Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies

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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. Obesity may therefore contribute to accelerated shortening of telomeres. Consequently, obese persons are more likely to have shorter telomeres, but the association between body mass index (BMI) and leukocyte telomere length (TL) might differ across the life span and between ethnicities and sexes.

Objective: A collaborative cross-sectional meta-analysis of observational studies was conducted to investigate the associations between BMI and TL across the 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 by using a random-effects model in which absolute [base pairs (bp)] and relative telomere to single-copy gene ratio (T/S ratio) TLs were regressed against BMI. Stratified analysis was performed by 3 age categories ("young": 18–60 y; "middle": 61–75 y; and "old": >75 y), sex, and ethnicity.

Results: Each unit increase in BMI corresponded to a −3.99 bp (95% CI: −5.17, −2.81 bp) difference in TL in the total pooled sample; among young adults, each unit increase in BMI corresponded to a −7.67 bp (95% CI: −10.03, −5.31 bp) difference. Each unit increase in BMI corresponded to a -1.58×10^{-3} unit T/S ratio (0.16% decrease; 95% CI: -2.14×10^{-3}, -1.01×10^{-3}) difference in age- and sex-adjusted relative TL in the total pooled sample; among young adults, each unit increase in BMI corresponded to a -2.58×10^{-3} unit T/S ratio (0.26% decrease; 95% CI: -3.92×10^{-3}, -1.25×10^{-3}). The associations were predominantly for the white pooled population. No sex differences were observed.

Conclusions: A 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. *Am J Clin Nutr* 2018;108:453–475.

Keywords: 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 (TL) 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 overall (7), studies in the elderly found no relation between TL and obesity and no relation between TL and mortality (8, 9). We hypothesized that obese persons will have shorter telomeres, compared with those of normal weight of the

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Supplemental Methods, Supplemental Results, Supplemental Figures 1 and 2, Supplemental Tables 1–3, and Study Protocol for Participating PIs are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: bp, base pair; PI, principal investigator; qPCR, quantitative polymerase chain reaction; TL, telomere length; T/S ratio, telomere to single-copy gene ratio.

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same chronological age, but that the association between obesity and TL will differ across the life span.

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

Two recent meta-analyses reported the negative association between BMI and TL on reported summary statistics in the literature, but they did not examine sex differences or the influence of age and ethnicity (7, 22). To further evaluate whether BMI is associated with TL, a large-scale, collaborative, cross-sectional meta-analysis was conducted across observational studies that collected information on BMI and TL 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 Telomere Maastricht collaborator (TELOMAAS) group. Because the relation between TL 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 until 10 November 2017 using PubMed (www.ncbi.nlm.nih.gov/pmc), EMBASE (ovidsp.tx.ovid.com), and the Cochrane (www.cochranelibrary.com) database without restrictions in language or publication date. Numerous studies have measured BMI and TL for purposes other than the association between TL and BMI as an outcome. Therefore, the search was rather broad and not narrowed to TL or BMI. On the basis of the existing relation between obesity, diabetes, and cardiovascular diseases, and because TL is related to aging, we completed a search in which terms related to these conditions were entered. In addition, 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 of the authors (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 reported a study of diabetes or cardiovascular disease, the full text was screened. No additional restrictions for study design 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 in 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 the Supplemental data ("**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, and ethnicity [when $\geq$70% of the individuals of a sample were 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 constituted 70% of the sample, the sample was classified as a mixed sample]; leukocyte TL; and BMI (kg/m^2) and whether BMI was measured or self-reported; white blood cell types from which DNA was extracted for telomere measurements; and method of TL measurement and of DNA storage (Supplemental Material: Study Protocol for Participating PIs). Two metrics were used for TL: absolute TL in base pairs (bp) and relative TL based on telomere to single-copy gene ratio (T/S ratio) (23). A T/S ratio of 0.8 indicates a relative TL, which is 80% of the reference used (100%).

The PI was free to provide the de-identified raw data or to perform linear regression analyses and provide summary statistics. If the PI provided raw data, one of the authors (MG) conducted the linear regression analyses with TL (bp or T/S ratio) as the outcome and BMI as the independent variable to obtain the summary statistics. Three sex groups were defined: men, women, and a combined group of men and women; 4 age groups were defined: "young" (18–60 y), "middle" (61–75 y), and "old" (>76 y) and a combined group of all subjects regardless of their age. For each study, $\leq$12 stratified linear regression analyses were conducted (stratified by the 3 sex groups and 4 age groups). The analyses that included all subjects regardless of sex were adjusted for sex; similarly, the analyses that included all subjects regardless of age were adjusted for age.

If the T/S ratio was used to estimate absolute TL without the use of reference DNA with the known absolute TL, 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 TL based on the T/S ratio was used for analyses and included in the analysis. The regression coefficients (β estimates) and SEs were then used in the meta-analyses. In the case of longitudinal data, one randomly selected measurement of TL along with the corresponding BMI and age for that time point were used in the analysis. The summary statistics thus included the results of 12 linear regression analyses, with TL (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 TL in bp or relative TL (T/S ratio) per unit increase in BMI. Study-specific regression coefficients (β estimates) and SEs were combined by using random-effects pooling in 12 meta-analyses. The assumption of a linear association between BMI and TL was verified by using the raw data provided by the PIs (Supplemental Methods, **Supplemental Results**).

Assessment of heterogeneity

Details are given in Supplemental Methods. Statistical heterogeneity between studies was estimated by using I^2 statistics (26, 27) for each of the 12 meta-analyses. Low heterogeneity was indicated by I^2 ≤25%, medium heterogeneity by I^2 of 25–50%, and high heterogeneity by I^2 >50% (27). To investigate potential effect modification of age and sex, meta-regression analysis was performed with age and sex separately incorporated as covariates. Age was therefore categorized into 3 age categories ["young" (18–60 y), "middle" (61–75 y), and "old" (>75 y)] and also into 2 age categories ["young" (18–60 y) and "other" (>60 y)]. Other potential sources of heterogeneity at the study level (effect modifiers) were also 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 with large sample sizes (n >5000), *3*) omitting studies that used the relative TL to estimate the absolute TL, *4*) stratification by method of measurement of TL [Southern blot compared with quantitative polymerase chain reaction (qPCR)], and *5*) using a cutoff of 90% for defining ethnicity (Supplemental Methods).

Statistical analyses were performed with the use of Stata software version 12.0 (StataCorp). All of the statistical tests were 2-sided; P values <0.05 were considered significant, except where otherwise specified.

RESULTS

Search

The search (PubMed, EMBASE, and Cochrane) yielded 5021 publications, from which 173 potentially relevant publications were identified. Some authors contributed to >1 publication. As a result, 153 corresponding authors were identified and contacted. Seventy-five corresponding authors responded positively, 69 authors did not respond, 6 declined to participate, and 3 authors did not have the requested data. Because 1 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 9 studies that used *1*) techniques other than Southern blots and qPCR or *2*) did not report TL in bp or T/S ratio, because the regression coefficients (β estimates) may not be directly comparable.

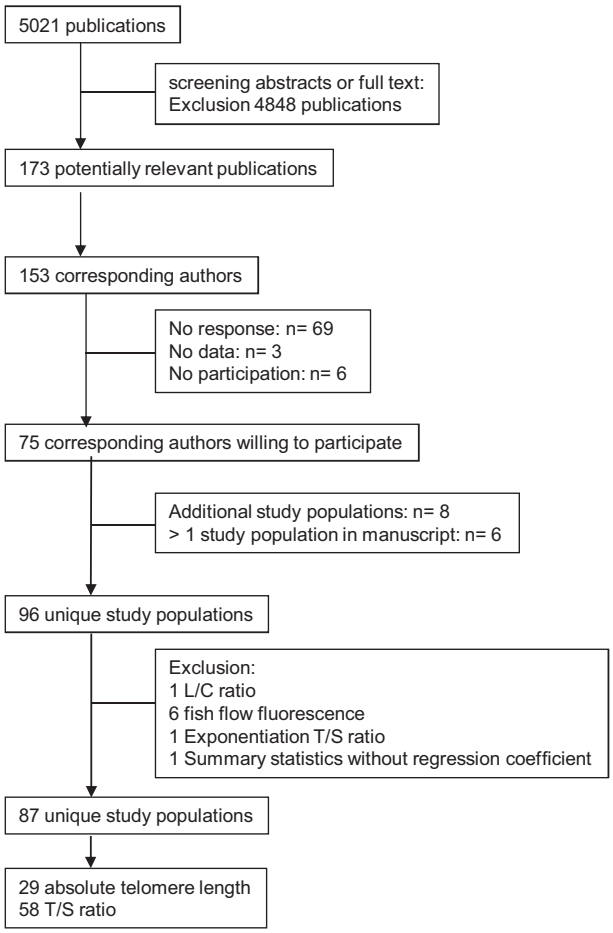

FIGURE 1 Study inclusion flow chart. L/C ratio, telomere/centromere ratio; T/S ratio, telomere to single-copy gene ratio.

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

Description of studies

The characteristics of the 87 studies included in this meta-analysis are provided in **Table 1**. Absolute TLs were obtained from 29 studies (3, 5, 13, 14, 17, 28–61; HyperGEN study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011), of which 4 studies estimated absolute TL on the basis of 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 TL (T/S ratio) (4, 15, 69–133; Utah Pedigree Study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011). One PI provided the data stratified by source of leukocytes (whole blood compared with buffy coat) (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 (18–60 y) consisted of 81,446 adults (51% men), the "middle" pooled sample (61–75 y) consisted of 42,991 adults (41%

TABLE 1
Characteristics of included study samples[1]

Ref	Study name	All, *n*	Men, *n*	Women, *n*	Age, *n*			Cell type	Telomere length measure	DNA	BMI	Data provided	design	Ethnicity (proportion white/black/Asian/Hispanic/Native American)
					18–60 y	>60–75 y	>75 y							
Absolute telomere length measured in base pairs														
(3, 28–31)	TwinsUK	3236	286	2950	2630	574	32	Leukocytes	Southern blot RF	Stored	Measured	Summary	Cohort	1/0/0/0/0
(17, 32–34)	Bogalusa	635	635	0	635	0	0	Leukocytes	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	Leukocytes	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	Leukocytes	Southern blot RF	NA	Measured	Summary	Cohort	1/0/0/0/0
(42)	COPD	178	89	89	113	60	5	Leukocytes	Real-time PCR	NA	Measured	Raw data	Case-control	1/0/0/0/0
(43)	Crete	109	109	0	0	0	109	Leukocytes	Real-time PCR	NA	Measured	Raw data	Cohort	1/0/0/0/0
(41)	Zutphen	189	189	0	0	68	121	Leukocytes	Real-time PCR	NA	Measured	Raw data	Cohort	1/0/0/0/0
(17)	Family Heart, African American	625	216	409	459	148	18	Leukocytes	Southern blot RF	NA	Measured	Summary	Cohort	0/1/0/0/0
(17)	Family Heart, white	2603	1170	1433	1419	997	187	Leukocytes	Southern blot RF	NA	Measured	Summary	Cohort	1/0/0/0/0
Not published	HyperGEN, African American	224	108	116	172	51	1	Leukocytes	Southern blot RF	NA	Measured	Summary	Cohort	0/1/0/0/0
Not published	HyperGEN, white	1240	612	628	799	426	15	Leukocytes	Southern Blot RF	NA	Measured	Summary	Cohort	1/0/0/0/0
(44, 45)	LSADT	525	171	354	0	82	443	Leukocytes	Southern blot RF	NA	Measured	Summary	Cohort	1/0/0/0/0
(46, 47)	Heart and Soul	954	777	177	274	451	229	Leukocytes	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	Leukocytes	Southern blot RF	Stored	Reported	Raw data	Cohort	1/0/0/0/0
(55)	Jerusalem LRC	620	413	207	620	0	0	Leukocytes	Southern blot RF	Buffy coat stored	Measured	Summary	Cohort	1/0/0/0/0
(56)	Jerusalem Palestinians	939	498	441	336	306	0	Leukocytes	Southern blot RF	Buffy coat stored	Measured	Summary	Cross-sectional	1/0/0/0/0

(*Continued*)

TABLE 1 *Continued*

Ref	Study name	All, *n*	Men, *n*	Women, *n*	Age, *n*			Cell type	Telomere length measure	DNA	BMI	Data provided	design	Ethnicity (proportion white/black/Asian/Hispanic/Native American)
					18–60 y	>60–75 y	>75 y							
(50–52)	Helsinki Businessmen Study	487	487	0	0	250	237	Leukocytes	Southern blot RF	Stored	Reported	Raw data	Cohort	1/0/0/0/0
(53)	Copenhagen General Population Study	45,069	20,422	24,647	26,040	14,525	4504	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(54)	SOLVABLE	152	0	152	136	16	0	PBMCs	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	PBMCs	Southern blot RF	Stored	Measured	Raw data	Cohort	1/0/0/0/0
(60)	Venado Tuerto 2	401	0	401	325	63	0	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Cohort	0/0/0/1/0
(61)	NHSC	672	333	339	534	138	0	Leukocytes	Southern blot RF	Stored	Measured	Summary	Cohort	0/0/1/0/0
Absolute telomere length estimated from T/S ratio														
(19, 62, 66, 67)	South Carolina	323	145	178	305	18	0	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(65)	RPCI	174	0	174	111	47	16	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1*/0/0/0/0
Telomere length based on T/S ratio														
(15)	MONICA	511	183	328	419	92	0	Leukocytes	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 published	Utah Pedigree Study	964	493	471	725	183	56	Leukocytes	Real-time PCR	NA	Measured	Summary	Cohort	1/0/0/0/0
(71, 72)	MESA, white	182	89	93	80	80	22	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(71, 72)	MESA, African American	278	125	153	141	109	28	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0/1/0/0/0
(71, 72)	MESA, Hispanic	518	252	266	245	231	42	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0/0/0/1/0
(73)	EARSII	395	395	0	395	0	0	Leukocytes	Real-time PCR	Unknown	Measured	Raw data	Case-control	1/0/0/0/0
(74)	UCLA MacArthur	233	115	118	0	144	89	Leukocytes	Real-time PCR	NA	Reported	Summary	Cohort	1/0/0/0/0

(*Continued*)

TABLE 1 *Continued*

Ref	Study name	All, *n*	Men, *n*	Women, *n*	Age, *n*			Cell type	Telomere length measure	DNA	BMI	Data provided	design	Ethnicity (proportion white/black/Asian/Hispanic/Native American)
					18–60 y	>60–75 y	>75 y							
(75)	Ashkenazi	359	191	168	50	179	130	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Cohort	1/0/0/0/0
(76)	Warsaw	714	246	468	235	411	68	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Unknown	Summary	Cohort	1/0/0/0/0
(78)	Sister Study I (Vanguard sample)	644	0	644	475	169	0	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.92/0.04/0/0.02/0.02
(79)	CAS	183	96	87	112	53	18	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Case-control	1/0/0/0/0
(80)	PATH 40	331	151	180	331	0	0	Leukocytes	Real-time PCR	Stored	Reported	Raw data	Cohort	0.95/0/0.03/0/0.02
(80)	PATH 60	294	157	137	0	294		Leukocytes	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	Leukocytes	Real-time PCR	Stored	Reported	Raw data	Case-control	1/0/0/0/0
(82)	Fels Longitudinal Study	257	116	104	196	54	7	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(83, 84)	ECRAN	188	38	150	121	41	26	PBMCs	Real-time PCR	NA	Measured	Raw data	Cohort	0/0/0/1/0
(85, 86)	Heart Scan Study	434	206	228	169	259	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(87, 88)	Boiler workers	104	104	0	97	7	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.85/0.09/0.02/0.03/0
(89, 90)	Mayo	2886	1470	1416	2001	709	176	Leukocytes	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	Leukocytes	Real-time PCR	NA	Measured	Raw data	Cohort	1/0/0/0/0
(93–95)	PREVEND	7991	3994	3997	6094	1897	0	Leukocytes	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	Leukocytes	Real-time PCR	NA	Measured	Summary	Cohort	0/0/0/0/1
(98)	PREDIMED-NAVARRA	521	236	285	81	401	38	Leukocytes	Real-time PCR	Stored	Measured	Summary	RCT	1/0/0/0/0
(99)	NHANES	7349	3542	3807	5034	1564	751	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.52/0.18/0/0.30/0
(100)	SWHS	2912	0	2912	1812	1100	0	Leukocytes	Real-time PCR	NA	Measured	Summary	Cohort	0/0/1/0/0
(101)	DHS, white	1073	493	580	821	245	7	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0

(*Continued*)

TABLE 1 *Continued*

Ref	Study name	All, *n*	Men, *n*	Women, *n*	Age, *n*			Cell type	Telomere length measure	DNA	BMI	Data provided	design	Ethnicity (proportion white/black/Asian/Hispanic/Native American)
					18–60 y	>60–75 y	>75 y							
(101)	DHS, black	1667	606	1061	1348	317	17	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0/1/0/0/0
(101)	DHS, Hispanic	464	194	270	412	51	1	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0/0/0/1/0
(102)	DALS	734	401	333	268	366	100	Leukocytes	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	Leukocytes	Real-time PCR	NA	Measured	Summary	Cohort	1/0/0/0/0
(112)	Former Athletes Study	586	586	0	1	376	209	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(104)	USKCS, whole blood	765	442	323	395	320	50	Leukocytes	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	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Measured	Summary	Case-control	1/0/0/0/0
(103)	Rotterdam Study	2231	944	1287	556	1272	404	Leukocytes	Real-time PCR	Stored	Measured	Summary	Case-control	1/0/0/0/0
(103)	KORA F3	3113	1509	1604	1768	1051	294	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(103)	KORA F4	3014	1457	1557	1824	943	247	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(148)	CAVASIC	315	315		155	160	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Case-control	1/0/0/0/0
(103, 149)	SAPHIR	1681	1055	626	1586	95	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1/0/0/0/0
(115)	CLHNS	3467	893	2574	3380	87	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0/0/1/0/0
(116)	NEW Study	437	0	437	304	131	2	Leukocytes	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	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.95/0.01/0.04/0/0
(118)	NESDA	2936	986	1950	2749	187	0	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.97/0.02/0.01/0/0
(119)	PRT	43	0	43	43	0	0	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Case-control	**
(120, 121)	UMS	67	67	0	65	1	1	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Cohort	1/0/0/0/0

(*Continued*)

TABLE 1 *Continued*

Ref	Study name	All, *n*	Men, *n*	Women, *n*	Age, *n*			Cell type	Telomere length measure	DNA	BMI	Data provided	design	Ethnicity (proportion white/black/Asian/Hispanic/Native American)
					18–60 y	>60–75 y	>75 y							
(122)	YMCA	1126	1126	0	1126	0	0	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Cohort	1/0/0/0/0
(123–125)	BASE-II	1894	946	948	441	1409	44	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	1**/0/0/0/0
(126)	Kyiv	82	20	62	36	33	13	Leukocytes	Real-time PCR	Stored	Measured	Raw data	Cohort	1/0/0/0/0
(127)	GAHR2	133	53	80	128	5	0	Leukocytes	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	PBMCs	Real-time PCR	Not stored	Measured	Raw data	Cohort	1/0/0/0/0
(129)	ACCT	904	454	450	469	361	74	Leukocytes	Real-time PCR	Stored	Measured	Summary	Cohort	0.98/0.01/0.01/0/0
(130)	RPE	975	466	509	975	0	0	Leukocytes	Real-time PCR	Stored	Reported	Raw data	Cohort	0/0/1/0/0
(131)	Sweden Mindfulness Study	172	21	151	167	5	0	Leukocytes	Real-time PCR	Stored	Reported	Raw data	RCT	1/0/0/0/0
(132)	EpiDREAM	4205	1565	2640	3363	770	72	Leukocytes	Real-time PCR	Stored	Reported	Summary	—	0.61/0.08/0.21/0.09/0
(133)	INTERHEART	3306	2601	705	2092	997	217	Leukocytes	Real-time PCR	Stored	Reported	Summary	Case-control	0.27/0.08/0.44/0.21/0

[1]*Not measured, but all of Eurasian descent; **not measured. ACCT, Anglo-Cardiff Collaborative Trial; BASE-II, Berlin Aging Study; CAS, calcific aortic valve stenosis study; CAVASIC, Cardiovascular Disease in Intermittent Claudication; CLHNS, Cebu Longitudinal Health and Nutrition Survey; COPD, Chronic Obstructive Lung disease cohort; CURES, Chennai Urban Rural Epidemiology Study; DALS, Diet, Activity and Lifestyle Study; DHS, Dallas Heart Study; EARSII, European Atherosclerosis Study II; ECRAN, Envejecimiento y Enfermedades Crónicas Asociadas a Nutrición (Aging and Nutrition Associated Chronic Disease); EpiDREAM, Epidemiologic study of the Screenes for DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication); ESTHER, Epidemiological Study on the Chances of Prevention, Early Recognition, and Optimised Treatment of Chronic Diseases in the Older Population; GAHR2, Prospective evaluation of Gender and Age differences in the impact of Hostility and Reactivity on intermediary coronary artery disease risk factors; HBCS, Helsinki Birth Cohort Study; HyperGEN, Hypertension Genetic Epidemiology Network study; KORA F3, Cooperative Health Research in the Region of Augsburg F3 (2004/2005) survey; KORA F4, Cooperative Health Research in the Region of Augsburg F4 (2006/2008) survey; LRC (Jerusalem), Lipid Research Clinic; LSADT, Longitudinal Study of Aging Danish Twins (https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/21041); MDCC, Malmö Diet and Cancer Cohort; MESA, Multi-Ethnic Study of Atherosclerosis (https://www.mesa-nhlbi.org/); MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; NA, not available (data provided by principal investigator); NESDA, The Netherlands Study of Depression and Anxiety; NESDO, The Netherlands Study of Depression in older persons; NEW, Nutrition and Exercise for Women; NHSC, Nutrition and Health in Southwest China study; PATH 40, Personality and Total Health Through Life Project AGE 40-44; PATH 60, Personality and Total Health Through Life Project AGE 60–64; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PREDIMED, Prevención con Dieta Mediterránea; PREVEND, Prevention of Renal and Vascular End-stage Disease; PRT, Progressive Resistance Training; RCT, randomized controlled trial; Ref, reference; RF, restriction fragment; RPCI, Roswell Park Cancer Institute; RPE, Richard Paul Ebstein; SAPHIR, Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk Study; SOLVABLE, Study of Lupus Vascular and Bone Longterm Endpoints; summary, summary statistics; SWHS, Shanghai Women's Health Study; T/S ratio, telomere to single-copy gene ratio; UMED, Uniwersytet MEDyczny w Łodzi (Medical University of Lodz (MUL)); UMS, ultra-marathon study; USKCS, US Kidney Cancer Study; YMCA, Young Men Cardiovascular Association; ZTL2008, Zannolli Telomere Length 2008.

men), and the "old" pooled sample (>75 y) consisted of 8495 adults (65% men). Overall, the majority of the adults were white (including Arab; 83%), followed by Asian (7%), African American (4%), and Hispanic and Native American (both 3%). Six studies provided data of mixed study populations stratified by ethnicity (17, 71, 72, 101, 132, 133; HyperGEN study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011). Sixty-five studies consisted of >70% white individuals (of which 60 had ≥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; HyperGEN study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011; Utah Pedigree Study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011). Four studies consisted only of African Americans (17, 71, 72, 101; HyperGEN study, unpublished data S. Hunt, A. Aviv, R. Cawthon 2011), 5 only of Asians (35, 61, 100, 115, 130), 1 study only of Native Americans (96, 97, 106, 107), and 4 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 TL and for relative TL yielded symmetric plots (**Supplemental Figure 1**, funnel plots). No publication bias was detected with the use of Egger's test or Begg's test. The "trim and fill" method added 1 hypothetical study to the meta-analysis for absolute TL. However, the recalculated summary estimate did not change and was still significant with its inclusion ($\beta = -3.99$; 95% CI: −5.16, −2.84; $P < 0.001$).

Statistical pooling

A summary of the β estimates of the meta-analysis is shown in **Tables 2** and **3**. An overview of the meta-analysis is shown **Supplemental Tables 2** and **3** in which the β estimates of all meta-analyses for absolute TL as the outcome (Supplemental Table 2) and of all meta-analyses for relative TL as the outcome (Supplemental Table 3) are presented. The accompanying forest plots are presented in the **Supplemental Figure 2**.

We confirmed that age was an effect modifier. Because the associations between BMI and TL did not differ significantly between men and women, the results of the sex-specific meta-analyses are shown only in the Supplemental Results.

Overall meta-analysis

Overall, sex- and age-adjusted absolute TL was significantly associated with BMI (Table 2, line 1). Each unit increase in BMI corresponded to a −3.99 bp (95% CI: −5.17, −2.81 bp; $I^2 = 0.6\%$) difference in absolute TL (Table 2, line 1; **Figure 2**). For example, the estimated difference in TL between a normal-weight individual with a BMI of 25 and an obese individual with a BMI >30 is (rounded) >20.0 bp and, if a larger difference is used (BMI: 20 compared with >30), is >39.9 bp. The estimated difference between normal weight and morbid obesity (BMI >40) is >59.9 bp. Overall, each unit increase in BMI corresponded to a -1.58×10^{-3} unit T/S ratio (0.16% decrease; 95% CI: -2.14×10^{-3}, -1.01×10^{-3}; $I^2 = 41.1\%$) difference in age- and sex-adjusted relative TL (Table 3, line 1). The estimated difference in relative TL between normal weight and obesity

TABLE 2
Summary of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and telomere length as the outcome and absolute telomere length (in base pairs) as the independent variable[1]

		Pooled sample[3]													
		All (total pooled sample)[2]				"Young" (18–60 y old)				"Middle"-aged (61–75 y old)				"Old" (>75 y old)			
Line	Ethnicity	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %
1	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
2	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
3	African American	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	
4	Hispanic	1	5.97	−149.97, 161.91		1	−45.64	−216.24, 124.95		1	212.68	−169.98, 595.34		0			
5	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			

[1] A random-effects model was used. Statistical heterogeneity was estimated by I^2 statistics for each of the meta-analyses. *$P < 0.05$ or $I^2 > 50\%$. "*n*" indicates number of studies.
[2] Adjusted for age and sex.
[3] Adjusted for sex.

TABLE 3
Summary of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and telomere length as the outcome and relative telomere length (T/S ratio) as the independent variable[1]

		Pooled sample[3]													
		All (total pooled sample)[2]				"Young" (18–60 y old)				"Middle"-aged (61–75 y old)				"Old" (>75 y old)			
Line	Ethnicity	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %	*n*	Estimate	95% CI	I^2, %
1	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
2	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
3	African American	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	
4	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*
5	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			
6	Native American	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	

[1]The unit of the estimates and 95% CI of the T/S ratio is 10^{-3}. A random-effects model was used. Statistical heterogeneity was estimated by I^2 statistics for each of the meta-analyses. *$P < 0.05$ or $I^2 > 50\%$. "*n*" indicates number of studies. T/S ratio, telomere to single-copy gene ratio.
[2]Adjusted for age and sex.
[3]Adjusted for sex.

is a ≥7.9 × 10^{-3} unit (0.79% difference) T/S ratio (Table 3, line 1; **Figure 3**) and between normal weight and morbid obesity is a ≥23.7 × 10^{-3} unit T/S ratio (2.37% difference).

Meta-analysis stratified by age categories

Analysis stratified by age category showed that in "young" adults (18–60 y) a unit increase in BMI corresponded to a −7.67 bp (95% CI: −10.03, −5.31 bp; $I^2 = 31.2\%$) difference in absolute TL (Table 2, line 1; **Figure 4**). In "middle"-aged adults (61–75 y) the overall association between BMI and TL was −1.65 bp (95% CI: −4.41, 1.11 bp; $I^2 = 19.7$) per unit increase in BMI. In "old" adults (>75 y) the overall association between BMI and TL was −5.89 bp (95% CI: −10.41, −1.37 bp; $I^2 = 5.3$) per unit increase in BMI (Table 2, line 1).

For relative TL, each unit increase in BMI corresponded to a −2.58 × 10^{-3} unit T/S ratio (0.26% decrease; 95% CI: −3.92 × 10^{-3}, −1.25 × 10^{-3}; $I^2 = 80.0\%$) difference in relative TL in young adults (Table 3, line 1; **Figure 5**). In "middle"-aged adults, the overall association between BMI and relative TL was found to be a −1.08 × 10^{-3} unit T/S ratio (0.1% decrease; 95% CI: −1.76 × 10^{-3}, −0.39 × 10^{-3}; $I^2 = 0.0$) per unit increase in BMI. For "old" adults no significant association [0.20 × 10^{-3} unit T/S ratio (0.02%); 95% CI: −1.40 × 10^{-3}, 1.80 × 10^{-3}; $I^2 = 0.0$] was found between BMI and relative TL (Table 3, line 1).

Meta-regression and sources of heterogeneity

Age and ethnicity were effect modifiers in the meta-regression analyses (Supplemental Results). Therefore, all of the analyses were stratified by ethnicity in addition to the originally planned analyses.

With absolute TL as the outcome, stratified analyses showed that all estimates were significant for the white pooled sample (Table 2, line 2) and also for the "middle" pooled Asian sample. However, the latter estimate was an outlier and based on just 1 study (Table 2, line 5).

With relative TL as the outcome, stratified analyses showed that the estimates (except for one estimate for the "old" pooled sample) were significant for the white pooled sample (Table 3, line 2). In addition, the estimates of the overall and "young" pooled Native American samples and the estimate of the "young" pooled Asian sample were significant (Table 3, lines 5 and 6).

Sensitivity analysis

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

DISCUSSION

This cross-sectional meta-analysis of 87 observational studies of adult pooled populations confirmed previous observations that BMI is negatively associated with TL. After stratification for age and ethnicity, the negative association between BMI and TL appeared to be stronger in the "young" pooled population (18–60 y) and in the white pooled population. Differences between men and women could not be confirmed.

On the basis of our estimates for absolute TL, an ∼5-unit higher BMI appears to be equivalent to a difference in TL of ∼20–38 bp or an ∼7.9 × 10^{-3} to 13 × 10^{-3} unit T/S ratio (0.79–1.3%

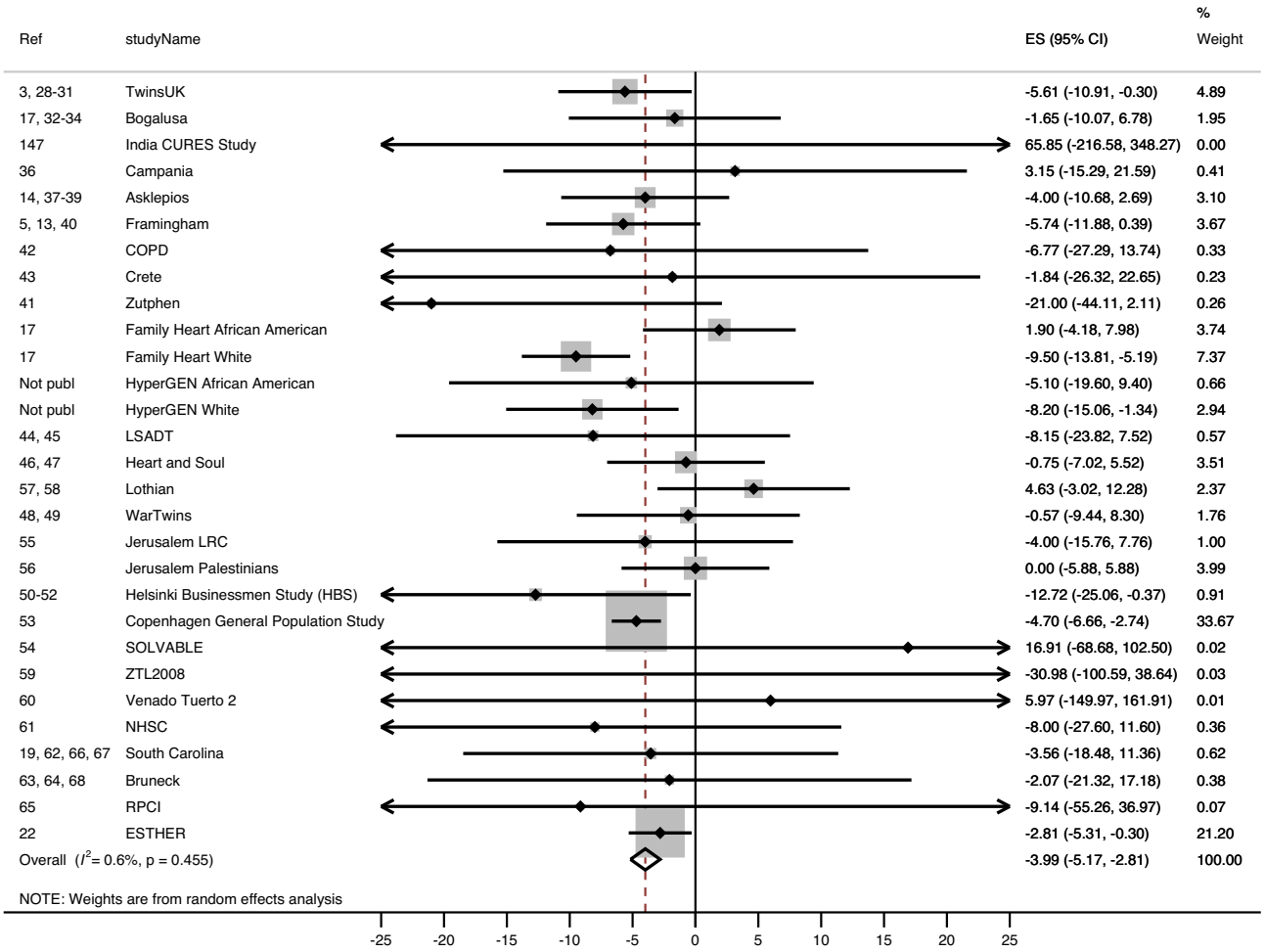

FIGURE 2 Forest plot of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and absolute telomere length (base pairs) as the outcome in the total pooled population. Random effect model was used and adjusted for age and sex. Statistical heterogeneity was estimated by I^2 statistics for each of the 12 meta-analyses. The shaded boxes indicate the inverse variance weighting of each estimate, and the size of the box indicates the weight. In case no shaded box is visible, the weight is very small. COPD, Chronic Obstructive Lung disease cohort; CURES, Chennai Urban Rural Epidemiology Study; ES, estimate; ESTHER, Epidemiological Study on the Chances of Prevention, Early Recognition, and Optimised Treatment of Chronic Diseases in the Older Population; HyperGEN, Hypertension Genetic Epidemiology Network study; LRC, Lipid Research Clinic; LSADT, Longitudinal Study of Aging Danish Twins (https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/21041); NHSC, Nutrition and Health in Southwest China study; RPCI, Roswell Park Cancer Institute; SOLVABLE, Study of Lupus Vascular and Bone Longterm Endpoints; ZTL2008, Zannolli Telomere Length 2008.

difference). Compared with an estimated average yearly decrease (i.e., ~25 bp/y or ~0.01 T/S ratio/y) in leucocyte TL in adults based on cross-sectional data (3, 32, 134–136), this is equivalent to an increase in biological age of ~1 y. A major disadvantage of cross-sectional analysis is the impossibility to infer causation. However, the robust association between higher BMI and lower TL found in this meta-analysis could highlight another potential area of concern for the obesity epidemic.

Because obesity and, more specifically, an increase in leptin and a decrease in adiponectin have been associated with low-grade inflammation and oxidative stress (137), the observed negative association between BMI and leukocyte TL may be due, in part, to the chronic inflammatory state associated with higher leptin. Recently, a negative association was observed between age-related relative TL and serum leptin in 7 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. Because a longitudinal intervention study showed that a reduction in BMI was linked to increasing TL over a 5-y period (98), it is also suggested that a common factor, such as chronic inflammation, is associated both with leptin resistance and with TL.

The negative association between BMI and TL was most apparent in the younger pooled population, in whom a stronger association was found for TL than in the other age groups. Three possible explanations could explain this observation. First, BMI could be a better marker for adiposity in younger individuals aged <60 y than in older individuals (22). Above 65 y 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 weighed 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 (138). Second, selective survival might be one of the causes of the stronger association found in the younger age category. As Manson et al. (139) stated, "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

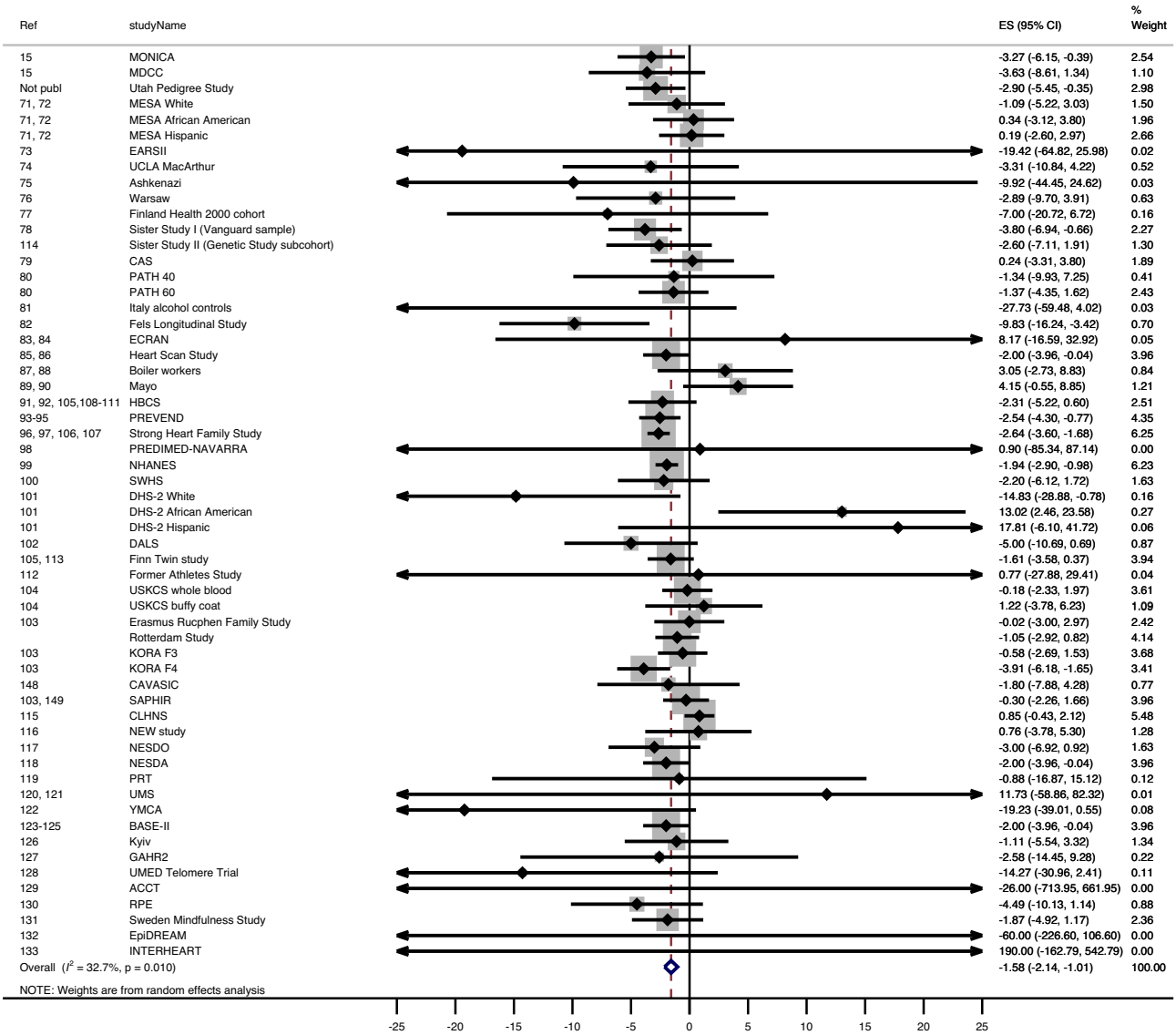

FIGURE 3 Forest plot of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and relative telomere length (T/S ratio) as outcome in the total pooled population. The unit of the estimates and 95% CI is 10^{-3}. A random-effects model was used and adjusted for age and sex. Statistical heterogeneity was estimated by I^2 statistics for each of the 12 meta-analyses. The shaded boxes indicate the inverse variance weighting of each estimate, and the size of the box indicates the weight. In case no shaded box is visible, the weight is very small. ACCT, Anglo-Cardiff Collaborative Trial; BASE-II, Berlin Aging Study; CAS, calcific aortic valve stenosis study; CAVASIC, Cardiovascular Disease in Intermittent Claudication; DALS, Diet, Activity and Lifestyle Study; DHS, Dallas Heart Study; EARSII, European Atherosclerosis Study II; ECRAN, Envejecimiento y Enfermedades Crónicas Asociadas a Nutrición (Aging and Nutrition Associated Chronic Diseas); EPIDREAM, Epidemiologic study of the Screenes for DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication); ES, estimate; GAHR2, Prospective evaluation of Gender and Age differences in the impact of Hostility and Reactivity on intermediary coronary artery disease risk factors; HBCS, Helsinki Birth Cohort Study; KORA F3, Cooperative Health Research in the Region of Augsburg F3 (2004/2005) survey; KORA F4, Cooperative Health Research in the Region of Augsburg F4 (2006/2008) survey; MDCC, Malmö Diet and Cancer Cohort; MESA, Multi-Ethnic Study of Atherosclerosis (https://www.mesa-nhlbi.org/); MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; NESDA, The Netherlands Study of Depression and Anxiety; NESDO, The Netherlands Study of Depression in older persons; NHANES, National Health and Nutrition Examination Survey; Not publ, not published; PATH 40, Personality and Total Health Through Life Project AGE 40-44; PATH 60, Personality and Total Health Through Life Project AGE 60-64; PREDIMED, Prevención con Dieta Mediterránea; PREVEND, Prevention of Renal and Vascular End-stage Disease; PRT, Progressive Resistance Training; Ref, reference; RPE, Richard Paul Ebstein; SAPHIR, Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk Study; SWHS, Shanghai Women's Health Study; T/S ratio, telomere to single-copy gene ratio; UMED, Uniwersytet MEDyczny w Łodzi (Medical University of Lodz (MUL)); UMS, ultra-marathon study; USKCS, US Kidney Cancer Study; YMCA, Young Men Cardiovascular Association.

60s, heart failure and weight loss due to debilitation and muscle wasting at age 70, and death at age 75". People who suffered from age-related diseases may have died and those who survived may therefore differ from those who died (140). 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 (139).

The magnitude of the negative association between BMI and leukocyte TL was found to be largest in the white pooled population. One possible explanation could be that TL

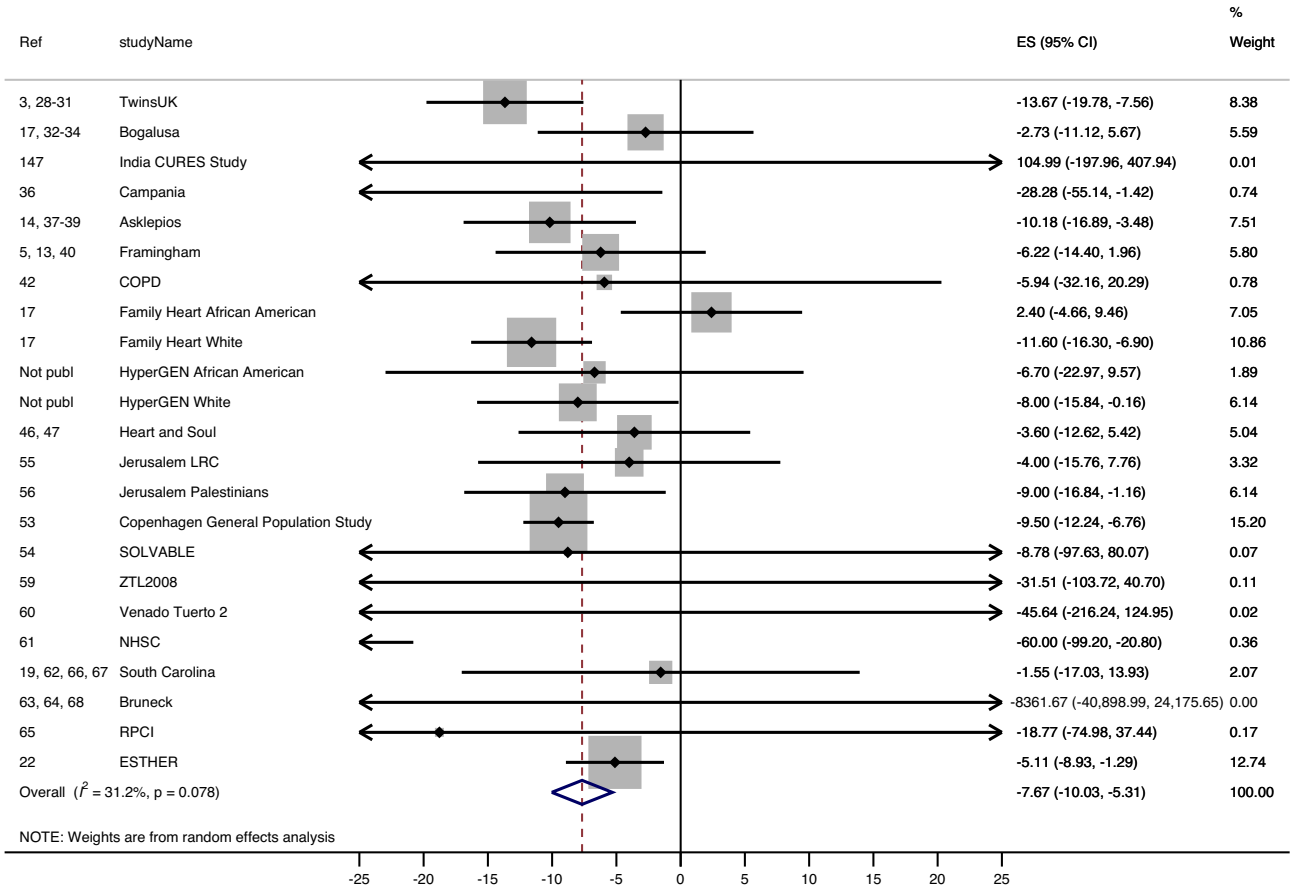

FIGURE 4 Forest plot of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and absolute telomere length (base pairs) as outcome in the "young" pooled population (age $\geq$18 and $\leq$60 y). A random-effects model was used and adjusted for sex. Statistical heterogeneity was estimated by I^2 statistics for each of the 12 meta-analyses. The shaded boxes indicate the inverse variance weighting of each estimate, and the size of the box indicates the weight. In case no shaded box is visible, the weight is very small. COPD, Chronic Obstructive Lung disease cohort; CURES, Chennai Urban Rural Epidemiology Study; ES, estimate; ESTHER, Epidemiological Study on the Chances of Prevention, Early Recognition, and Optimised Treatment of Chronic Diseases in the Older Population; HyperGEN, Hypertension Genetic Epidemiology Network study; LRC, Lipid Research Clinic; LSADT, Longitudinal Study of Aging Danish Twins (https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/21041); NHSC, Nutrition and Health in Southwest China study; Not publ, not published; Ref, reference; RPCI, Roswell Park Cancer Institute; SOLVABLE, Study of Lupus Vascular and Bone Longterm Endpoints; ZTL2008, Zannolli Telomere Length 2008.

differs between different cell types (141) and that leukocyte cell subpopulations (142) differ between whites and African Americans. However, because only 4 samples consisted of African Americans, more research is required to resolve whether this observation explains the racial differences in association between TL and BMI for white and African Americans or whether this is a false-positive finding. Second, it was reported that the estimation of visceral adipose tissue, the most relevant tissue that determines the risk of developing chronic metabolic diseases, was different in white and African American adults (143). At a higher BMI or increased waist circumference, white adults had higher amounts of visceral adipose tissue than African-American adults (137). Because the presence of leptin resistance or markers of inflammation was 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 compared with whites. In addition, the one study sample consisting of 3256 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 leukocyte TL was negatively correlated with C-reactive protein.

One of the main strengths of this study is that we did not rely on publications only. Instead, we contacted PIs, which, in turn, pointed us toward important studies we may have missed to obtain the data used in the meta-analysis. In addition, we incorporated 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 >140,000 individuals. Although it is impossible to make a direct comparison with the unpublished β estimates of the nonresponders, 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 TL. Because of the large variation in adult TL, as well as biological and measurement variation (qPCR), 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 significant association of -3.99 bp or a -1.58×10^{-3} unit T/S ratio (0.16%) per unit increase in BMI. Because 36% of our meta-analyses showed a significant association with estimates in the same direction and of the same magnitude (except for 3 estimates of extreme magnitude of one Asian sample in the "middle"-aged

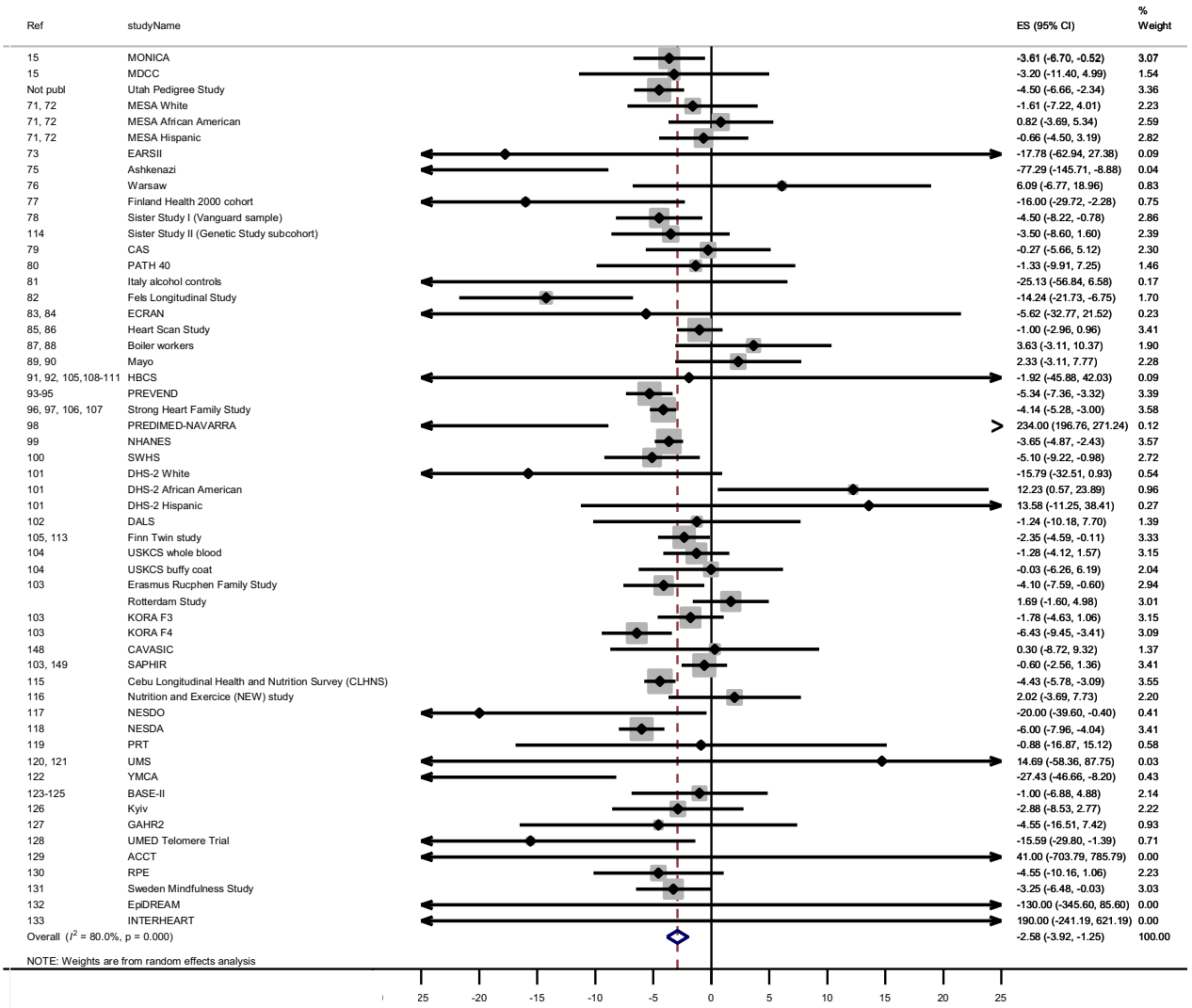

FIGURE 5 Forest plot of the β estimates (regression coefficients) from the meta-analysis of the association between BMI and relative telomere length (T/S ratio) as the outcome in the "young" pooled population (age $\geq$18 y and $\leq$60 y). The unit of the estimates and 95% CI is 10^{-3}. A random-effects model was used and adjusted for sex. Statistical heterogeneity was estimated by I^2 statistics for each of the 12 meta-analyses. The shaded boxes indicate the inverse variance weighting of each estimate, and the size of the box indicates the weight. In case no shaded box is visible, the weight is very small. ACCT, Anglo-Cardiff Collaborative Trial; BASE-II, Berlin Aging Study; CAS, calcific aortic valve stenosis study; CAVASIC, Cardiovascular Disease in Intermittent Claudication; DALS, Diet, Activity and Lifestyle Study; DHS, Dallas Heart Study; EARSII, European Atherosclerosis Study II; ECRAN, Envejecimiento y Enfermedades Crónicas Asociadas a Nutrición (Aging and Nutrition Associated Chronic Diseas); EpiDREAM, Epidemiologic study of the Screenes for DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication); ES, estimate; GAHR2, Prospective evaluation of Gender and Age differences in the impact of Hostility and Reactivity on intermediary coronary artery disease risk factors; HBCS, Helsinki Birth Cohort Study; KORA F3, Cooperative Health Research in the Region of Augsburg F3 (2004/2005) survey; KORA F4, Cooperative Health Research in the Region of Augsburg F4 (2006/2008) survey; MDCC, Malmö Diet and Cancer Cohort; MESA, Multi-Ethnic Study of Atherosclerosis (https://www.mesa-nhlbi.org/); MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; NESDA, The Netherlands Study of Depression and Anxiety; NESDO, The Netherlands Study of Depression in older persons; Not publ, not published; PATH 40, Personality and Total Health Through Life Project AGE 40–44; PREDIMED, Prevención con Dieta Mediterránea; PREVEND, Prevention of Renal and Vascular End-stage Disease; PRT, Progressive Resistance Training; Ref, reference; RPE, Richard Paul Ebstein; SAPHIR, Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk Study; SWHS, Shanghai Women's Health Study; T/S ratio, telomere-to–single-copy gene ratio; UMED, Uniwersytet MEDyczny w Łodzi (Medical University of Lodz (MUL)); UMS, ultra-marathon study; USKCS, US Kidney Cancer Study; YMCA, Young Men Cardiovascular Association.

population), we assume that false positive reporting is only of minor concern.

Two recent meta-analyses, which relied on published data, also reported negative associations between BMI and TL. The first smaller scale meta-analysis reported negative regression coefficients on the association between TL and BMI (22), of which 5 studies were also included in this meta-analysis (13, 14, 19, 82, 144). The larger-scale meta-analysis reported a weak negative correlation, a standardized mean difference of 0.84 (95% CI: 0.22, 1.46) between obese individuals and normal-weight individuals, and an OR of 1.39 (95% CI: 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

(∼8400 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 TL (3, 139, 145), which may have caused an underestimation of the inverse association between BMI and TL. In addition, inflammation was not directly measured. We were also not able to measure telomere attrition because we did not incorporate longitudinal data, and reverse causation cannot be excluded. However, there are very few large-scale studies with repeated measures of TL.

The lengths of telomeres at different ages are highly correlated, and it has been suggested that most of the variation in leukocyte TL in adults is a result of TL at birth and that therefore the impact of environmental and lifestyle factors is rather small (145, 146). In addition, Benetos et al. (145) described that ranking of individuals into deciles according to their TL barely changes across adult life. Our meta-analysis shows that a 5-unit increase in BMI corresponds to a change of ∼20 bp or even ∼38 bp in the younger pooled population, which is equivalent to 1-y greater biological age, irrespective of ranking.

In summary, a higher BMI is associated with shorter telomeres, especially in the younger pooled population. Being aware of the fact that the association between BMI and TL differs across the life span can lead to further research. Although no causal inference can be drawn and residual confounding may exist, 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 slower biological aging of the population. However, meta-analyses of longitudinal studies that can evaluate change in body weight alongside change in TL are warranted.

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