vasc Biol. 2006;26:e114-7.
80. Mather KA, Jorm AF, Milburn PJ, Tan X, Easteal S, Christensen H. No associations between telomere length and age-sensitive indicators of physical function in mid and later life. J Gerontol A Biol Sci Med Sci. 2010;65:792-9.
81. Pavanello S, Hoxha M, Dioni L, Bertazzi PA, Snenghi R, Nalesso A, Ferrara SD, Montisci M, Baccarelli A. Shortened telomeres in individuals with abuse in alcohol consumption. Int J Cancer. 2011;129:983-92.

82. Lee M, Martin H, Firpo MA, Demerath EW. Inverse association between adiposity and telomere length: The Fels Longitudinal Study. Am J Hum Biol. 2011;23:100-6.
83. Barrera G, Cases T, Bunout D, de la Maza MP, Leiva L, Rodriguez JM, Hirsch S. Associations between socioeconomic status, aging and functionality among older women. Geriatric nursing. 2014.
84. Bunout D, Barrera G, de la Maza MP, Leiva L, Hirsch S. Effect of weight maintenance or gain in a 10 years period over telomere length, sirtuin 1 and 6 expression and carotid intima media thickness. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2014.
85. Jackowska M, Hamer M, Carvalho LA, Erusalimsky JD, Butcher L, Steptoe A. Short sleep duration is associated with shorter telomere length in healthy men: findings from the Whitehall II cohort study. PLoS One. 2012;7:e47292.
86. Zalli A, Carvalho LA, Lin J, Hamer M, Erusalimsky JD, Blackburn EH, Steptoe A. Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. Proc Natl Acad Sci U S A. 2014;111:4519-24.
87. Wong JY, De Vivo I, Lin X, Christiani DC. Cumulative PM(2.5) exposure and telomere length in workers exposed to welding fumes. Journal of toxicology and environmental health Part A. 2014;77:441-55.
88. Wong JY, De Vivo I, Lin X, Grashow R, Cavallari J, Christiani DC. The association between global DNA methylation and telomere length in a longitudinal study of boilermakers. Genetic epidemiology. 2014;38:254-64.
89. Boardman LA, Litzelman K, Seo S, Johnson RA, Vanderboom RJ, Kimmel GW, Cunningham JM, Gangnon RE, Engelman CD, Riegert-Johnson DL, et al. The association of telomere length with colorectal cancer differs by the age of cancer onset. Clinical and translational gastroenterology. 2014;5:e52.
90. Skinner HG, Gangnon RE, Litzelman K, Johnson RA, Chari ST, Petersen GM, Boardman LA. Telomere length and pancreatic cancer: a case-control study. Cancer Epidemiol Biomarkers Prev. 2012;21:2095-100.
91. Savolainen K, Eriksson JG, Kajantie E, Lahti M, Raikkonen K. The history of sleep apnea is associated with shorter leukocyte telomere length: the Helsinki Birth Cohort Study. Sleep medicine. 2014;15:209-12.
92. Savolainen K, Raikkonen K, Kananen L, Kajantie E, Hovatta I, Lahti M, Lahti J, Pesonen AK, Heinonen K, Eriksson JG. History of mental disorders and leukocyte telomere length in late adulthood: the Helsinki Birth Cohort Study (HBCS). J Psychiatr Res. 2012;46:1346-53.
93. Hoen PW, Rosmalen JG, Schoevers RA, Huzen J, van der Harst P, de Jonge P. Association between anxiety but not depressive disorders and leukocyte telomere length after 2 years of follow-up in a population-based sample. Psychological medicine. 2013;43:689-97.
94. Huzen J, Wong LS, van Veldhuisen DJ, Samani NJ, Zwinderman AH, Codd V, Cawthon RM, Benus GF, van der Horst IC, Navis G, et al. Telomere length loss due to smoking and metabolic traits. Journal of internal medicine. 2014;275:155-63.
95. Kingma EM, de Jonge P, van der Harst P, Ormel J, Rosmalen JG. The association between intelligence and telomere length: a longitudinal population based study. PLoS One. 2012;7:e49356.
96. Zhao J, Zhu Y, Lin J, Matsuguchi T, Blackburn E, Zhang Y, Cole SA, Best LG, Lee ET, Howard BV. Short leukocyte telomere length predicts risk of diabetes in american indians: the strong heart family study. Diabetes. 2014;63:354-62.

97. Zhu Y, Voruganti VS, Lin J, Matsuguchi T, Blackburn E, Best LG, Lee ET, MacCluer JW, Cole SA, Zhao J. QTL mapping of leukocyte telomere length in American Indians: the Strong Heart Family Study. Aging. 2013;5:704-16.
98. Garcia-Calzon S, Gea A, Razquin C, Corella D, Lamuela-Raventos RM, Martinez JA, Martinez-Gonzalez MA, Zalba G, Marti A. Longitudinal association of telomere length and obesity indices in an intervention study with a Mediterranean diet: the PREDIMED-NAVARRA trial. International journal of obesity. 2014;38:177-82.
99. Needham BL, Adler N, Gregorich S, Rehkopf D, Lin J, Blackburn EH, Epel ES. Socioeconomic status, health behavior, and leukocyte telomere length in the National Health and Nutrition Examination Survey, 1999-2002. Social science & medicine. 2013;85:1-8.
100. Cui Y, Cai Q, Qu S, Chow WH, Wen W, Xiang YB, Wu J, Rothman N, Yang G, Shu XO, et al. Association of leukocyte telomere length with colorectal cancer risk: nested case-control findings from the Shanghai Women's Health Study. Cancer Epidemiol Biomarkers Prev. 2012;21:1807-13.
101. Kozlitina J, Garcia CK. Red blood cell size is inversely associated with leukocyte telomere length in a large multi-ethnic population. PLoS One. 2012;7:e51046.
102. Pellatt AJ, Wolff RK, Lundgreen A, Cawthon R, Slattery ML. Genetic and lifestyle influence on telomere length and subsequent risk of colon cancer in a case control study. International journal of molecular epidemiology and genetics. 2012;3:184-94.
103. Broer L, Raschenberger J, Deelen J, Mangino M, Codd V, Pietilainen KH, Albrecht E, Amin N, Beekman M, de Craen AJ, et al. Association of adiponectin and leptin with relative telomere length in seven independent cohorts including 11,448 participants. European journal of epidemiology. 2014;29:629-38.
104. Hofmann JN, Baccarelli A, Schwartz K, Davis FG, Ruterbusch JJ, Hoxha M, McCarthy BJ, Savage SA, Wacholder S, Rothman N, et al. Risk of renal cell carcinoma in relation to blood telomere length in a population-based case-control study. Br J Cancer. 2011;105:1772-5.
105. Kajantie E, Pietilainen KH, Wehkalampi K, Kananen L, Raikkonen K, Rissanen A, Hovi P, Kaprio J, Andersson S, Eriksson JG, et al. No association between body size at birth and leucocyte telomere length in adult life--evidence from three cohort studies. Int J Epidemiol. 2012;41:1400-8.
106. Chen S, Lin J, Matsuguchi T, Blackburn E, Yeh F, Best LG, Devereux RB, Lee ET, Howard BV, Roman MJ, et al. Short leukocyte telomere length predicts incidence and progression of carotid atherosclerosis in American Indians: the Strong Heart Family Study. Aging. 2014;6:414-27.
107. Chen S, Yeh F, Lin J, Matsuguchi T, Blackburn E, Lee ET, Howard BV, Zhao J. Short leukocyte telomere length is associated with obesity in American Indians: The strong heart family study. Aging. 2014;6:380-9.
108. Savolainen K, Eriksson JG, Kajantie E, Lahti J, Raikkonen K. Telomere length and hypothalamic-pituitary-adrenal axis response to stress in elderly adults. Psychoneuroendocrinology. 2015;53:179-84.
109. Savolainen K, Eriksson JG, Kajantie E, Pesonen AK, Raikkonen K. Associations between the five-factor model of personality and leukocyte telomere length in elderly men and women: The Helsinki Birth Cohort Study (HBCS). J Psychosom Res. 2015.
110. Savolainen K, Eriksson JG, Kananen L, Kajantie E, Pesonen AK, Heinonen K, Raikkonen K. Associations between early life stress, self-reported traumatic experiences across the lifespan and leukocyte telomere length in elderly adults. Biological psychology. 2014;97:35-42.
111. Tiainen AM, Mannisto S, Blomstedt PA, Moltchanova E, Perala MM, Kaartinen NE, Kajantie E, Kananen L, Hovatta I, Eriksson JG. Leukocyte telomere length and its relation to

food and nutrient intake in an elderly population. European journal of clinical nutrition. 2012;66:1290-4.
112. Laine MK, Eriksson JG, Kujala UM, Raj R, Kaprio J, Backmand HM, Peltonen M, Sarna S. Effect of intensive exercise in early adult life on telomere length in later life in men. Journal of sports science & medicine. 2015;14:239-45.
113. Loukola A, Wedenoja J, Keskitalo-Vuokko K, Broms U, Korhonen T, Ripatti S, Sarin AP, Pitkaniemi J, He L, Happola A, et al. Genome-wide association study on detailed profiles of smoking behavior and nicotine dependence in a twin sample. Molecular psychiatry. 2014;19:615-24.
114. Kim S, Sandler DP, Carswell G, De Roo LA, Parks CG, Cawthon R, Weinberg CR, Taylor JA. Telomere length in peripheral blood and breast cancer risk in a prospective case-cohort analysis: results from the Sister Study. Cancer Causes Control. 2011;22:1061-6.
115. Eisenberg DT, Hayes MG, Kuzawa CW. Delayed paternal age of reproduction in humans is associated with longer telomeres across two generations of descendants. Proc Natl Acad Sci U S A. 2012;109:10251-6.
116. Mason C, Risques RA, Xiao L, Duggan CR, Imayama I, Campbell KL, Kong A, Foster-Schubert KE, Wang CY, Alfano CM, et al. Independent and combined effects of dietary weight loss and exercise on leukocyte telomere length in postmenopausal women. Obesity (Silver Spring). 2013;21:E549-54.
117. Comijs HC, van Marwijk HW, van der Mast RC, Naarding P, Oude Voshaar RC, Beekman AT, Boshuisen M, Dekker J, Kok R, de Waal MW, et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. BMC Res Notes. 2011;4:524.
118. Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, Cuijpers P, De Jong PJ, Van Marwijk HW, Assendelft WJ, et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res. 2008;17:121-40.
119. Miranda-Furtado CL, Ramos FK, Kogure GS, Santana-Lemos BA, Ferriani RA, Calado RT, Dos Reis RM. A Nonrandomized Trial of Progressive Resistance Training Intervention in Women With Polycystic Ovary Syndrome and Its Implications in Telomere Content. Reprod Sci. 2016;23:644-54.
120. Denham J, Nelson CP, O'Brien BJ, Nankervis SA, Denniff M, Harvey JT, Marques FZ, Codd V, Zukowska-Szczechowska E, Samani NJ, et al. Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors. PLoS One. 2013;8:e69377.
121. Chilton WL, Marques FZ, West J, Kannourakis G, Berzins SP, O'Brien BJ, Charchar FJ. Acute exercise leads to regulation of telomere-associated genes and microRNA expression in immune cells. PLoS One. 2014;9:e92088.
122. Bloomer LD, Nelson CP, Denniff M, Christofidou P, Debiec R, Thompson J, Zukowska-Szczechowska E, Samani NJ, Charchar FJ, Tomaszewski M. Coronary artery disease predisposing haplogroup I of the Y chromosome, aggression and sex steroids--genetic association analysis. Atherosclerosis. 2014;233:160-4.
123. Gerstorf D, Bertram L, Lindenberger U, Pawelec G, Demuth I, Steinhagen-Thiessen E, Wagner GG. Editorial. Gerontology. 2016;62:311-5.
124. Bertram L, Bockenhoff A, Demuth I, Duzel S, Eckardt R, Li SC, Lindenberger U, Pawelec G, Siedler T, Wagner GG, et al. Cohort profile: The Berlin Aging Study II (BASE-II). Int J Epidemiol. 2014;43:703-12.

125. Meyer A, Salewsky B, Buchmann N, Steinhagen-Thiessen E, Demuth I. Relative Leukocyte Telomere Length, Hematological Parameters and Anemia - Data from the Berlin Aging Study II (BASE-II). Gerontology. 2016;62:330-6.
126. Khalangot M, Krasnienkov D, Vaiserman A, Avilov I, Kovtun V, Okhrimenko N, Koliada A, Kravchenko V. Leukocyte telomere length is inversely associated with post-load but not with fasting plasma glucose levels. Exp Biol Med (Maywood). 2017;242:700-8.
127. Starnino L, Busque L, Tardif JC, D'Antono B. Psychological Profiles in the Prediction of Leukocyte Telomere Length in Healthy Individuals. PLoS One. 2016;11:e0165482.
128. Kasielski M, Eusebio MO, Pietruczuk M, Nowak D. The relationship between peripheral blood mononuclear cells telomere length and diet - unexpected effect of red meat. Nutr J. 2016;15:68.
129. McDonnell BJ, Yasmin, Butcher L, Cockcroft JR, Wilkinson IB, Erusalimsky JD, McEniery CM. The age-dependent association between aortic pulse wave velocity and telomere length. J Physiol. 2017;595:1627-35.
130. Yim OS, Zhang X, Shalev I, Monakhov M, Zhong S, Hsu M, Chew SH, Lai PS, Ebstein RP. Delay discounting, genetic sensitivity, and leukocyte telomere length. Proc Natl Acad Sci U S A. 2016;113:2780-5.
131. Wang X, Sundquist K, Hedelius A, Palmer K, Memon AA, Sundquist J. Leukocyte telomere length and depression, anxiety and stress and adjustment disorders in primary health care patients. BMC Psychiatry. 2017;17:148.
132. Gerstein HC, Yusuf S, Holman R, Bosch J, Pogue J, Investigators DT. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. Diabetologia. 2004;47:1519-27.
133. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-52.
134. van der Harst P, van der Steege G, de Boer RA, Voors AA, Hall AS, Mulder MJ, van Gilst WH, van Veldhuisen DJ, Group M-HS. Telomere length of circulating leukocytes is decreased in patients with chronic heart failure. Journal of the American College of Cardiology. 2007;49:1459-64.
135. Steenstrup T, Hjelmborg JV, Mortensen LH, Kimura M, Christensen K, Aviv A. Leukocyte telomere dynamics in the elderly. European journal of epidemiology. 2013;28:181-7.
136. Muezzinler A, Zaineddin AK, Brenner H. A systematic review of leukocyte telomere length and age in adults. Ageing Res Rev. 2013;12:509-19.
137. Benetos A, Kark JD, Susser E, Kimura M, Sinnreich R, Chen W, Steenstrup T, Christensen K, Herbig U, von Bornemann Hjelmborg J, et al. Tracking and fixed ranking of leukocyte telomere length across the adult life course. Aging Cell. 2013;12:615-21.
138. de Heredia FP, Gomez-Martinez S, Marcos A. Obesity, inflammation and the immune system. The Proceedings of the Nutrition Society. 2012;71:332-8.
139. Spiegelman D, Israel RG, Bouchard C, Willett WC. Absolute fat mass, percent body fat, and body-fat distribution: which is the real determinant of blood pressure and serum glucose? Am J Clin Nutr. 1992;55:1033-44.
140. Manson JE, Bassuk SS, Hu FB, Stampfer MJ, Colditz GA, Willett WC. Estimating the number of deaths due to obesity: can the divergent findings be reconciled? Journal of women's health. 2007;16:168-76.
141. Aviv A, Valdes AM, Spector TD. Human telomere biology: pitfalls of moving from the laboratory to epidemiology. Int J Epidemiol. 2006;35:1424-9.

142. Lin J, Epel E, Cheon J, Kroenke C, Sinclair E, Bigos M, Wolkowitz O, Mellon S, Blackburn E. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. Journal of immunological methods. 2010;352:71-80.
143. Freedman DS, Gates L, Flanders WD, Van Assendelft OW, Barboriak JJ, Joesoef MR, Byers T. Black/white differences in leukocyte subpopulations in men. Int J Epidemiol. 1997;26:757-64.
144. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, Ravussin E, Ryan DH, Smith SR, Katzmarzyk PT. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity (Silver Spring). 2011;19:402-8.
145. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Walston J, Kimura M, Aviv A. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. Am J Epidemiol. 2007;165:14-21.
146. Broer L, Codd V, Nyholt DR, Deelen J, Mangino M, Willemsen G, Albrecht E, Amin N, Beekman M, de Geus EJ, et al. Meta-analysis of telomere length in 19,713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. European journal of human genetics : EJHG. 2013;21:1163-8.
147. Adaikalakoteswari A, Balasubramanyam M, Mohan V. Telomere shortening occurs in Asian Indian Type 2 diabetic patients. Diabet Med. 2005;22:1151-6.
148. Raschenberger J, Kollerits B, Hammerer-Lercher A, Rantner B, Stadler M, Haun M, Klein-Weigel P, Fraedrich G, Kronenberg F. The association of relative telomere length with symptomatic peripheral arterial disease: results from the CAVASIC study. Atherosclerosis. 2013;229:469-74.
149. Heid IM, Wagner SA, Gohlke H, Iglseder B, Mueller JC, Cip P, Ladurner G, Reiter R, Stadlmayr A, Mackevics V, et al. Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. Diabetes. 2006;55:375-84.

Table 1 Characteristics of included Study samples

ref	Study Name	all	men	women	18 - 60 yrs	> 60 - 75 yrs	> 75 yrs	Cell type	telomere length measure	DNA	BMI	data provided	design	Ethnicity (proportion) White/ Black/ Asian/ Hispanic/ Native American
		n	n	n	n	n	n							
Absolute telomere length measured in base pairs (bp)														
(3, 28-31)	TwinsUK	3236	286	2950	2630	574	32	Leucocytes	Southern Blot RF	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(17, 32-34)	Bogalusa	635	635	0	635	0	0	Leucocytes	Southern Blot RF	unknown	measured	raw data	cohort	0.71 / 0.29 / 0 / 0 / 0
(147)	India CURES Study	40	20	20	37	3	0	Leucocytes	Southern Blot RF	stored	measured	raw data	case-control	0 / 0 / 1 / 0 / 0
(36)	Campania	528	251	277	320	100	108	Leucocytes	Southern Blot RF	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(14, 37-39)	Asklepios	2509	1218	1291	2509	0	0	Leucocytes	Southern Blot RF	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(5, 13, 40)	Framingham	1146	557	589	658	444	44	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(42)	COPD	178	89	89	113	60	5	Leucocytes	Real Time PCR	NA	measured	raw data	case-control	1 / 0 / 0 / 0 / 0
(43)	Crete	109	109	0	0	0	109	Leucocytes	Real Time PCR	NA	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(41)	Zutphen	189	189	0	0	68	121	Leucocytes	Real Time PCR	NA	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(17)	Family Heart African American	625	216	409	459	148	18	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	0 / 1 / 0 / 0 / 0
(17)	Family Heart White	2603	1170	1433	1419	997	187	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
Not publ	HyperGEN African American	224	108	116	172	51	1	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	0 / 1 / 0 / 0 / 0
Not publ	HyperGEN White	1240	612	628	799	426	15	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(44, 45)	LSADT	525	171	354	0	82	443	Leucocytes	Southern Blot RF	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(46, 47)	Heart and Soul	954	777	177	274	451	229	Leucocytes	Real Time PCR	unknown	measured	summary	cohort	0.60 / 0.16 / 0.12 / 0.09 / 0.03
(57, 58)	Lothian	1057	530	527	0	1057	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(48, 49)	WarTwins	639	639	0	0	86	553	Leucocytes	Southern Blot RF	stored	reported	raw data	cohort	1 / 0 / 0 / 0 / 0
(55)	Jerusalem LRC	620	413	207	620	0	0	Leucocytes	Southern Blot RF	Buffy coat stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(56)	Jerusalem Palestinians	939	498	441	336	306	0	Leucocytes	Southern Blot RF	Buffy coat stored	measured	summary	cross-sectional	1 / 0 / 0 / 0 / 0
(50-52)	Helsinki Businessmen Study (HBS)	487	487	0	0	250	237	Leucocytes	Southern Blot RF	stored	reported	raw data	cohort	1 / 0 / 0 / 0 / 0
(53)	Copenhagen General Population Study	45069	20422	24647	26040	14525	4504	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(54)	SOLVABLE	152	0	152	136	16	0	PBMC	Real Time PCR	stored	measured	summary	case-control	0.70 / 0.22 / 0.03 / 0.05 / 0
(59)	ZTL2008	25	17	8	24	1	0	PBMC	Southern Blot RF	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(60)	Venado Tuerto 2	401	0	401	325	63	0	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	0 / 0 / 0 / 1 / 0
(61)	NHSC	672	333	339	534	138	0	Leucocytes	Southern Blot RF	stored	measured	summary	cohort	0 / 0 / 1 / 0 / 0

Absolute telomere length estimated from Telomere to Single Copy Gene ratio (T/S ratio)														
(19, 62, 66, 67)	South Carolina	323	145	178	305	18	0	Leucocytes	Real Time PCR	unknown	measured	summary	cohort	0.57 / 0.41 / 0.01 / 0.01 / 0
(63, 64, 68)	Bruneck	800	395	405	363	315	122	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(65)	RPCI	174	0	174	111	47	16	Leucocytes	Real Time PCR	stored	reported	raw data	case-control	0.93 / 0.05 / 0 / 0 / 0.02
(22)	ESTHER	3559	1583	1976	1432	2127	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1* / 0 / 0 / 0 / 0
Telomere length based on Telomere to Single Copy Gene ratio (T/S ratio)														
(15)	MONICA	511	183	328	419	92	0	Leucocytes	Real Time PCR	NA	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(15)	MDCC	476	330	146	199	277	0	granulocytes	Real Time PCR	NA	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
Not publ	Utah Pedigree Study	964	493	471	725	183	56	Leucocytes	Real Time PCR	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(71, 72)	MESA White	182	89	93	80	80	22	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(71, 72)	MESA African American	278	125	153	141	109	28	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0 / 1 / 0 / 0 / 0
(71, 72)	MESA Hispanic	518	252	266	245	231	42	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0 / 0 / 0 / 1 / 0
(73)	EARSII	395	395	0	395	0	0	Leucocytes	Real Time PCR	unknown	measured	raw data	case-control	1 / 0 / 0 / 0 / 0
(74)	UCLA MacArthur	233	115	118	0	144	89	Leucocytes	Real Time PCR	NA	reported	summary	cohort	1 / 0 / 0 / 0 / 0
(75)	Ashkenazi	359	191	168	50	179	130	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(76)	Warsaw	714	246	468	235	411	68	Leucocytes	Real Time PCR	stored	measured	raw data	case-control	1 / 0 / 0 / 0 / 0
(77)	Finland Health 2000 cohort	938	350	588	754	137	47	Leucocytes	Real Time PCR	stored	unknown	summary	cohort	1 / 0 / 0 / 0 / 0
(78)	Sister Study I (Vanguard sample)	644	0	644	475	169	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.83 / 0.07 / 0.02 / 0.02 / 0.05
(114)	Sister Study II (Genetic Study subcohort)	734	0	734	548	186	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.92 / 0.04 / 0 / 0.02 / 0.02
(79)	CAS	183	96	87	112	53	18	Leucocytes	Real Time PCR	stored	measured	raw data	case-control	1 / 0 / 0 / 0 / 0
(80)	PATH 40	331	151	180	331	0	0	Leucocytes	Real Time PCR	stored	reported	raw data	cohort	0.95 / 0 / 0.03 / 0 / 0.02
(80)	PATH 60	294	157	137	0	294		Leucocytes	Real Time PCR	stored	reported	raw data	cohort	0.97 / 0 / 0.02 / 0 / 0.01
(81)	Italy alcohol controls	258	258	0	255	3	0	Leucocytes	Real Time PCR	stored	reported	raw data	case-control	1 / 0 / 0 / 0 / 0
(82)	Fels Longitudinal Study	257	116	104	196	54	7	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(83, 84)	Ecran	188	38	150	121	41	26	PBMC	Real Time PCR	NA	measured	raw data	cohort	0 / 0 / 0 / 1 / 0
(85, 86)	Heart Scan Study	434	206	228	169	259	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(87, 88)	Boiler workers	104	104	0	97	7	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.85 / 0.09 / 0.02 / 0.03
(89, 90)	Mayo	2886	1470	1416	2001	709	176	Leucocytes	Real Time PCR	NA	measured	raw data	case-control	0.98 / 0 / 0.01 / 0.01 / 0
(91, 92, 105, 108-111)	HBCS	1962	911	1051	703	1259	0	Leucocytes	Real Time PCR	NA	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(93-95)	PREVEND	7991	3994	3997	6094	1897	0	Leucocytes	Real Time PCR	NA	measured	summary	cohort	0.96 / 0.01 /0.02 / 0 / 0.01

(96, 97, 106, 107)	Strong Heart Family Study	3256	1315	1941	2834	340	82	Leucocytes	Real Time PCR	NA	measured	summary	cohort	0 / 0 / 0 / 0 / 1
(98)	PREDIMED-NAVARRA	521	236	285	81	401	38	Leucocytes	Real Time PCR	stored	measured	summary	RCT	1 / 0 / 0 / 0 / 0
(99)	NHANES	7349	3542	3807	5034	1564	751	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.52 / 0.18 / 0 / 0.30 / 0
(100)	SWHS	2912	0	2912	1812	1100	0	Leucocytes	Real Time PCR	NA	measured	summary	cohort	0 / 0 / 1 / 0 / 0
(101)	DHS white	1073	493	580	821	245	7	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(101)	DHS black	1667	606	1061	1348	317	17	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0 / 1 / 0 / 0 / 0
(101)	DHS hispanic	464	194	270	412	51	1	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0 / 0 / 0 / 1 / 0
(102)	DALS	734	401	333	268	366	100	Leucocytes	Real Time PCR	stored	measured	summary	case-control	0.96 / 0 / 0 / 0.03 / 0
(105, 113)	FinnTwin study	2096	1101	995	1589	385	122	Leucocytes	Real Time PCR	NA	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(112)	Former Athletes Study	586	586	0	1	376	209	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(104)	USKCS whole blood	765	442	323	395	320	50	Leucocytes	Real Time PCR	stored	measured	summary	case-control	0.61 / 0.39 / 0 / 0 / 0
(104)	USKCS buffy coat	126	70	56	87	36	3	Leucocytes	Real Time PCR	stored	measured	summary	case-control	0.66 / 0.34 / 0 / 0 / 0
(103)	Erasmus Rucphen Study	2449	1082	1367	1900	499	50	Leucocytes	Real Time PCR	stored	measured	summary	case-control	1 / 0 / 0 / 0 / 0
	Rotterdam Study	2231	944	1287	556	1272	404	Leucocytes	Real Time PCR	stored	measured	summary	case-control	1 / 0 / 0 / 0 / 0
(103)	KORA F3	3113	1509	1604	1768	1051	294	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(103)	KORA F4	3014	1457	1557	1824	943	247	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(148)	CAVASIC	315	315		155	160	0	Leucocytes	Real Time PCR	stored	measured	summary	case-control	1 / 0 / 0 / 0 / 0
(103, 149)	SAPHIR	1681	1055	626	1586	95	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1 / 0 / 0 / 0 / 0
(115)	Cebu Longitudinal Health and Nutrition Survey (CLHNS)	3467	893	2574	3380	87	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0 / 0 / 1 / 0 / 0
(116)	Nutrition and Exercise for Women (NEW) Study	437	0	437	304	131	2	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	0.85 / 0.08 / 0.02 / 0.03 / 0.02
(117)	NESDO	495	173	322	17	354	124	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.95 / 0.01 / 0.04 / 0 / 0
(118)	NESDA	2936	986	1950	2749	187	0	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.97 / 0.02 / 0.01 / 0 / 0
(119)	PRT	43	0	43	43	0	0	Leucocytes	Real Time PCR	stored	measured	raw data	case-control	**
(120, 121)	UMS	67	67	0	65	1	1	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(122)	YMCA	1126	1126	0	1126	0	0	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(123-125)	BASE II	1894	946	948	441	1409	44	Leucocytes	Real Time PCR	stored	measured	summary	cohort	1** / 0 / 0 / 0 / 0
(126)	Kyiv	82	20	62	36	33	13	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0
(127)	GAHR2	133	53	80	128	5	0	Leucocytes	Real Time PCR	stored	measured	raw data	cohort	0.93 / 0.01 / 0.01 / 0.05 / 0
(128)	UMED telomere trial	28	7	21	26	2	0	PBMC	Real Time PCR	Not stored	measured	raw data	cohort	1 / 0 / 0 / 0 / 0

(129)	ACCT	904	454	450	469	361	74	Leucocytes	Real Time PCR	stored	measured	summary	cohort	0.98 / 0.01 / 0.01 / 0 / 0
(130)	RPE	975	466	509	975	0	0	Leucocytes	Real Time PCR	stored	reported	raw data	cohort	0 / 0 / 1 / 0 / 0
(131)	Sweden Mindfulness Study	172	21	151	167	5	0	Leucocytes	Real Time PCR	stored	reported	raw data	RCT	1 / 0 / 0 / 0 / 0
(132)	EpiDREAM	4205	1565	2640	3363	770	72	Leucocytes	Real Time PCR	stored	reported	summary		0.61 / 0.08 / 0.21 / 0.09 / 0
(133)	INTERHEART	3306	2601	705	2092	997	217	Leucocytes	Real Time PCR	stored	reported	summary	case-control	0.27 / 0.08 / 0.44 / 0.21 / 0

NA=not available; data provided by PI: summary=summary statistics
*= not measured, but all Eurasian descent. ** not measured

Table 2 Summary of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and telomere length

	All together (total pooled sample, adjusted for age)				"Young" pooled sample (age ≥18 and ≤ 60 years)				"Middle " pooled sample (60 < age ≤ 75 years)				"Old" pooled sample (age > 75 years)			
	N	estimate	95%C.I.	I^2 (%)	N	estimate	95%C.I.	I^2 (%)	N	estimate	95%C.I.	I^2 (%)	N	estimate	95%C.I.	I^2 (%)
Absolute telomere length (base pairs (bp)) as outcome																
Overall	29	**-3.99**	**-5.17, -2.81**	0.6	23	**-7.67**	**-10.03, -5.31**	31.2	22	-1.65	-4.41, 1.11	19.7	16	**-5.89**	**-10.41, -1.37**	5.3
White	21	**-4.36**	**-5.87, -2.85**	11.3	15	**-8.77**	**-10.42, -7.12**	0.0	15	**-2.06**	**-4.06, -0.06**	0.0	13	**-6.97**	**-12.29, -1.64**	15.4
African Am.	2	0.86	-4.75, 6.46	0.0	2	0.960	-5.51, 7.43	1.2	2	4.36	-7.25, 15.97	0.0	1	74.70	-76.02, 225.42	
Hispanic	1	5.97	-149.97, 161.91		1	-45.64	-216.24, 124.95		1	212.68	-169.98, 595.34		1			
Asian	2	-7.65	-27.20, 11.91	0.0	2	-48.70	-130.38, 32.99	10.8	1	**90.00**	**27.28, 152.72**		0			
Native Am.	0				0				0				0			
Relative telomere length (Telomere to Single Copy Gene ratio (T/S ratio*10^{-3})) as outcome																
Overall	58	**-1.58**	**-2.14, -1.01**	32.7	55	**-2.58**	**-3.92, -1.25**	**80.0**	50	**-1.08**	**-1.76, -0.39**	0.0	29	0.20	-1.40, 1.80	0.0
white	43	**-1.87**	**-2.44, -1.31**	8.1	40	**-2.80**	**-4.77, -0.82**	**84.1**	37	**-1.65**	**-2.45, -0.86**	0.0	21	-0.28	-2.29, 1.73	0.0
African Am.	2	5.66	-6.60, 17.92	**80.0**	2	5.21	-5.67, 16.08	68.7	2	0.08	-6.20, 6.36	0.0	1	-0.74	-12.62, 11.14	
Hispanic	3	2.53	-5.18, 10.25	17.7	3	-0.42	-4.19, 3.34	0.0	3	2.31	-2.35, 6.97	0.0	2	27.29	-40.32, 94.61	**77.7**
Asian	3	-1.11	-4.23, 2.02	60.4	3	**-4.50-**	**-5.75, -3.25**	0.0	2	2.18	-2.90, 7.27	0.0	0			
Native Am.	1	**-2.64**	**-3.60, -1.68**		1	**-4.14**	**-5.28, -3.00**		1	2.23	-1.00, 5.46		1	4.68	-2.35, 11.71	

N= number of studies; Am. = American; The unit of the **estimates and 95%C.I. of T/S ratio is 10^{-3}**; Random effect model was used and adjusted for age if analyzed all together (the total study population) and adjusted for sex; Statistical heterogeneity was estimated by Q and I^2 statistics for each of the twelve meta-analyses; Bold: p< 0.05 or I^2>50%

LEGEND OF FIGURES

Figure 1

Inclusion flow chart

Figure 2

Title

Forest plot of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and absolute telomere length (bp) as outcome in the total pooled population

Legend

ES= estimate; Random effect model was used and adjusted for age and sex; Statistical heterogeneity was estimated by Q and I^2 statistics for each of the twelve meta-analyses; The shaded boxes indicate the inverse variance weighing of each estimate and the size of the box indicates the weight. In case no shaded box is visible, weight is very small.

Figure 3

Title

Forest plot of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and relative telomere length (T/S ratio) (B) as outcome in the total pooled population

Legend

The **unit of the estimates and 95%C.I. is 10^{-3}**; ES= estimate; Random effect model was used and adjusted for age and sex; Statistical heterogeneity was estimated by Q and I^2 statistics for each of the twelve meta-analyses; The shaded boxes indicate the inverse variance weighing of each estimate and the size of the box indicates the weight. In case no shaded box is visible, weight is very small.

Figure 4

Title

Forest plot of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and absolute telomere length (bp) as outcome in the "young" pooled population (age ≥18 and ≤ 60 years)

Legend

ES= estimate; Random effect model was used and adjusted for sex; Statistical heterogeneity was estimated by Q and I^2 statistics for each of the twelve meta-analyses; The shaded boxes indicate the inverse variance weighing of each estimate and the size of the box indicates the weight. In case no shaded box is visible, weight is very small.

Figue 5

Title

Forest plot of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and relative telomere length (T/S ratio) (B) as outcome in the “young” pooled population (age ≥18 and ≤ 60 years)

Legend

The **unit of the estimates and 95%C.I. is 10^{-3}**; ES= estimate; Random effect model was used and adjusted for sex; Statistical heterogeneity was estimated by Q and I^2 statistics for each of the twelve meta-analyses; The shaded boxes indicate the inverse variance weighing of each estimate and the size of the box indicates the weight. In case no shaded box is visible, weight is very small.