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METHODS

SEARCH

Search: Telomere* and ("Obesity"[Mesh] OR "Adiposity"[Mesh] OR "Overweight"[Mesh] OR "Body Constitution"[Mesh] OR "Body Composition"[Mesh] OR “Body Weight”[Mesh] OR “Body Mass Index”[Mesh] OR “Body Fat Distribution”[Mesh] OR “Waist-Hip Ratio”[Mesh] OR “Waist Circumference”[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Body Weight"[Mesh] OR "Body Size"[Mesh] OR “Body Constitution"[Mesh] OR Obesity OR Adiposity OR Overweight OR "Body Constitution" OR "Body Constitutions" OR "Body Composition" OR "Body Compositions" OR “Body Weight” OR “Body Mass Index” OR BMI OR “Body Fat Distribution” OR “fat distribution” OR “body fat” OR “body fat weight” OR “fat weight” OR “Waist-Hip Ratio” OR WHR OR “Waist Circumference” OR "Obesity, Abdominal" OR “Abdominal Obesities” OR “Abdominal Obesity” OR “Central Obesity” OR “Obesity, Central” OR "Body Weight" OR "Body Size" OR “Body Constitution" OR "Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Metabolic Syndrome X"[Mesh] OR "Insulin Resistance"[Mesh] OR "Hyperinsulinism"[Mesh] OR "Glucose Intolerance"[Mesh] OR“Hyperglycemia”[Mesh] OR "Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "Metabolic Syndrome X" OR "Insulin Resistance" OR "Hyperinsulinism" OR “Diabetes Mellitus, Non Insulin Dependent” OR “Diabetes Mellitus, Non-Insulin-Dependent” OR “Non-Insulin-Dependent Diabetes Mellitus” OR “Type 2 Diabetes Mellitus” OR “Diabetes Mellitus, Type II” OR NIDDM OR “Insulin Resistance Syndrome X” OR “Metabolic X Syndrome” OR “Dysmetabolic Syndrome X” OR “Metabolic Cardiovascular Syndrome” OR “glucose intolerance” OR “glucose intolerances” OR IGT OR “impaired glucose intolerance” OR hyperglycaemia OR hyperglycemia OR "Cardiovascular Diseases"[Mesh] OR “Myocardial Ischemia"[Mesh] OR “Acute coronary syndrome"[Mesh] OR “Angina Pectoris"[Mesh] OR “Coronary disease"[Mesh] OR “Coronary artery disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR “Hypertension"[Mesh] OR "Cardiovascular” OR "Cardiovascular Diseases" OR “Cardiovascular Disease” OR “Myocardial Ischemia" OR “Myocardial Ischemias” OR “Ischemic Heart Disease” OR “Ischemic Heart Diseases” OR “Acute coronary syndrome" OR “Acute Coronary Syndromes” OR “Coronary Syndrome” OR “coronary Syndromes” OR “Angina Pectoris" OR “AP” OR “Coronary disease" OR “Coronary diseases" OR “Coronary Heart Disease” OR “Coronary Heart Diseases” OR “CHD” OR “Coronary artery disease” OR “Coronary artery diseases” OR “CAD” OR “Coronary Atherosclerosis” OR "Myocardial Infarction" OR “Myocardial Infarctions” OR “Myocardial Infarct” OR “Myocardial Infarcts” OR Hypertension OR “Cardiovascular aging” OR aging OR "Cohort Studies"[Mesh] OR cohort OR "Case-Control Studies"[Mesh] OR Case Control) Filters: Humans.

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VERIFICATION OF THE LINEAR ASSUMPTION

To evaluate the linear assumption between BMI and telomere length multilevel regression analyses were performed to account for the difference between the study samples by adding a random intercept to the model. Models in which a quadratic term for BMI was included were compared to the models without a quadratic term for BMI by Akaike information criterion (AIC). Either absolute telomere length (bp) or relative telomere length (T/S ratio) was considered as the outcome measure. For these analyses the raw data provided by the PIs could be analysed.

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ASSESSING HETEROGENEITY

Meta-regression and sources of heterogeneity (effect modifiers)

Statistical heterogeneity between studies was estimated by I^2 statistics [25,26] 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% [26].

To confirm the expected differences in association for age and sex, meta-regression analysis was performed with age and sex as potential effect modifiers. Age was divided 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.

Other potential sources of heterogeneity at study level (effect modifiers) were investigated by meta-regression analysis. The following effect modifiers were considered: (1) general factors: ethnicity (percentage of the total study sample, i.e. percentage of population being white, African American, Native American, Asian, and Hispanic), study design, level at which the data was provided (i.e. raw data or summary statistics), (2) factors related to telomere length measurement: cell type in which telomere length was determined, technique of telomere length measurement, storage of DNA, and, whether absolute telomere length was estimated from T/S ratio or was measured directly and (3) factors related to BMI: assessment of BMI based on self-report or measured height and weight. When heterogeneity for a given source was observed ($p<0.05$), stratified analyses were performed.

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SENSITIVITY ANALYSES

To evaluate whether the summary estimates for BMI were affected by individual studies, we performed outlier analyses by omitting one study at a time.

To evaluate whether studies with large sample sizes (n > 5000) affected the summary estimates, analyses were repeated without these large studies. However, only the Copenhagen General population Study (45,069 individuals) and the PREVEND STUDY (7,991 INDIVIDUALS) and NHANES study (7,348 individuals) had sample sizes of that magnitude.

The analyses with absolute telomere length as the outcome were repeated without the three studies that used the relative telomere length to estimate the absolute telomere length. In addition, analyses were stratified by method of measurement of telomere length (Southern blot vs. q-PCR).

In a sensitivity analysis a cut off value of 90% was used to classify a sample of a particular ethnicity. When at least 90% 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 90% of the sample, the sample was classified as a mixed sample.

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RESULTS

VERIFICATION OF THE LINEAR ASSUMPTION

Absolute telomere length

In the multilevel regression analysis with absolute telomere length (base pairs;bp) as outcome measure eleven study populations were included: Bogalusa, India CURES Study, Campania, Asklepios, COPD, Crete, Zutphen, War Twins, Businessmen Study (HBS), ZTL2008, Venado Tuerto 2 and RPCI.

For absolute telomere length models considering a linear association did not differ significantly from models with a non-linear association, based on AIC. The most parsimonious model is preferred and one can conclude that the association between BMI and telomere length can be considered linear (Table 1).

Relative telomere length

In the multilevel regression analysis with relative telomere length (T/S ratio) as outcome measure thirteen study populations were included: MONICA, MDCC, EARSII, Ashkenazi, Warsaw, CAS, PATH40, PATH60, Italy alcohol controls, Ecran, Mayo, HBCS, Nutrition and Exercise for Women (NEW) Study, PRT, UMS, YMCA, Kyiv, GAHR2, UMED telomere trial, RPE, and the Sweden Mindfulness Study.

For relative telomere length conclusions considering a linear relationship between BMI and telomere length are not easy to draw. Forty three percent of the PIs provided raw data, which consisted of only 15% of the total individuals (11,710 / 76,456 individuals). The telomere length of the YMCA study sample (n=1,139) was long (mean TS ratio of 4563.50 (SD 1001.72)) as compared to all other study samples (n= 10,571; mean TS ratio of 1050.47 (SD 739.29)). Also the YMCA study was very young (mean age 19.03 years (SD 3.47)) as compared to all other study samples (mean age 52.50 years (SD 16.33)).

It turned out that models considering a linear association differed significantly from models with a non-linear association, based on AIC. However, this was completely explained by the contribution of the

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YMCA study. In Supplemental Table 1 the values of the model fit (AIC) and estimates and standard error (SE) of the multilevel regression analyses with and without the YMCA study sample are presented.

Based on the raw data in our possession one can conclude that the association between BMI and telomere length can be considered linear, at least at older age. However, because a subset was used for these analyses and not the complete data set, it is possible that lack of power could also be a reason for not showing a non-linear association.

Supplemental Table 1 Association between BMI and telomere length based on multilevel regression analysis

		Unadjusted				Adjusted for sex and age			
		Model fit	Estimate	SE	p-value	Model fit	Estimate	SE	p-value
Absolute telomere length (base pairs; bp) as outcome									
Model 1	BMI	111,886.9	-70.42	50.04	0.16	111,748.4	-32.47	50.17	0.51
	BMI*BMI		0.99	0.83	0.23		0.47	0.83	0.57
Model 2	BMI	111,886.3	-11.69	8.52	0.17	111,746.8	-4.19	8.49	0.62
T/S ratio as outcome YMCA study sample included									
Model 1	BMI	182,538.2	-20.42	7.06	0.004	182,517.5	-16.00	7.13	0.03
	BMI*BMI		0.31	0.12	0.009		0.24	0.12	0.04
Model 2	BMI	182,543.0	-2.21	1.29	0.07	182,519.6	-1.76	1.29	0.17
T/S ratio as outcome YMCA study sample excluded									
Model 1	BMI	162,933.5	-13.91	6.69	0.04	162,911.3	-9.49	6.76	0.16
	BMI*BMI		0.21	0.11	0.05		0.15	0.11	0.18
Model 2	BMI	162,935.3	-1.07	1.21	0.38	162,911.1	-0.66	1.21	0.58

Legend: the unit of the estimate and standard error (SE) with T/S ratio as outcome are in 10^{-3}.

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HETEROGENEITY

Sex and age

With absolute telomere length as the outcome, age was an effect modifier in the meta-regression analyses in women (beta= 3.22 (SE 1.54; 95%C.I. 0.12, 6.32; p=0.04). When age was divided into two age groups, age was an effect modifier in the overall association and in women (overall: beta = 5.08 (SE 1.68; 95%C.I. 1.73, 8.43; p= 0.004); women: beta= 6.10 (SE 1.76; 95%C.I. 2.56, 9.64; p= 0.001).

Sex was never an effect modifier.

With relative telomere length as the outcome, age was an effect modifier in overall analyses and in women (overall: beta= $1.56*10^{-3}$ (SE $0.65*10^{-3}$; 95%C.I. $0.26*10^{-3}$, $2.85*10^{-3}$; p= 0.02); women: beta= $1.82*10^{-3}$ (SE $0.53*10^{-3}$; 95%C.I. $0.77*10^{-3}$, $2.86*10^{-3}$; p=0.001). If age was divided into two categories age was an effect modifier in overall analyses and in women (overall: beta= $1.94*10^{-3}$ (S.E. $0.87*10^{-3}$; 95%C.I. $0.22*10^{-3}$, $3.66*10^{-3}$; p=0.03); women: beta=$2.26*10^{-3}$ (SE $0.69*10^{-3}$; 95%C.I. $0.89*10^{-3}$, $3.62*10^{-3}$; p= 0.001).

Sex was never an effect modifier.

Ethnicity

With absolute telomere length as the outcome, ethnicity (white, African American) was an effect modifier in the meta-regression analyses in the young study sample (both sexes white: beta= -9.05 (SE 3.44; 95%C.I. -16.21, -1.89; p= 0.02); both sexes African American: beta= 10.80 (SE 3.55; 95%C.I. 3.43, 18.18; p=0.006).
Ethnicity (Asian) was also an effect modifier in the meta-regression analyses in the middle aged study sample (both sexes Asian: beta= 71.36 (SE 4.03; 95% C.I. 17.34, 125.68; p=0.01).

With relative telomere length as the outcome, ethnicity (African American, Asian) was an effect modifier in the analyses of total study sample (both sexes African American: beta= 3.56 (SE 1.68; 95% C.I. 0.18, 6.93; p=0.04); both sexes Asian: beta= $1.88*10^{-3}$ (SE $0.86*10^{-3}$; 95%C.I. $0.17*10^{-3}$, $3.60*10^{-3}$; p= 0.03).
Ethnicity (white, native Americans) was also an effect modifier in the meta-regression analyses in the middle aged study sample (both sexes white (Monte Carlo permutation: p< 0.001); both sexes Native American: beta= $3.44*10^{-3}$ (SE $1.69*10^{-3}$; 95% C.I. $0.05*10^{-3}$, $6.85*10^{-3}$; p=0.05); women white: beta= $-4.94*10^{-3}$ (SE $1.29*10^{-3}$; 95%C.I. $-7.54*10^{-3}$, $-2.34*10^{-3}$; p< 0.001); women Native Americans: beta= $5.12*10^{-3}$ (SE $1.83*10^{-3}$; 95%C.I. $1.41*10^{-3}$, $8.82*10^{-3}$; p= 0.008).

Finally, cell type was an effect modifier in the old study sample (both sexes overall: beta= $70.04*10^{-3}$ (SE $33.08*10^{-3}$; 95%C.I. $2.17*10^{-3}$,$137.91*10^{-3}$; p= 0.04); women overall: beta= $69.90*10^{-3}$ (SE $33.08*10^{-3}$; 95%C.I. $1.77*10^{-3}$, $138.04*10^{-3}$; p= 0.05), but only one study (Ecran) did not use leucocytes.

Since ethnicity was identified as an effect modifier, all analyses were stratified by ethnicity in addition to the originally planned analyses. Although population sizes of studies with non-white populations were small and their results should be interpreted with caution, these populations were included for completeness. Analyses were not stratified by cell type, as cell type was only an effect modifier in the old study sample and within this sample only one study did not use leucocytes. No other sources of effect modifiers were discovered (all p-values >0.05).

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SENSITIVITY ANALYSES

Omitting one study at a time resulted in no substantial change of the summary estimate. After exclusion of the large Copenhagen General Population Study the estimate of absolute telomere length change became -3.94 bp per BMI unit (95%C.I. -5.21 to -2.66) instead of -3.99 (95%C.I. -5.17 to -2.81) and after excluding the large NHANES study the estimate of the relative telomere length change per unit BMI remained the same $-1.58*10^{-3}$ units T/S ratio (95%C.I. $-2.16*10^{-3}$, $-1.01*10^{-3}$) instead of $-1.58*10^{-3}$ (95%C.I. $-2.14*10^{-3}$, $-1.01*10^{-3}$). And changed not substantial when excluding the large PREVEND study (beta= $-1.57*10^{-3}$ (95%C.I. $-2.12*10^{-3}$, $-1.01*10^{-3}$)).

Excluding both the NHANES study and the PREVEND study the estimate of the relative telomere length change per unit BMI did not change substantially $-1.51*10^{-3}$ units T/S ratio (95%C.I. $-2.14*10^{-3}$, $-0.89*10^{-3}$).

Repeating the analysis with absolute telomere length as the outcome without the three studies that used the relative telomere length to estimate the absolute telomere length yielded almost the same summary estimate which was -4.12 bp (95%C.I. -5.77, -2.47).

Stratified analysis by method of measurement yielded an estimate of -4.65 bp (95%C.I. -6.76 to -2.54) for the Southern blots method and -3.56 bp (95%C.I. -5.01, -2.11) for q-PCR method.

If, in the case of absolute telomere length, a cut off value of 90% was chosen to define a population as white, resulting in one study (Bogalusa) omitted, the summary estimate changed from -4.36 to -4.45 bp (95%C.I. -6.05, -2.86). For relative telomere length the summary estimate changed from $-1.87*10^{-3}$ to $-1.88*10^{-3}$ units T/S ratio (95%C.I. $-2.41*10^{-3}$, $-1.35*10^{-3}$) with three studies (Sister Study I (Vanguard sample) and Boiler workers and NEW study) omitted.

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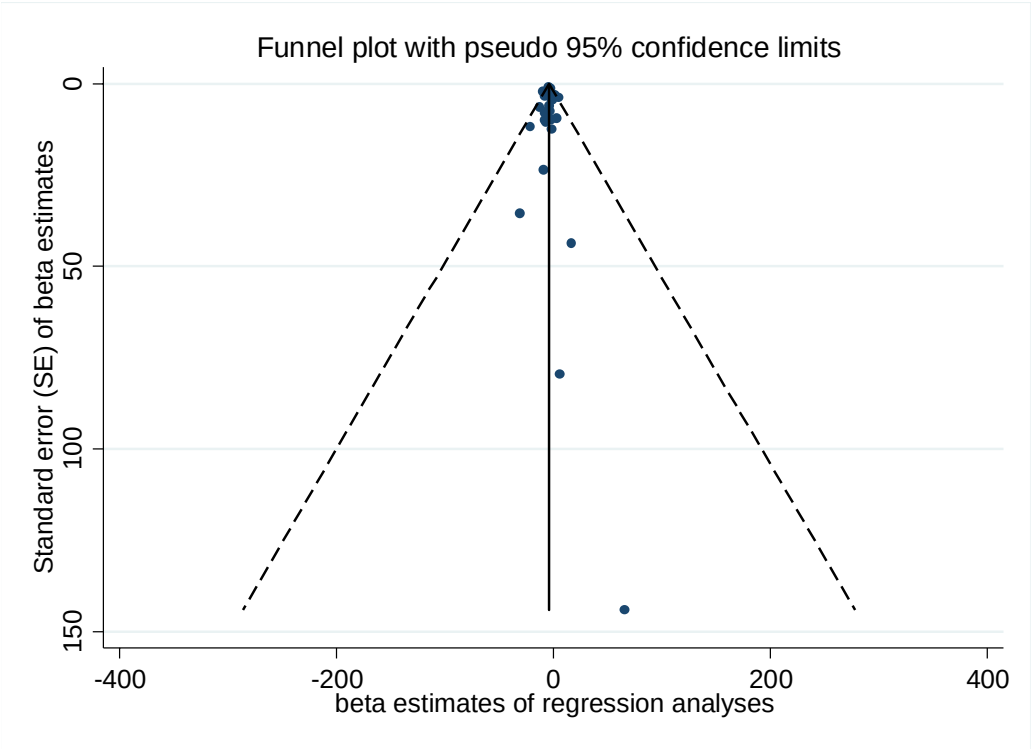
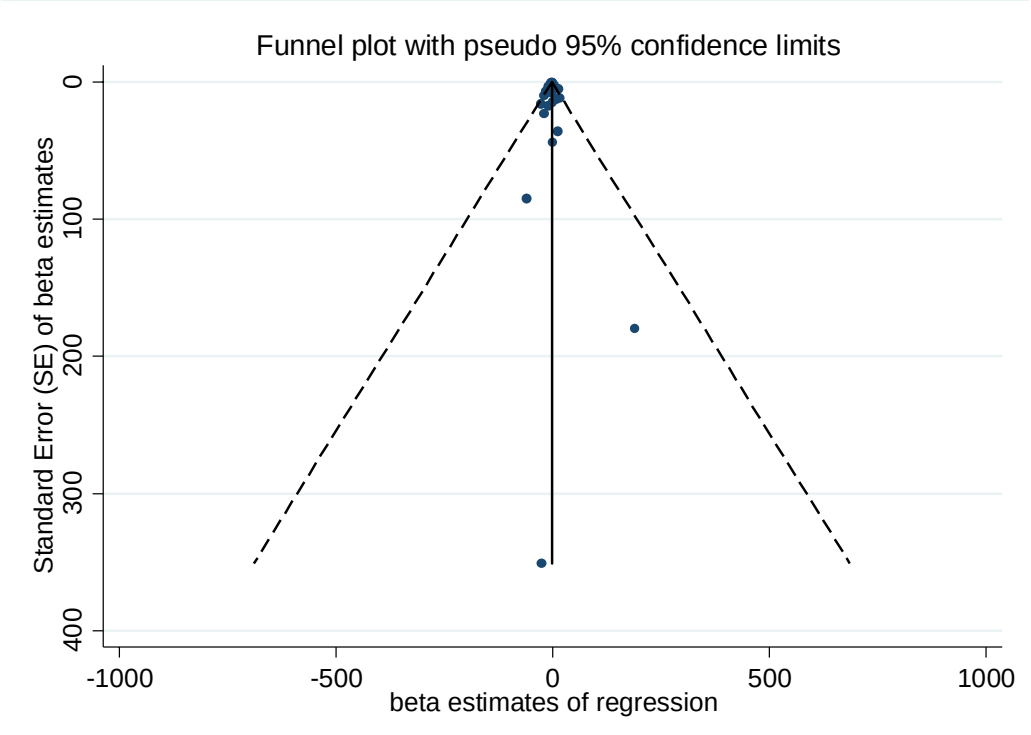
SUPPLEMENTAL FIGURE 1 FUNNEL PLOTS

Funnel plot for absolute telomere length (base pairs; bp) of the total pooled population



Funnel plot for relative telomere length (T/S ratio) of the total pooled population



Supplemental Table 2 Summary of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and telomere length as outcome and absolute telomere length (base pairs (bp)) as independent variable

	All together (total pooled sample)*				"Young" pooled sample (18-60 yr) **				"Middle " pooled sample (61-75 yr) **				"Old" pooled sample (> 75 yr) **			
	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 (%)
Both sexes (Men and Women)																
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	0.96	-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	-130.01	-0.0003, 1700	
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			
Men																
Overall	26	**-4.05**	**-6.93, -1.16**	35.4	20	**-8.32**	**-12.41, -4.24**	42.6	19	-0.52	-5.98, 4.95	41.5	14	-3.69	-9.05, 1.67	0.0
white	20	**-4.46**	**-7.59, -1.30**	39.0	14	**-9.26**	**-13.45, -5.07**	41.8	14	-2.02	-7.21, 3.18	33.5	12	-4.49	-10.11, 1.13	0.0
African Am.	2	-3.83	-14.33, 6.68	0.0	2	-4.38	-16.46, 7.71	7.0	2	3.09	-20.84, 27.02	0.0	1	-101.30	-885.68, 683.08	
Hispanic	0				0				0				0			
Asian	2	-98.73	-303.66, 106.20	**58.8**	2	-117.10	-316.36, 82.16	44.8	1	**90.00**	**27.28, 152.72**		0			
Native Am.	0				0				0				0			
Women																
Overall	24	**-4.44**	**-5.94, -2.94**	0.0	22	**-8.56**	**-10.57, -6.55**	0.0	19	-2.32	-4.81, 0.17	1.4	11	-6.41	-12.84, 0.03	0.0
white	16	**-4.57**	**-6.13, -3.01**	0.0	14	**-9.04**	**-11.15, -6.93**	0.0	12	**-2.60**	**-5.02, -0.09**	0.0	8	-7.67	-16.88, 1.54	18.7
African Am.	2	-0.86	-7.54, 5.82	0.0	2	-0.80	-8.56, 6.97	0.0	2	3.68	-10.21, 17.57	0.0	1	-14.80	-67.52, 37.92	
Hispanic	1	5.97	-149.97, 161.91		1	-45.64	-216.24, 124.95		1	212.68	-169.98, 595.34		0			
Asian	2	11.28	-27.78, 50.34	0.0	2	18.50	-226.57, 236.57	45.3	1	**100.00**	**21.60, 178.40**		0			
Native Am.	0				0				0				0			

N= number of studies; Am. = American; Random effect model was used; *adjusted for age and sex; **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%

Supplemental Table 3 Summary of the beta estimates (regression coefficients) from the meta-analysis of the association between BMI and telomere length as outcome and relative telomere length (Telomere to Single Copy Gene ratio (T/S ratio)) as independent variable

	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 (%)
Both sexes (Men and Women)																
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	
Men																
Overall	53	**-1.60**	**-2.52, -0.69**	30.7	50	**-2.88**	**-4.49, -1.27**	59.0	42	-0.96	-2.51, 0.60	25.9	28	-3.40	-9.49, 2.67	**70.2**
white	40	**-1.94**	**-3.04, -0.84**	26.1	37	**-3.47**	**-5.67, -1.27**	61.7	32	-1.34	-3.38, 0.70	38.9	21	-7.00	-15.76, 1.77	**77.2**
African Am.	2	-1.16	-10.39, 12.69	38.6	2	2.39	-11.17, 15.96	39.5	2	-2.29	-13.36, 8.78	0.0	1	-0.39	-22.18, 21.41	
Hispanic	3	-2.12	-6.54, 2.31	0.0	3	-2.99	-8.61, 2.62	0.0	3	0.45	-8.17, 9.06	0.0	1	2.04	-9.98, 14.06	
Asian	2	-0.42	-9.30, 8.45	**78.4**	2	-0.79	-9.41, 7.83	**77.5**	0				0			
Native Am.	1	**-2.31**	**-3.72, -0.90**		1	**-3.96**	**-5.57, -2.36**		1	0.61	-6.04, 7.26		1	5.93	-5.39, 17.25	
Women																
Overall	51	**-1.49**	**-2.11, -0.87**	26.1	49	**-3.03**	**-4.03, -2.02**	49.7	46	**-1.25**	**-2.14, -0.37**	0.0	27	0.37	-1.77, 2.50	2.4
white	36	**-1.65**	**-2.30, -1.01**	5.0	34	**-3.08**	**-4.42, -1.74**	**50.1**	33	**-2.20**	**-3.23, -1.16**	0.0	19	-0.06	-2.88, 2.75	6.5
African Am.	2	6.10	-5.70, 17.91	**71.3**	2	4.67	-3.87, 13.21	39.9	2	1.43	-6.29, 9.14	0.8	1	-1.66	-15.20, 11.89	
Hispanic	3	7.25	-6.05, 20.55	39.3	3	1.14	-4.74, 7.02	2.4	3	3.03	-2.53, 8.59	0.0	2	28.54	-36.12, 93.20	**75.4**
Asian	3	0.04	-1.26, 1.34	0.5	3	**-5.61**	**-6.96, -4.26**	0.0	2	2.18	-2.90, 7.27	0.0	0			
Native Am.	1	**-2.92**	**-4.11, -1.73**		1	**-4.42**	**-5.81, -3.03**		1	3.54	0.11, 6.98		1	4.67	-3.14, 12.48	

N= number of studies; Am. = American The unit of the **estimates and 95%C.I. is 10^{-3}**; Random effect model was used; *adjusted for age and sex; **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%

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SUPPLEMENTAL FOREST PLOTS

Forest plots of the beta estimates (regression coefficients; ES) of the meta-analysis of the association between BMI and telomere length as outcome in all pooled populations

Either absolute telomere length (base pairs; bp) or relative telomere length (T/S ratio) was the outcome

Random effect model was used and adjusted for age if all together (the total pooled population) were analyzed and adjusted for sex if men and women were analyzed together; 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.

Young= “Young” pooled population; age ≥18 and ≤ 60 years

Middle= “Middle” pooled population; age 60 < age ≤ 75 years

Old= “Old” pooled population; age > 75 years

ES=estimate

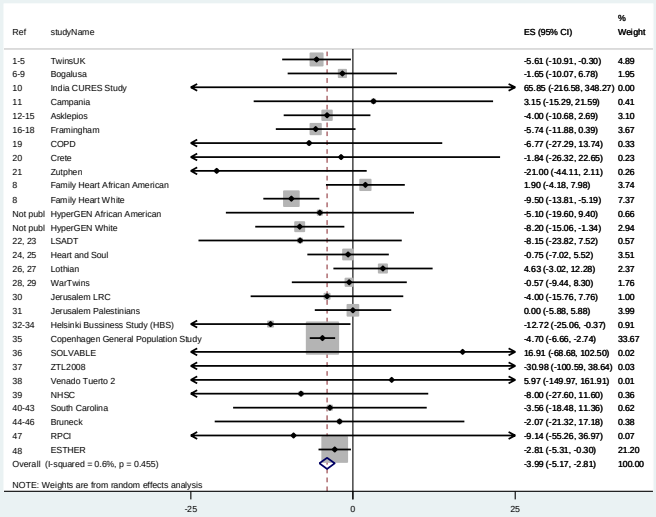
The estimate of T/S ratio is $*10^{-3}$;

The corresponding references can be found after the last forest plot.

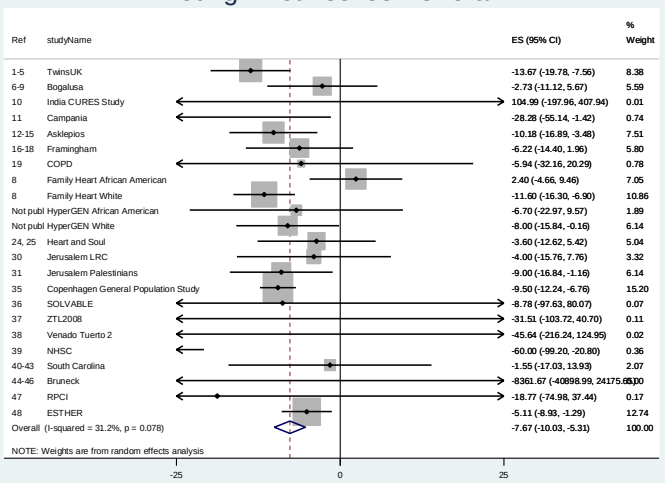
Online Supporting Material

Absolute telomere length (base pairs; bp): Both sexes – Overall

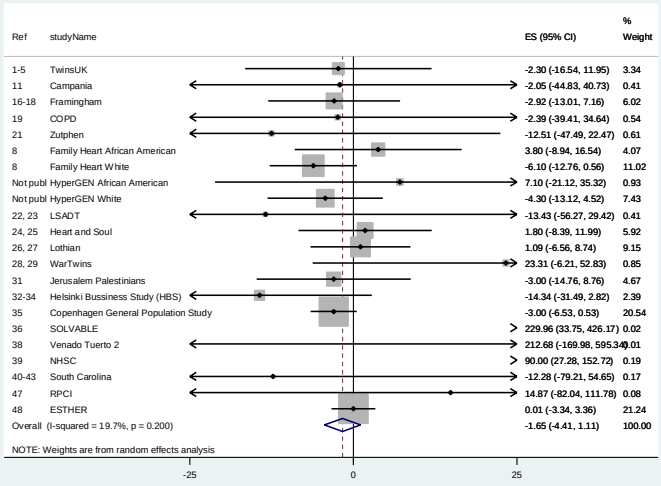
All together - Both sexes - Overall



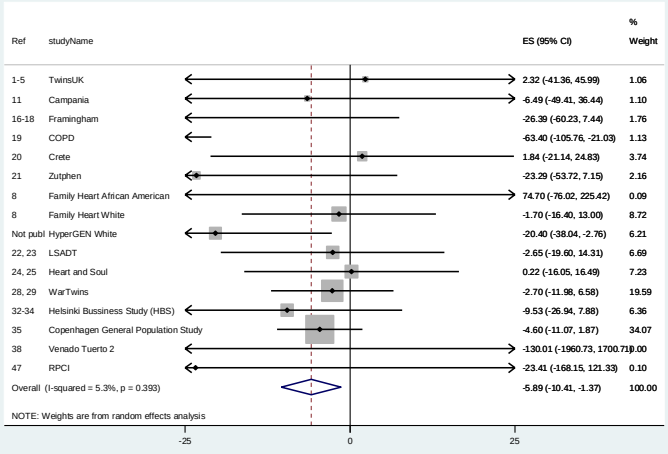
Young - Both sexes - Overall



Middle - Both sexes - Overall



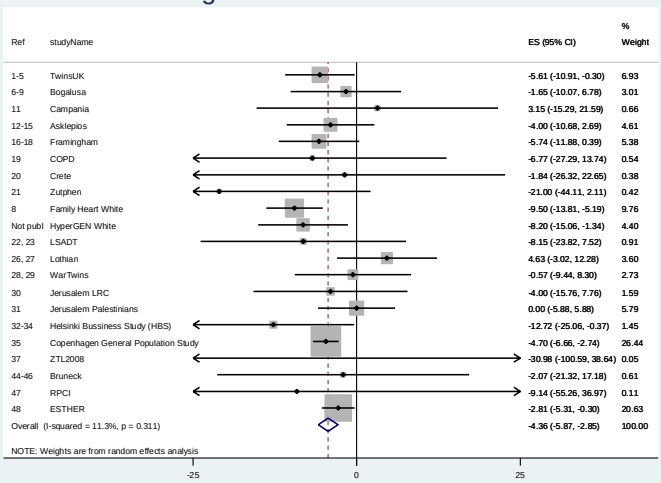
Old - Both sexes - Overall



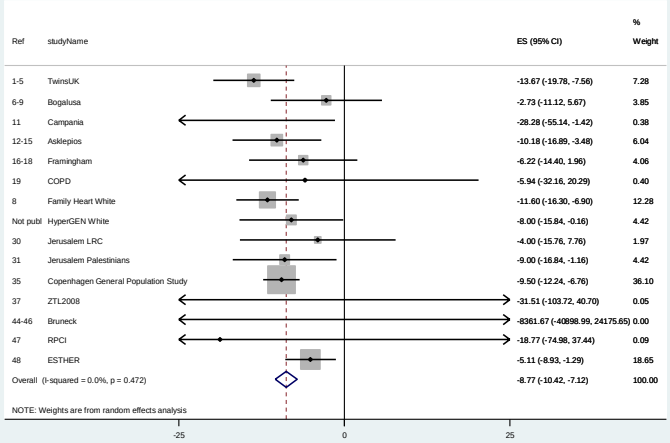
Absolute telomere length (base pairs; bp):

Both sexes – white

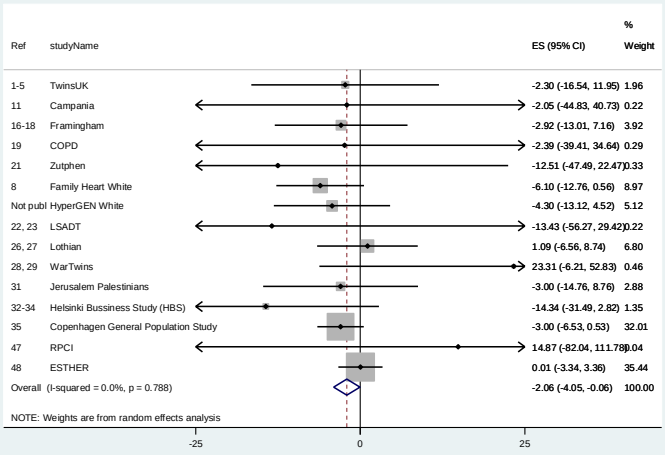
All together - Both sexes - white



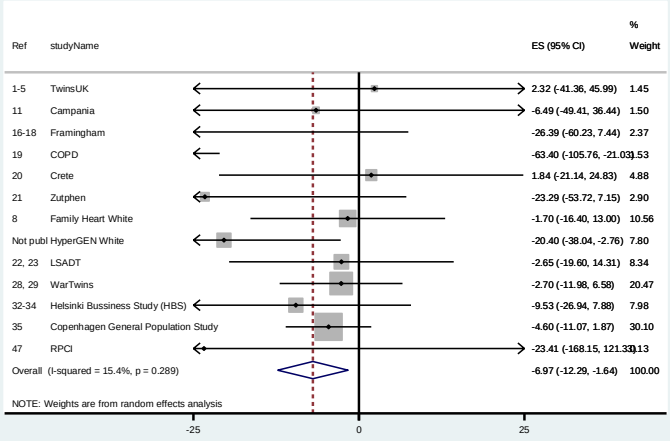
Young - Both sexes - white



Middle - Both sexes - white



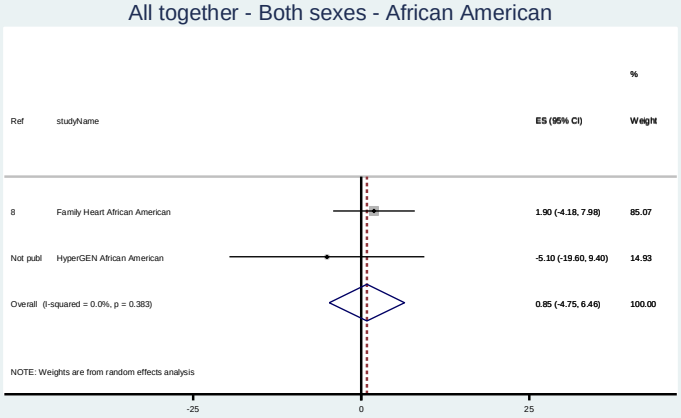
Old - Both sexes - white



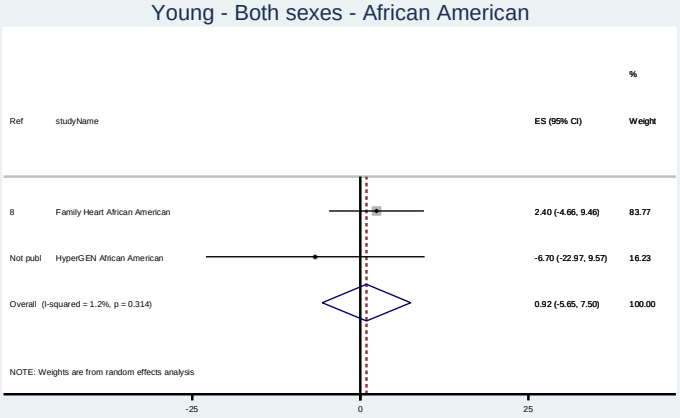
Absolute telomere length (base pairs; bp):

Both sexes – African American

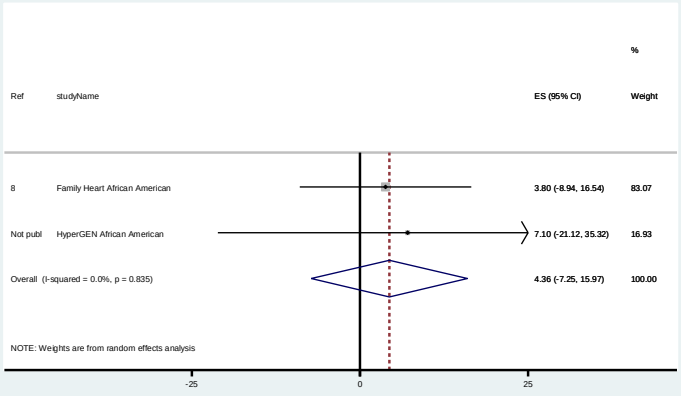
All together - Both sexes - African American



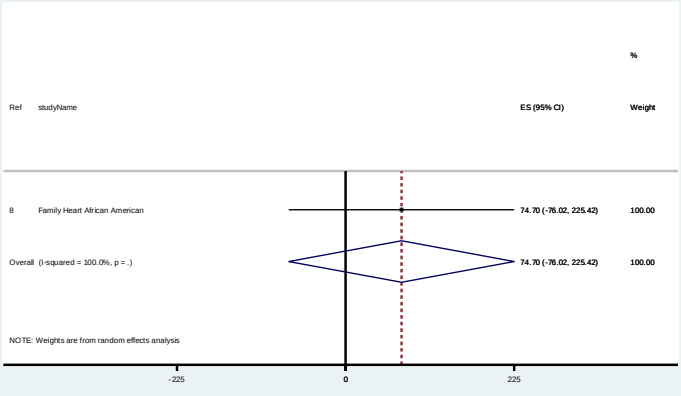
Young - Both sexes - African American



Middle - Both sexes - African American

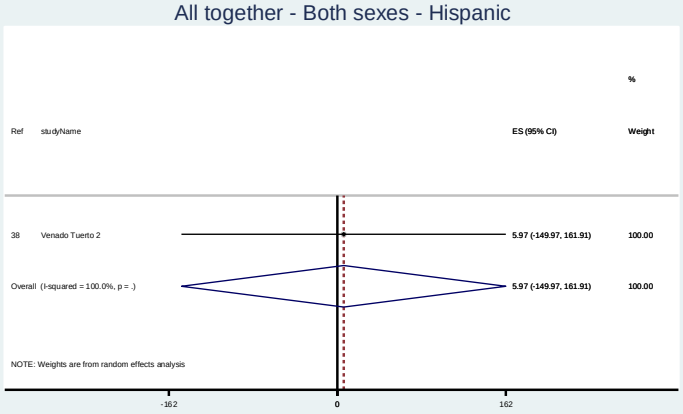


Old - Both sexes - African American



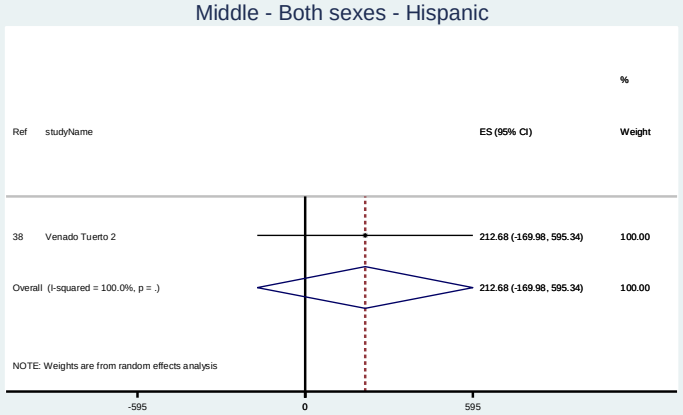
Absolute telomere length (base pairs; bp): Both sexes - Hispanic

All together - Both sexes - Hispanic

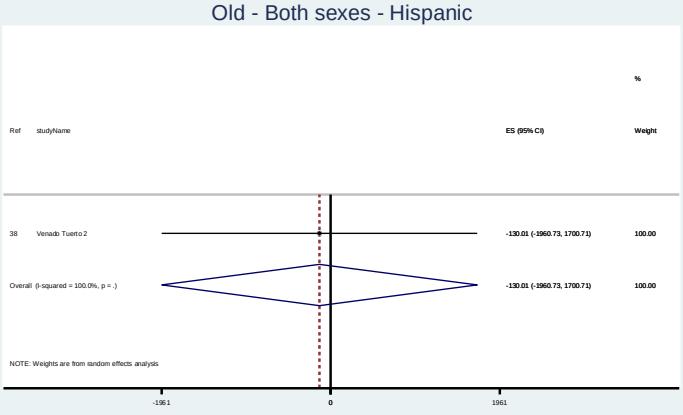


Young - Both sexes - Hispanic

Middle - Both sexes - Hispanic

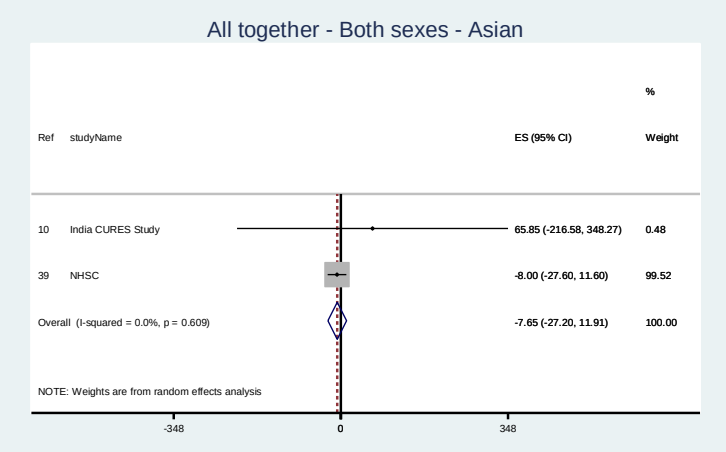


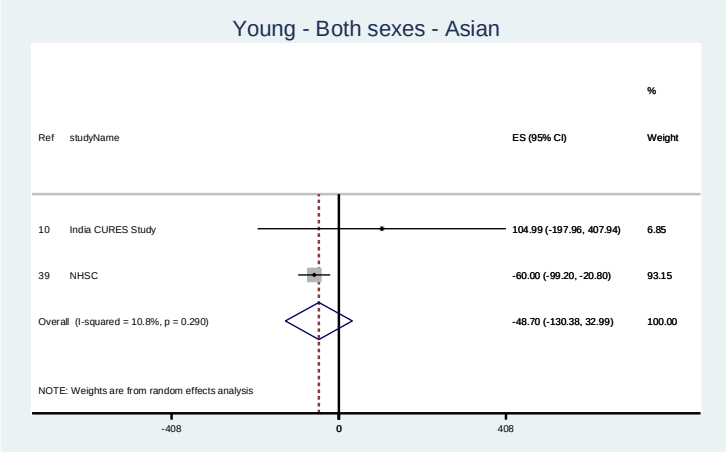
Old - Both sexes - Hispanic

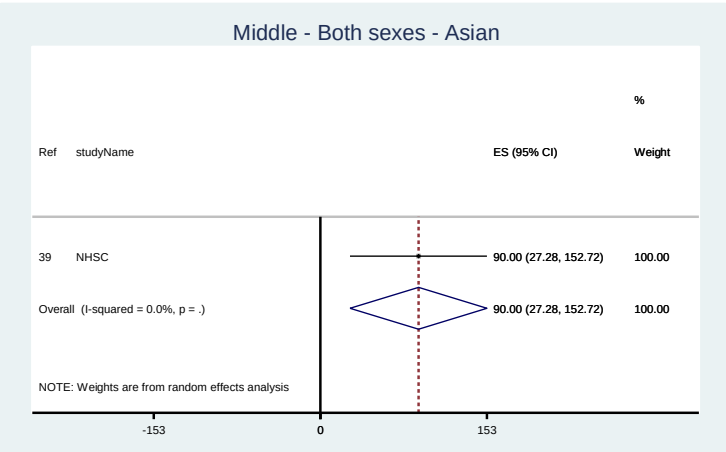


Absolute telomere length (base pairs; bp):

Both sexes - Asian



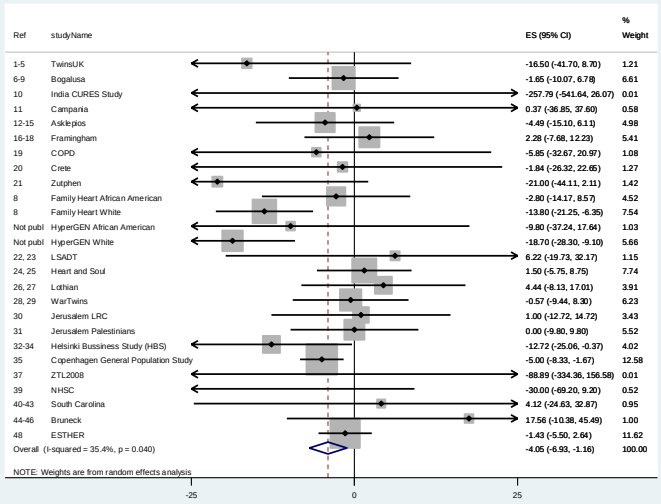




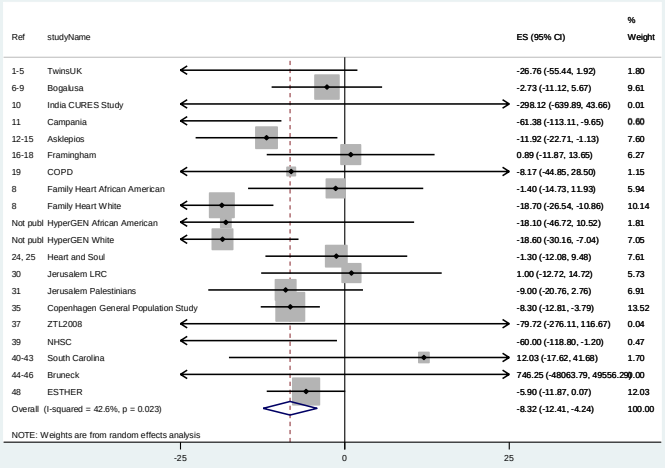
Absolute telomere length (base pairs; bp):

Men – Overall

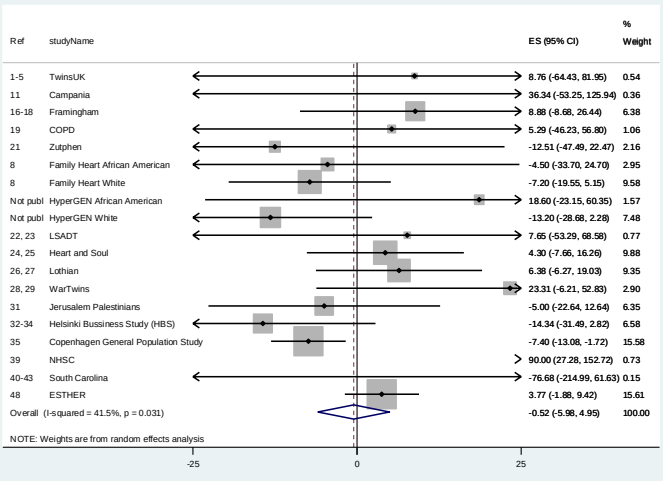
All together - Men - Overall



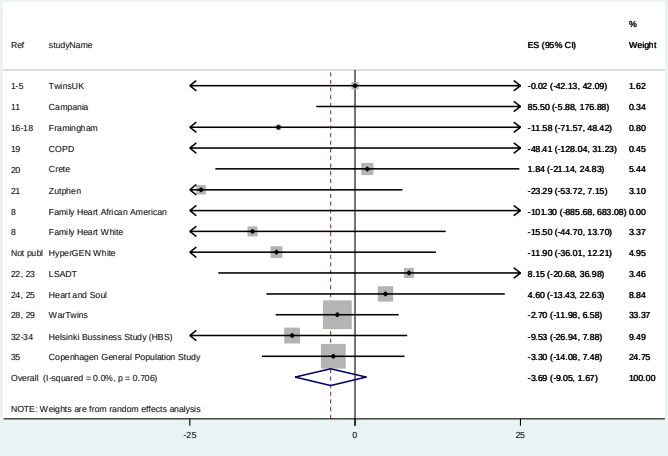
Young - Men - Overall



Middle - Men - Overall



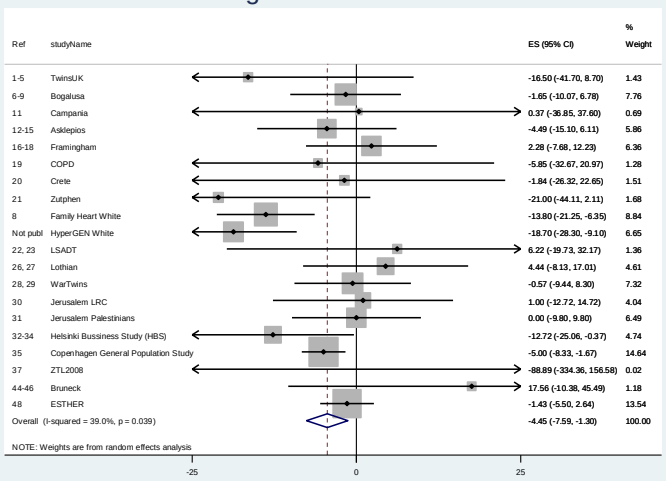
Old - Men - Overall



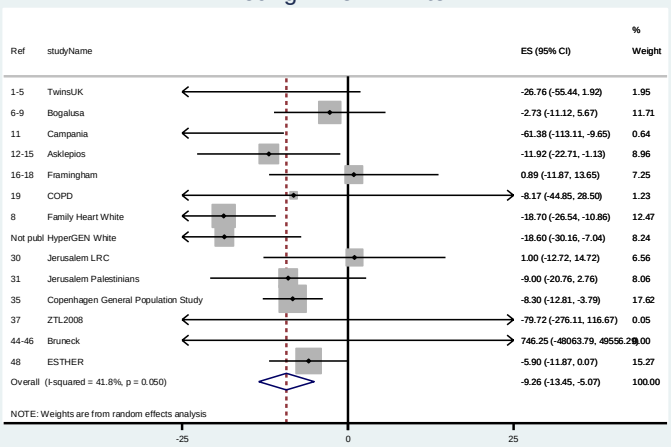
Absolute telomere length (base pairs; bp):

Men - white

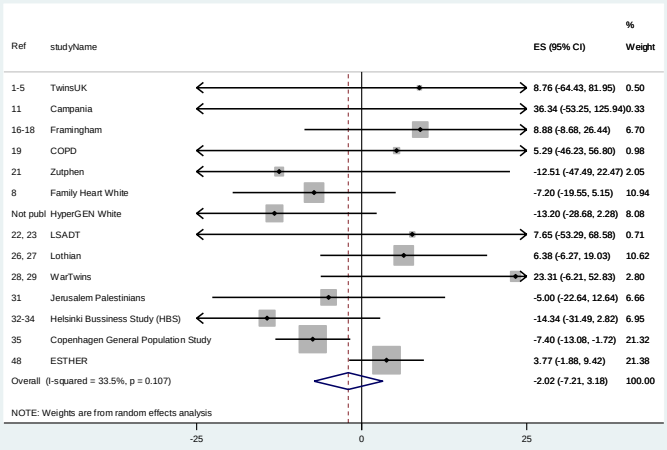
All together - Men - white



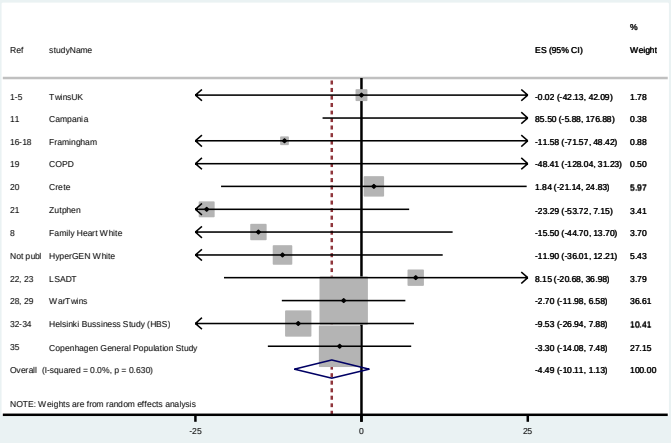
Young - Men - white



Middle - Men - white



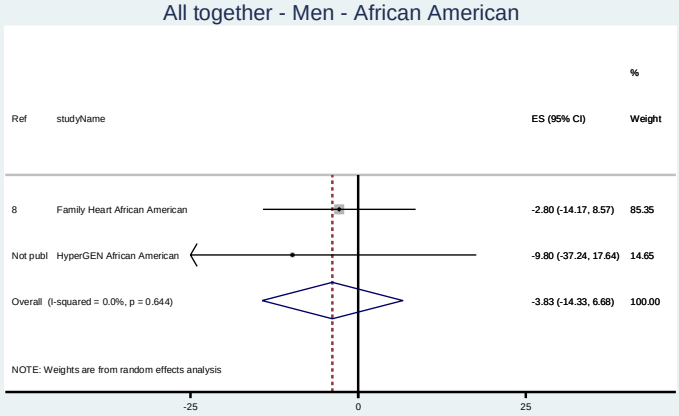
Old - Men - white



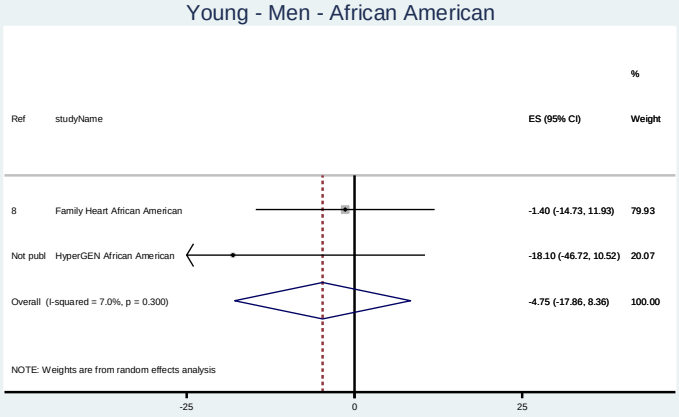
Absolute telomere length (base pairs; bp):

Men – African American

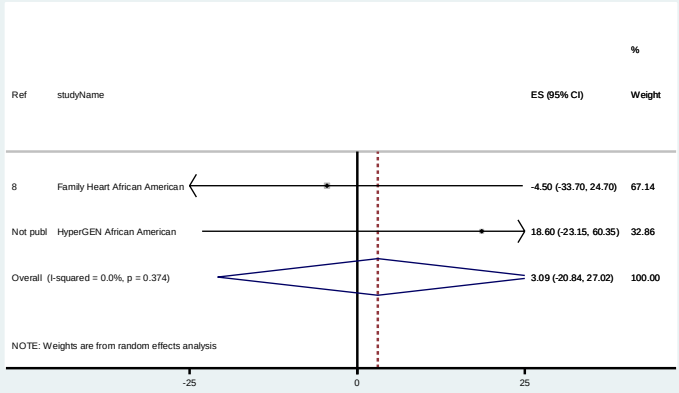
All together - Men - African American



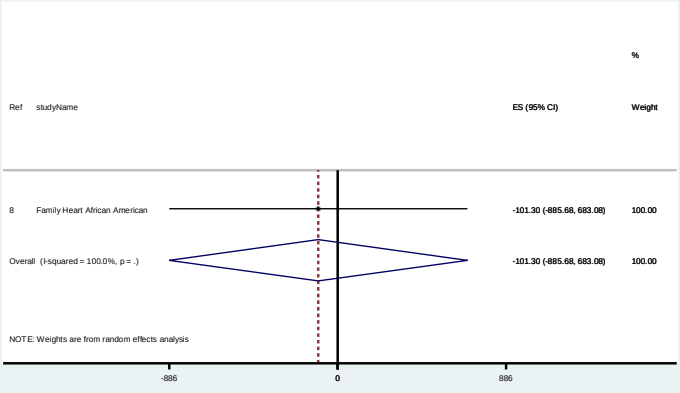
Young - Men - African American



Middle - Men - African American



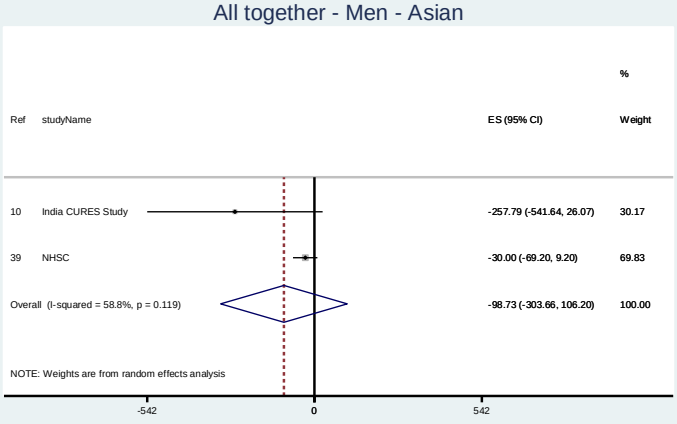
Old - Men - African American



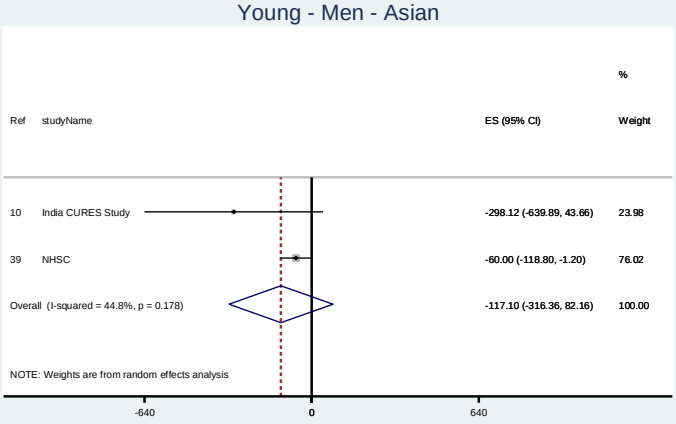
Absolute telomere length (base pairs; bp):

Men - Asian

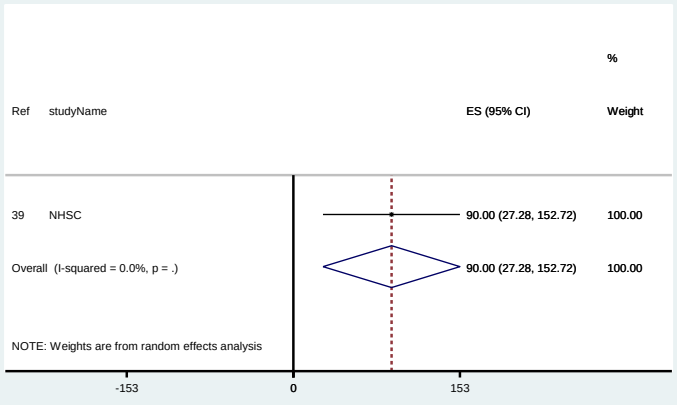
All together - Men - Asian



Young - Men - Asian



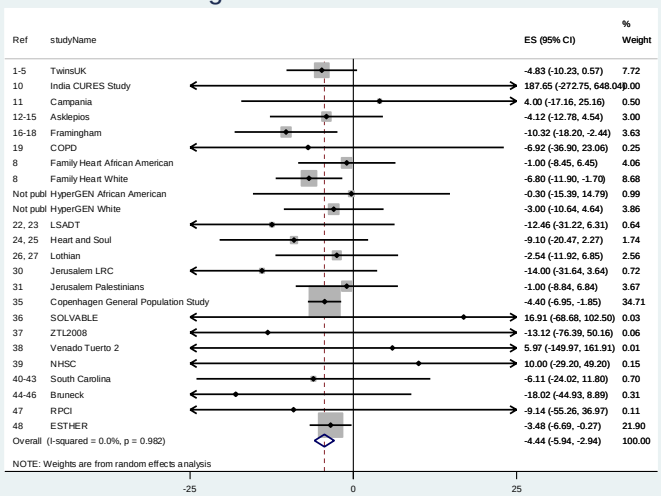
Middle - Men - Asian



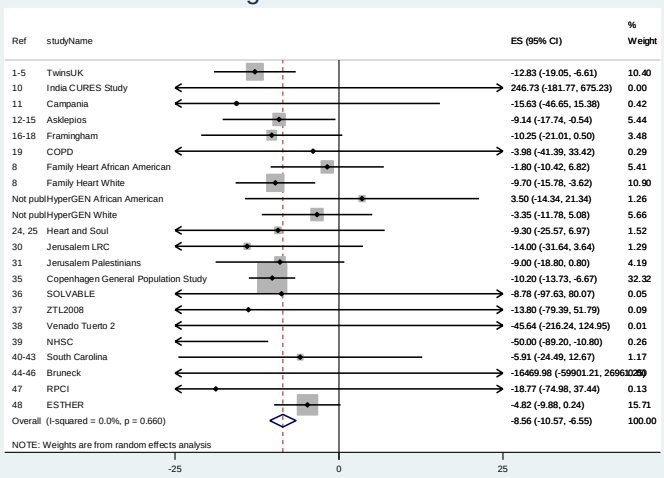
Absolute telomere length (base pairs; bp):

Women - Overall

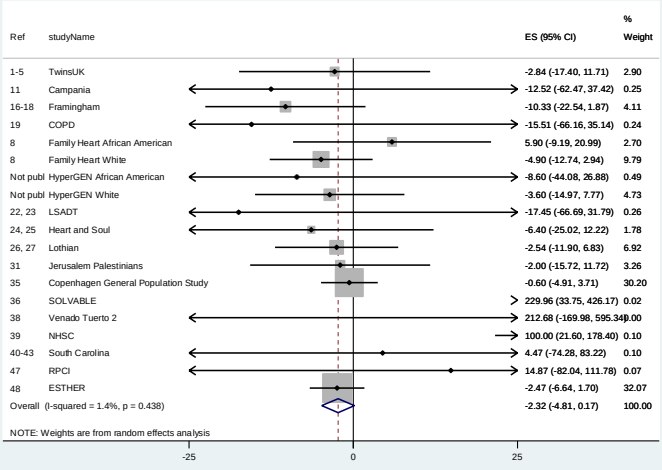
All together - Women - Overall



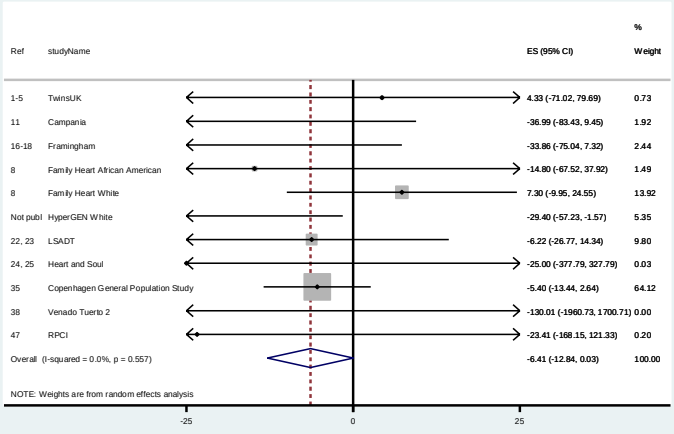
Young - Women - Overall



Middle - Women - Overall



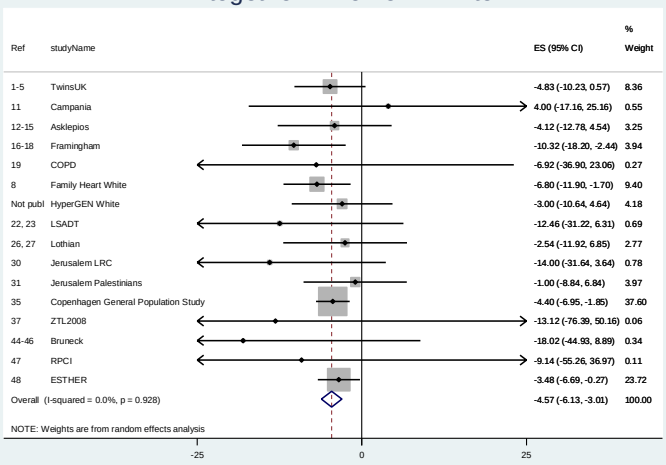
Old - Women - Overall



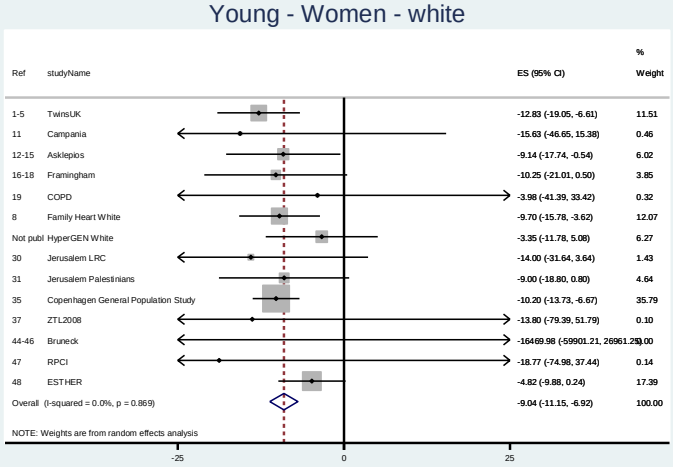
Absolute telomere length (base pairs; bp):

Women – white

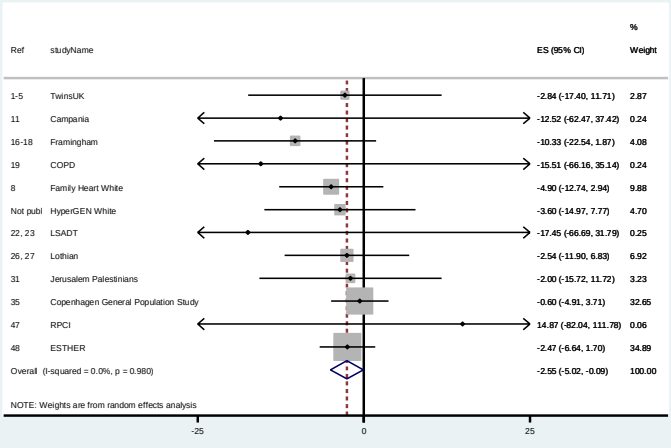
All together - Women - white



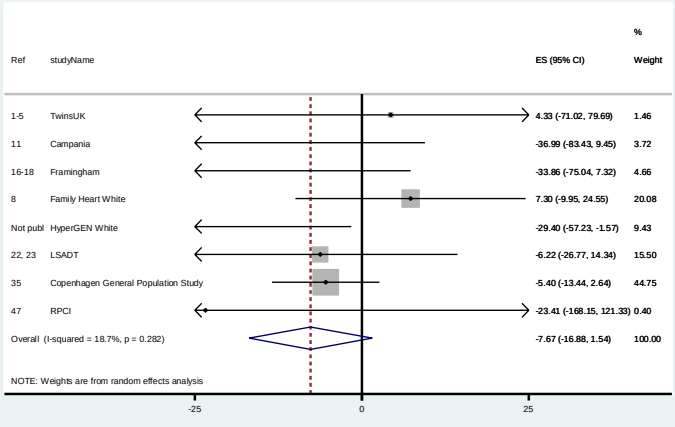
Young - Women - white



Middle - Women - white



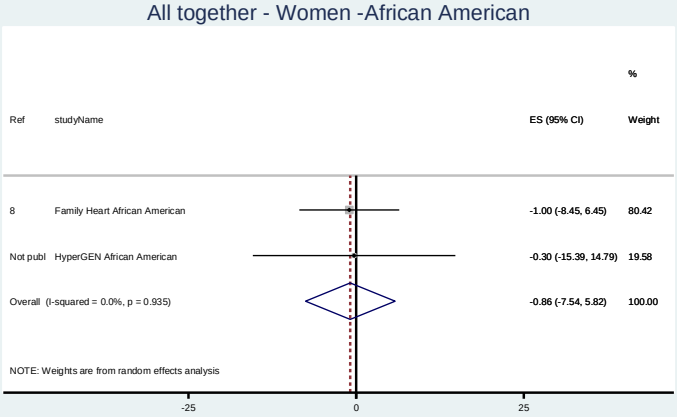
Old - Women - white



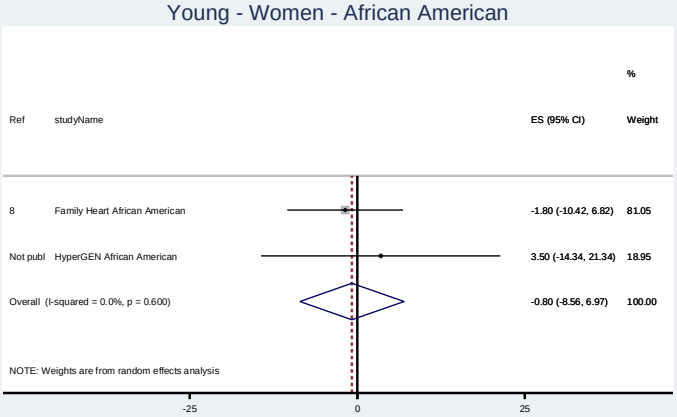
Absolute telomere length (base pairs; bp):

Women – African American

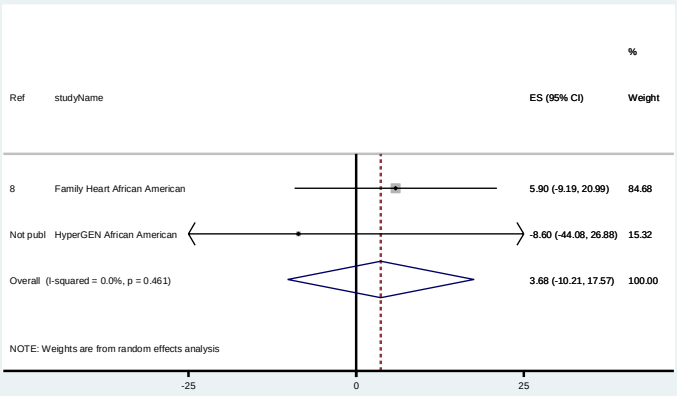
All together - Women -African American



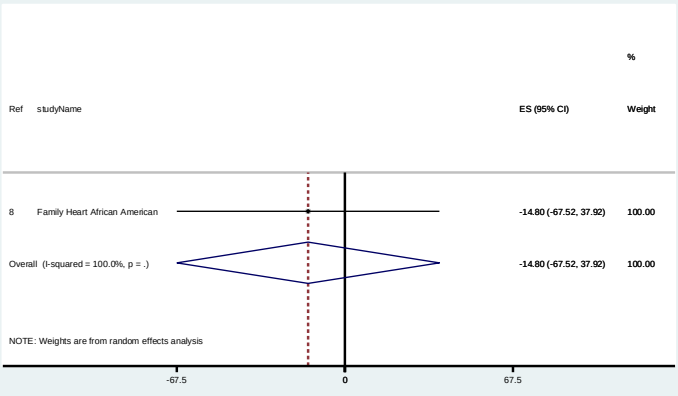
Young - Women - African American



Middle - Women - African American



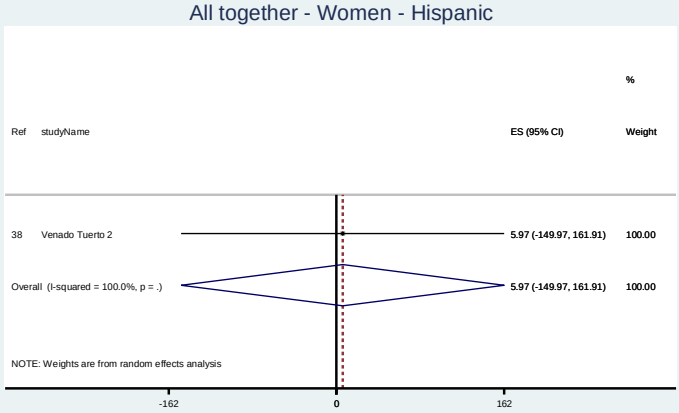
Old - Women - African American



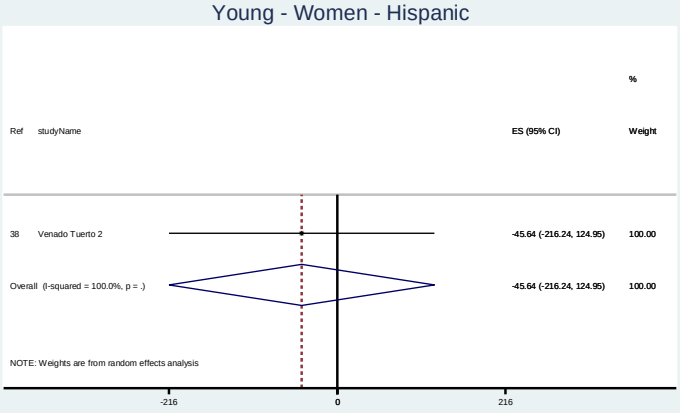
Absolute telomere length (base pairs; bp):

Women - Hispanic

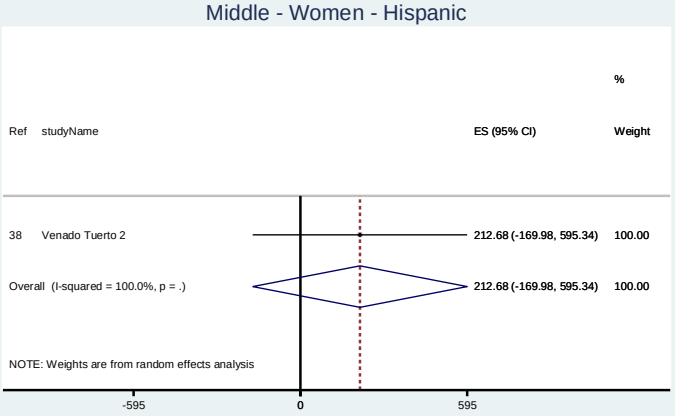
All together - Women - Hispanic



Young - Women - Hispanic

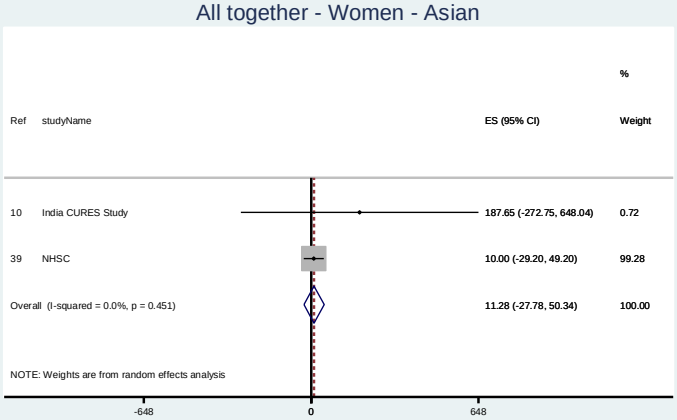


Middle - Women - Hispanic

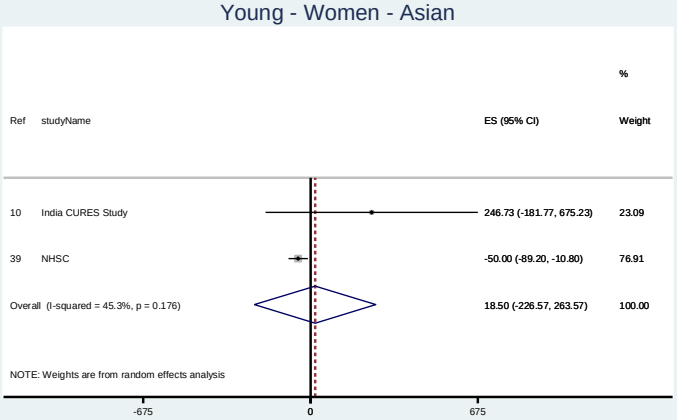


Absolute telomere length (base pairs; bp): Women - Asian

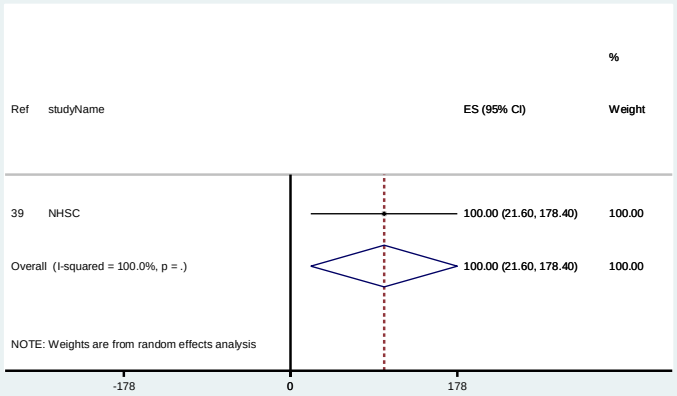
All together - Women - Asian



Young - Women - Asian



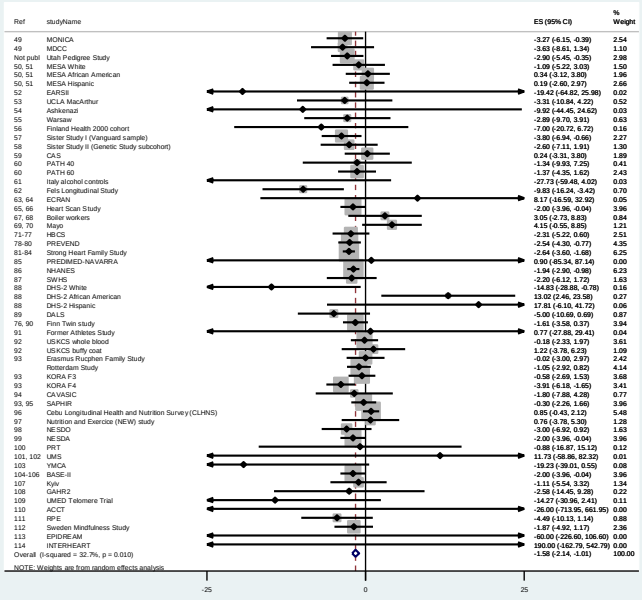
Middle - Women - Asian



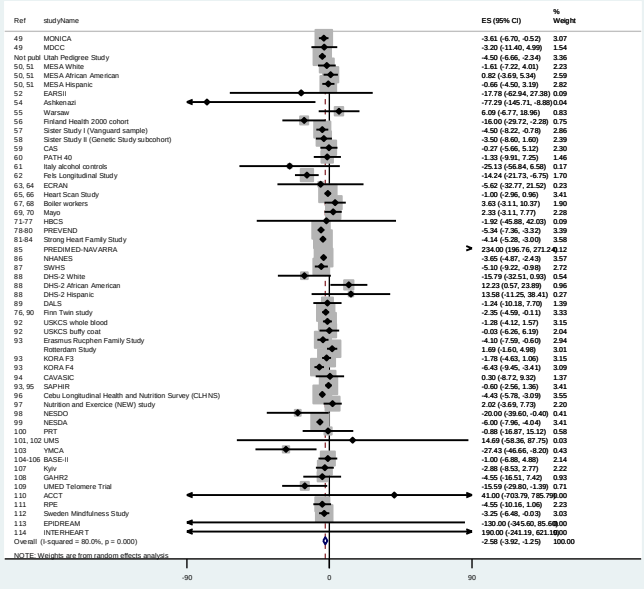
Relative telomere length (T/S ratio):

Both sexes - Overall

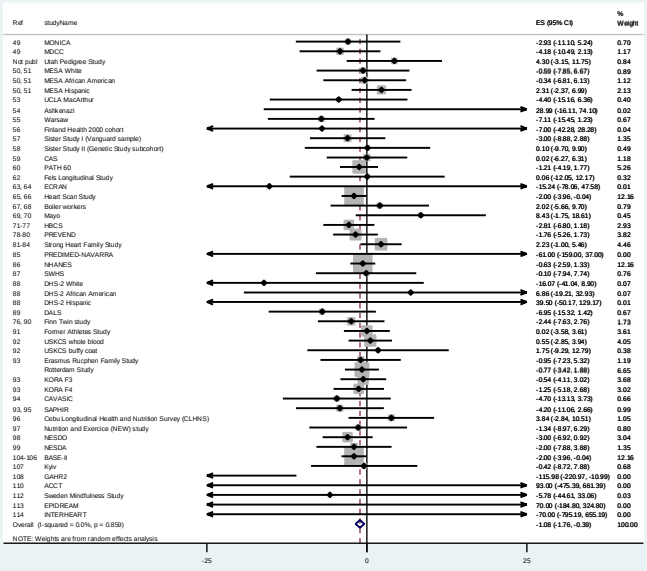
All together - Both sexes - Overall



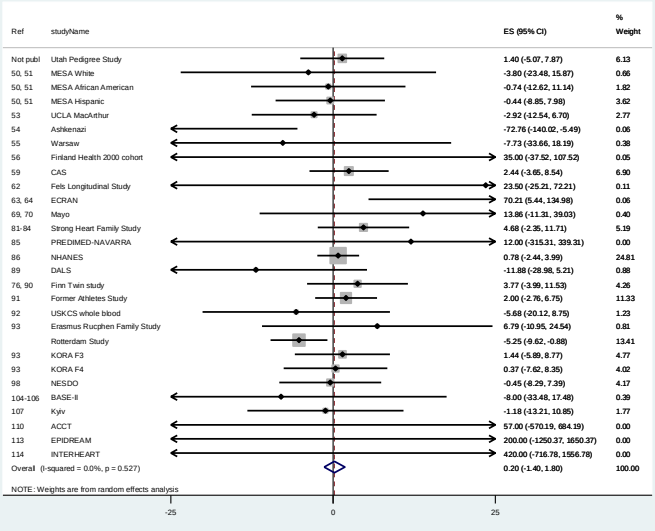
Young - Both sexes - Overall



Middle - Both sexes - Overall



Old - Both sexes - Overall

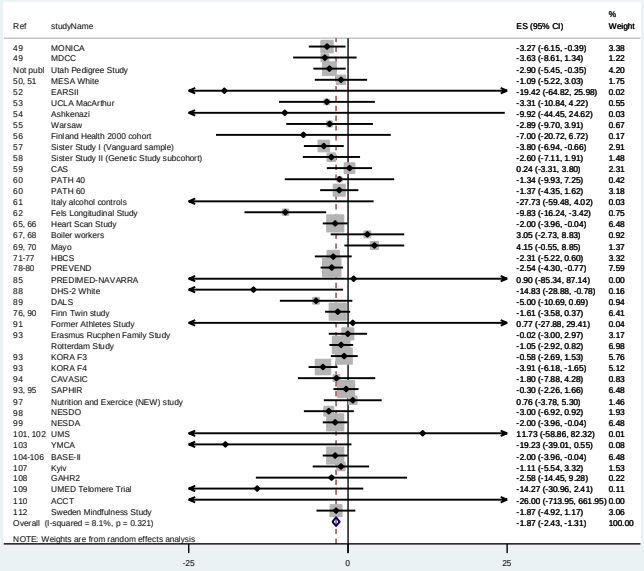


Online Supporting Material

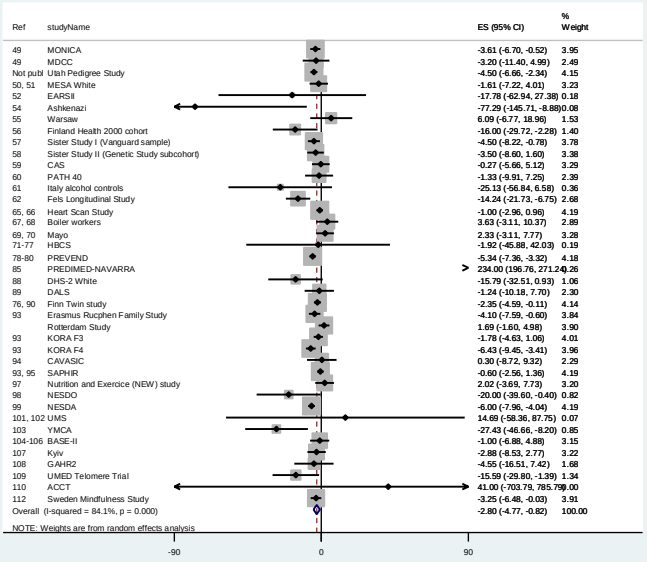
Relative telomere length (T/S ratio):

Both sexes - white

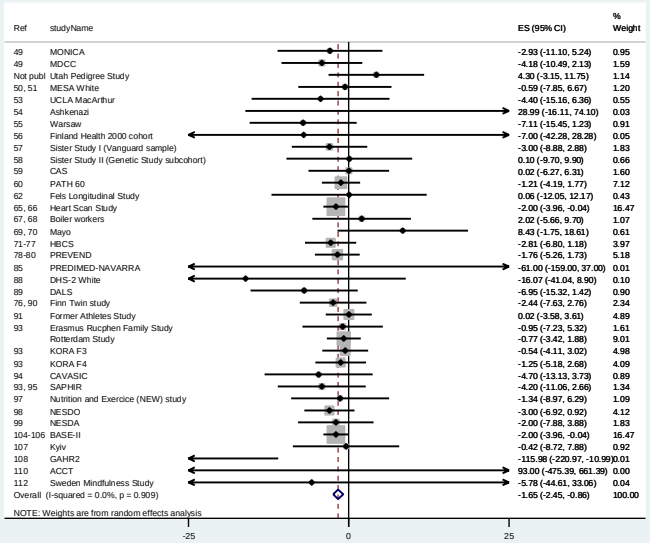
All together - Both sexes - white



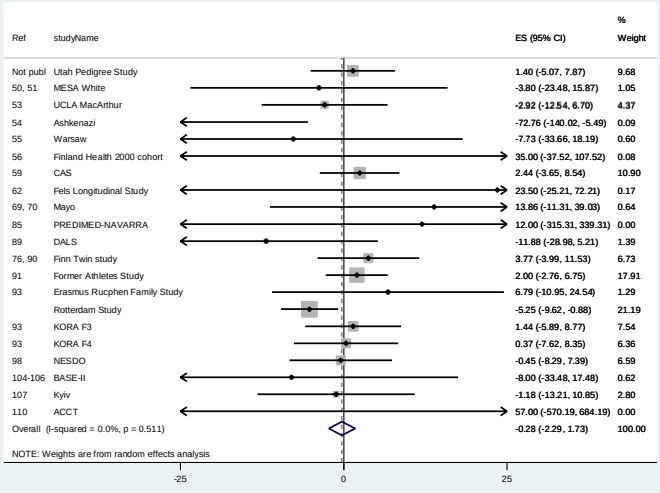
Young - Both sexes - white



Middle - Both sexes - white



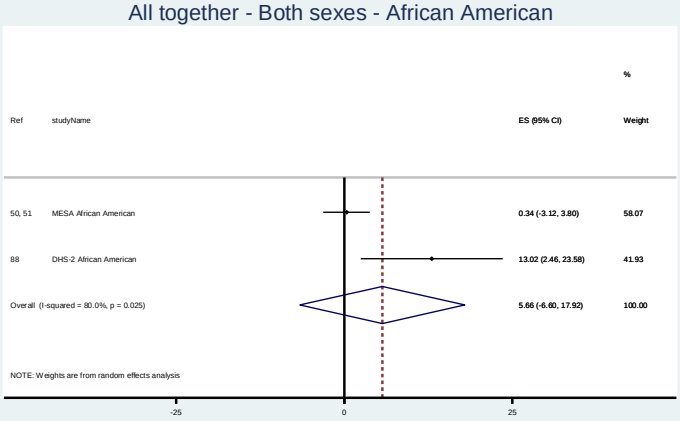
Old - Both sexes - white



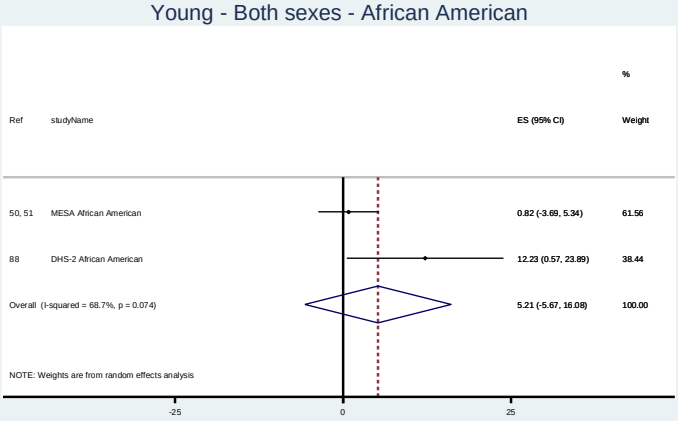
Relative telomere length (T/S ratio):

Both sexes – African American

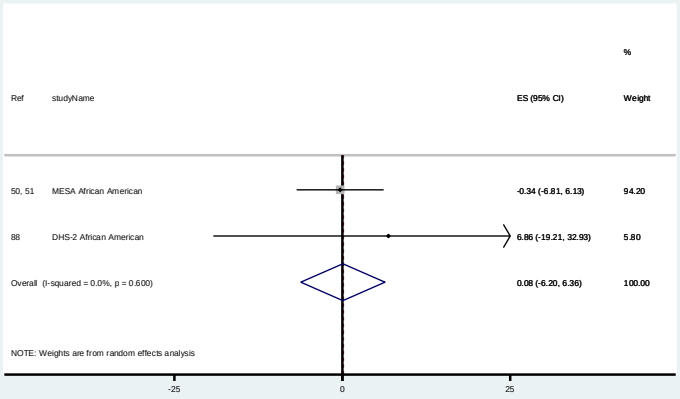
All together - Both sexes - African American



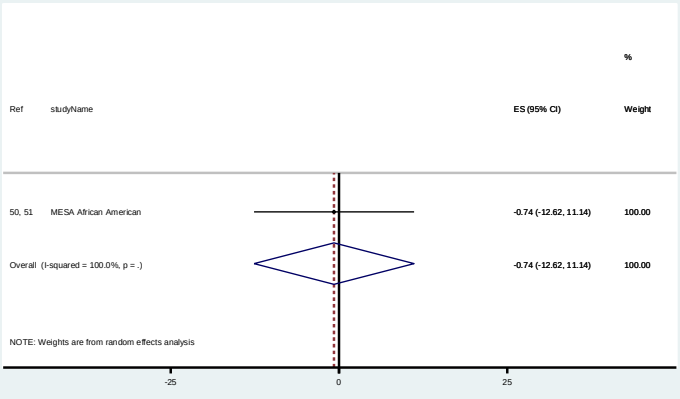
Young - Both sexes - African American



Middle - Both sexes - African American



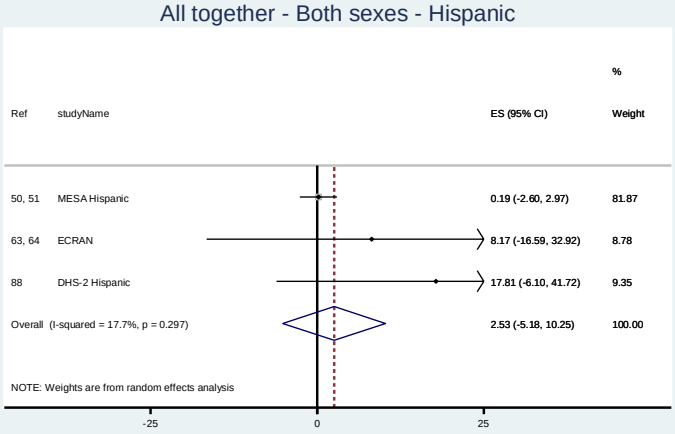
Old - Both sexes - African American



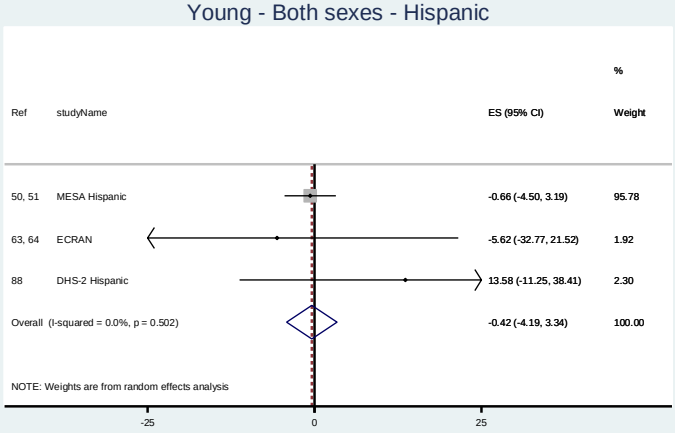
Relative telomere length (T/S ratio):

Both sexes - Hispanic

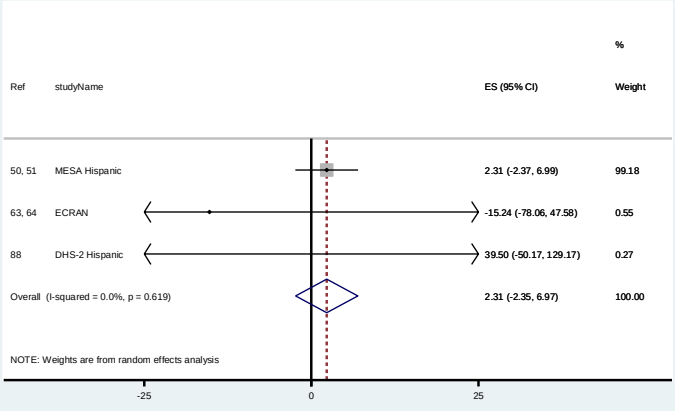
All together - Both sexes - Hispanic



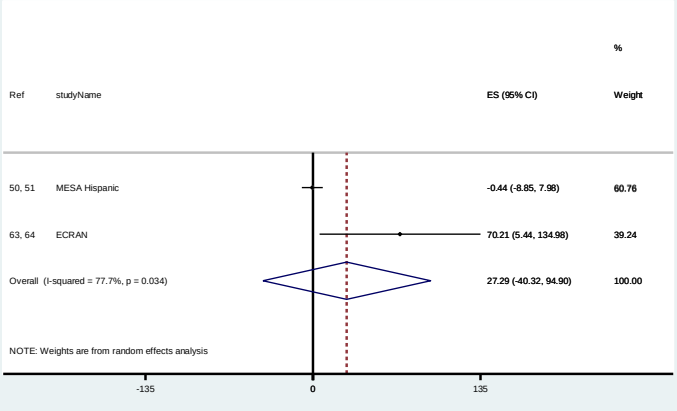
Young - Both sexes - Hispanic



Middle - Both sexes - Hispanic



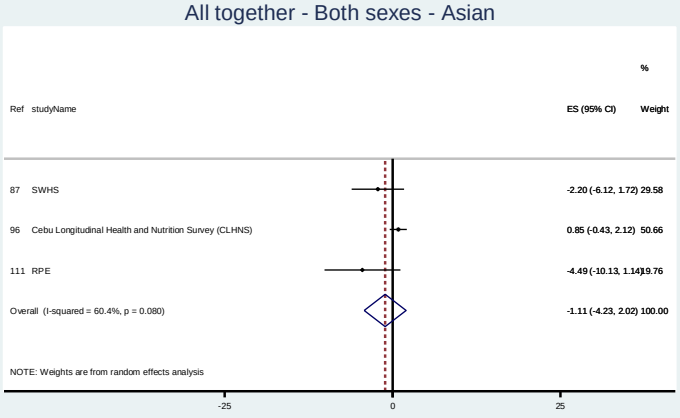
Old - Both sexes - Hispanic



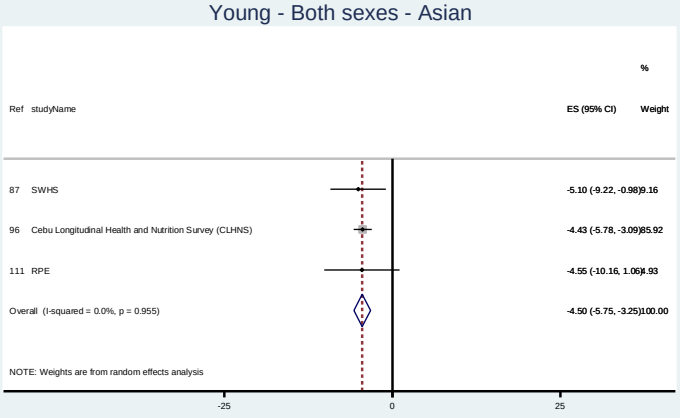
Relative telomere length (T/S ratio):

Both sexes - Asian

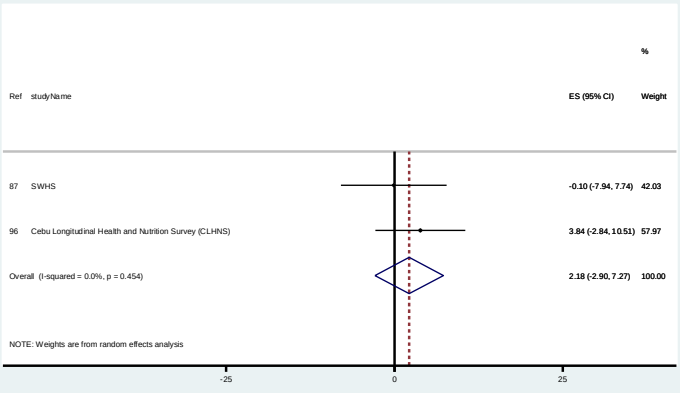
All together - Both sexes - Asian



Young - Both sexes - Asian



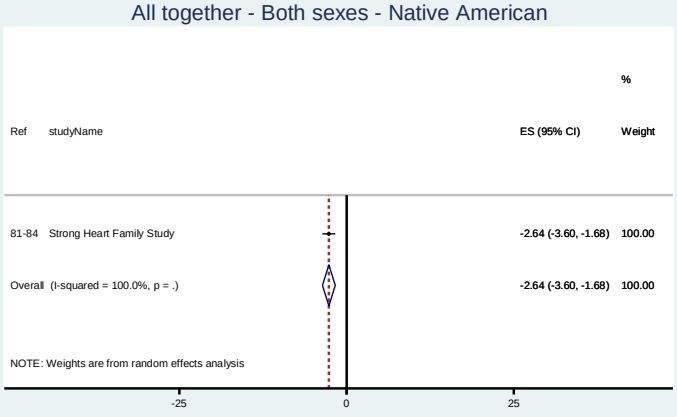
Middle - Both sexes - Asian



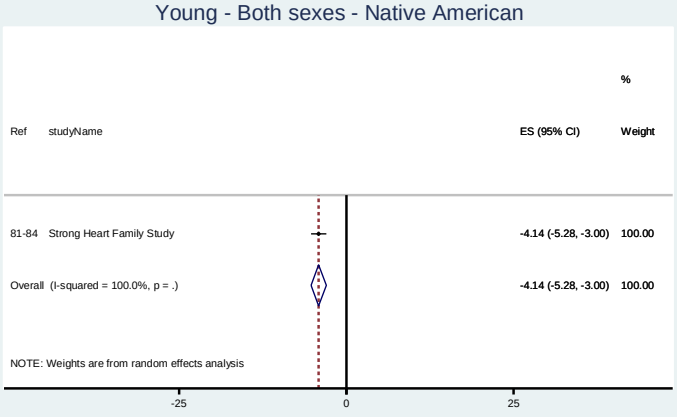
Relative telomere length (T/S ratio):

Both sexes – Native American

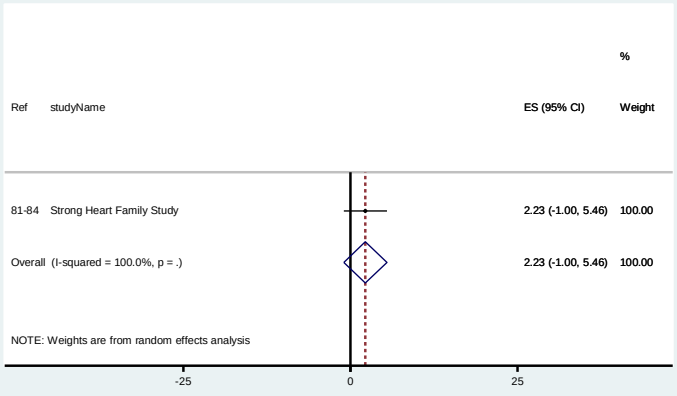
All together - Both sexes - Native American



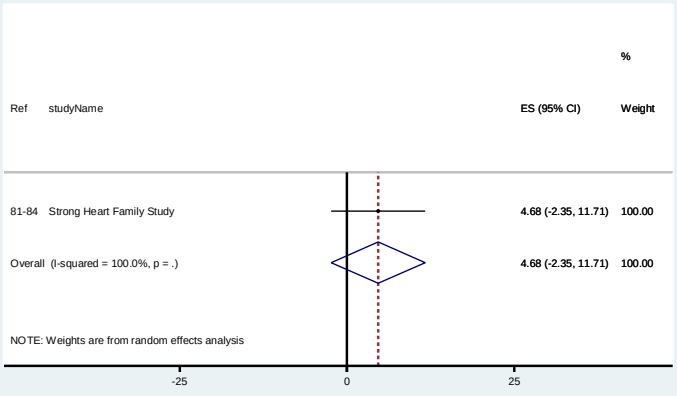
Young - Both sexes - Native American



Middle - Both sexes - Native American



Old - Both sexes - Native American

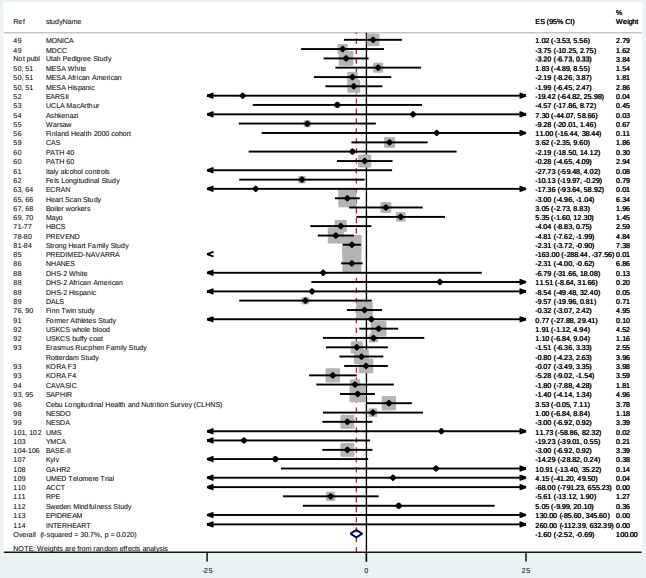


Online Supporting Material

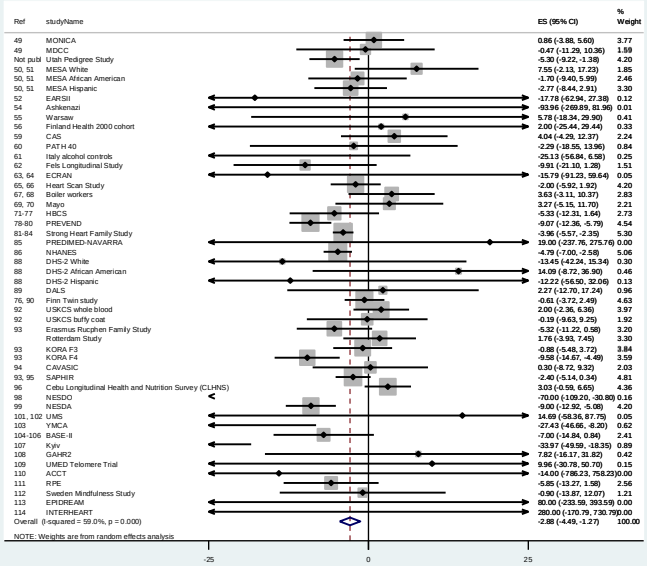
Relative telomere length (T/S ratio):

Men - Overall

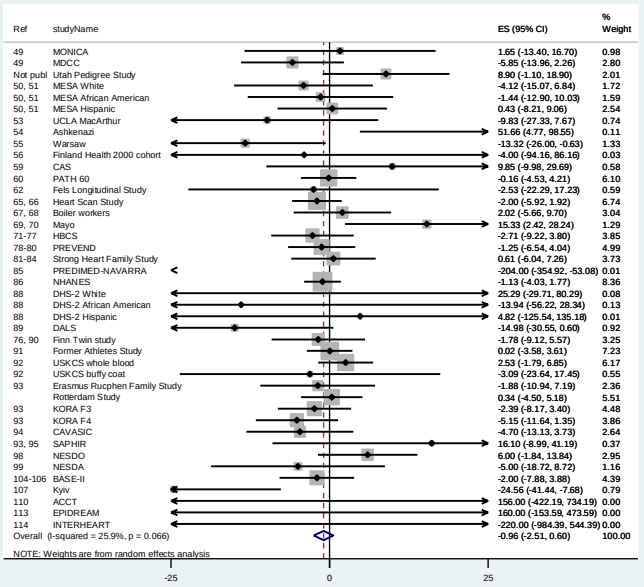
All together - Men - Overall



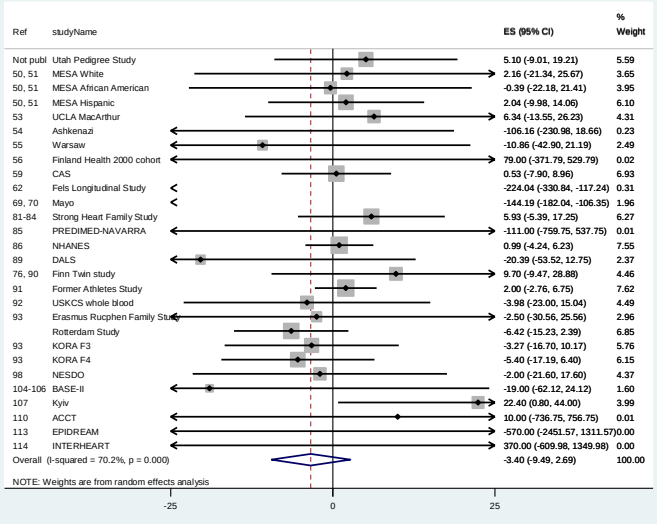
Young - Men - Overall



Middle - Men - Overall



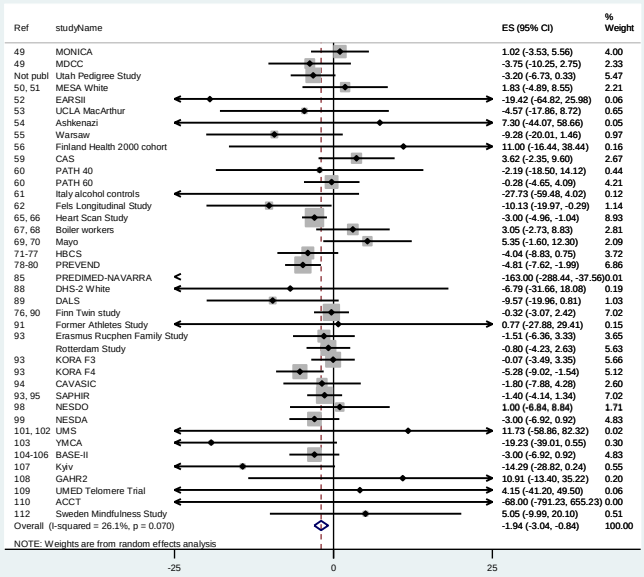
Old - Men - Overall



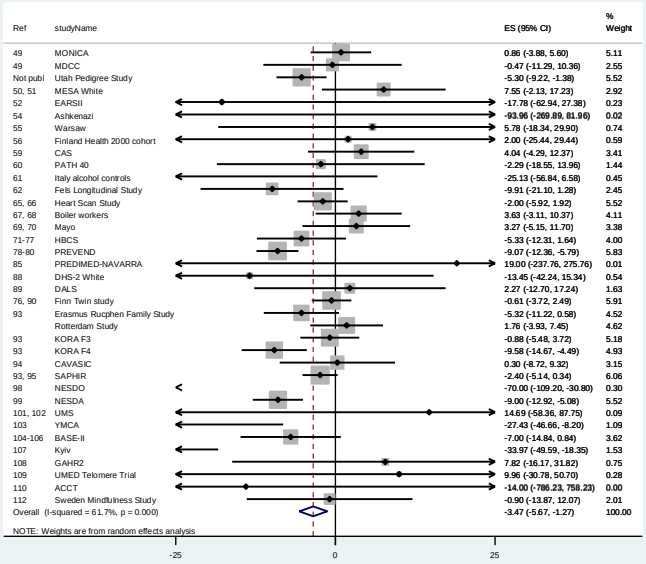
Relative telomere length (T/S ratio):

Men - white

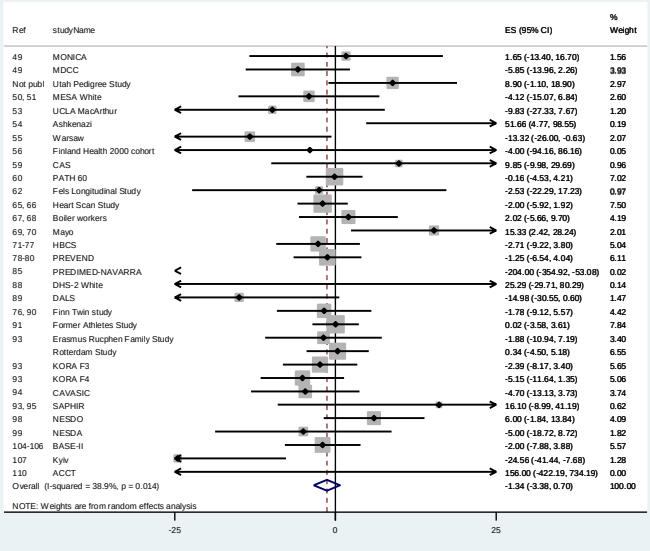
All together - Men - white



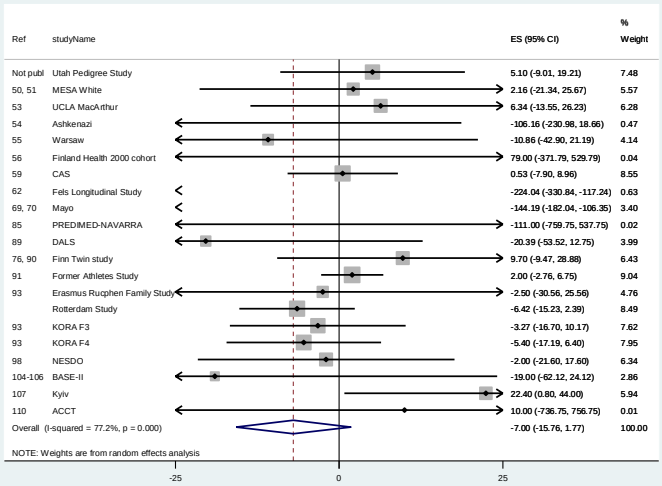
Young - Men - white



Middle - Men - white



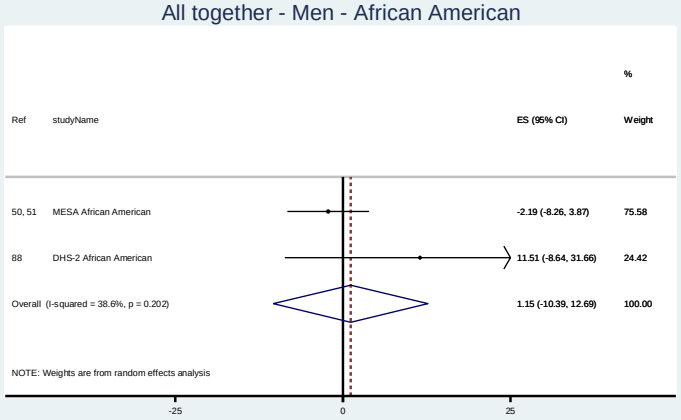
Old - Men - white



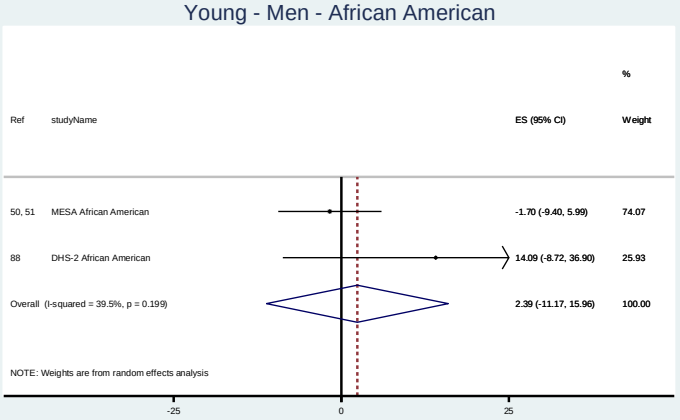
Relative telomere length (T/S ratio):

Men – African American

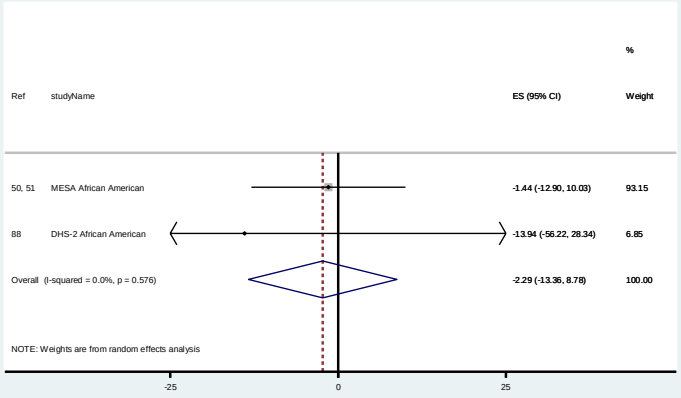
All together - Men - African American



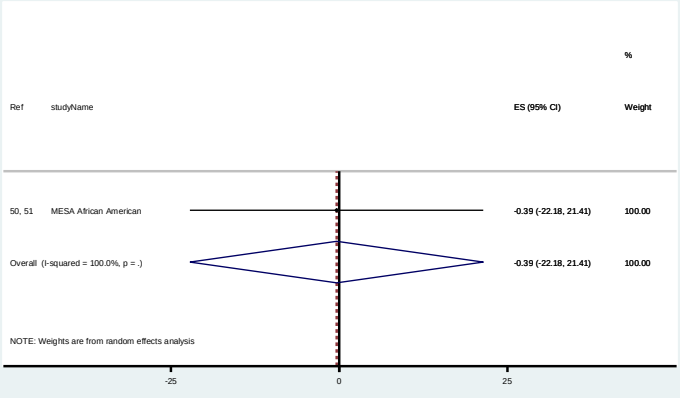
Young - Men - African American



Middle - Men - African American



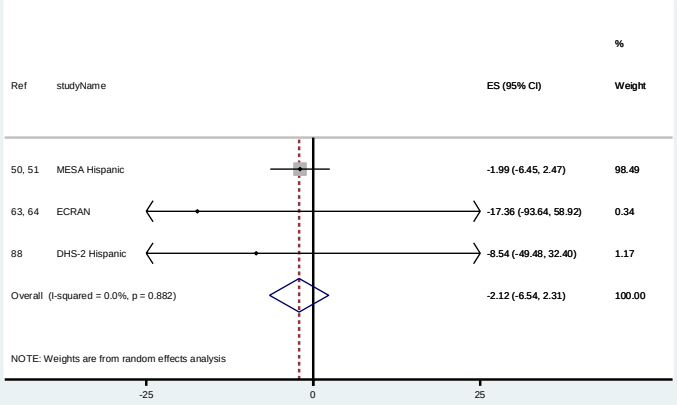
Old - Men - African American



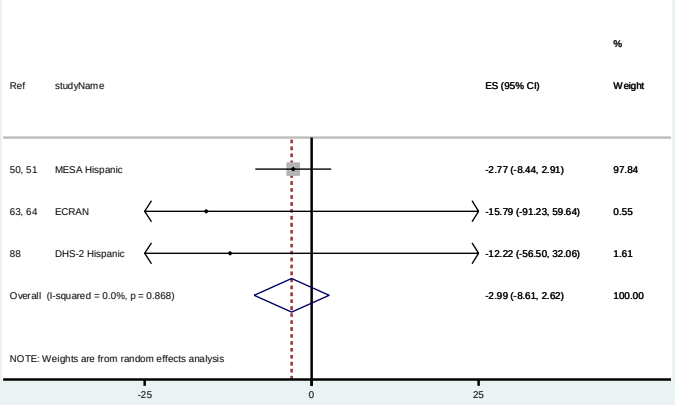
Relative telomere length (T/S ratio):

Men - Hispanic

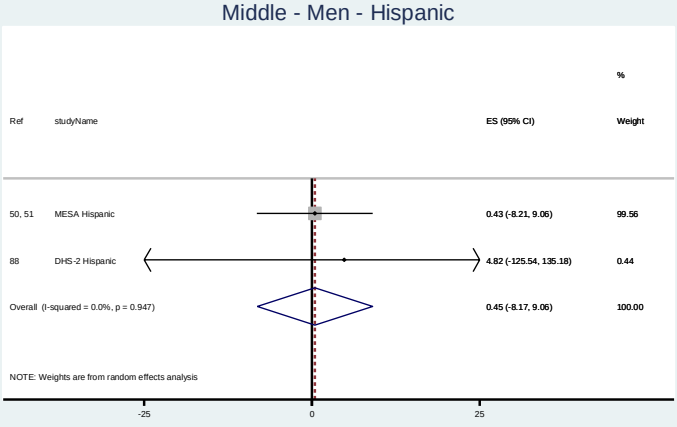
All together - Men - Hispanic



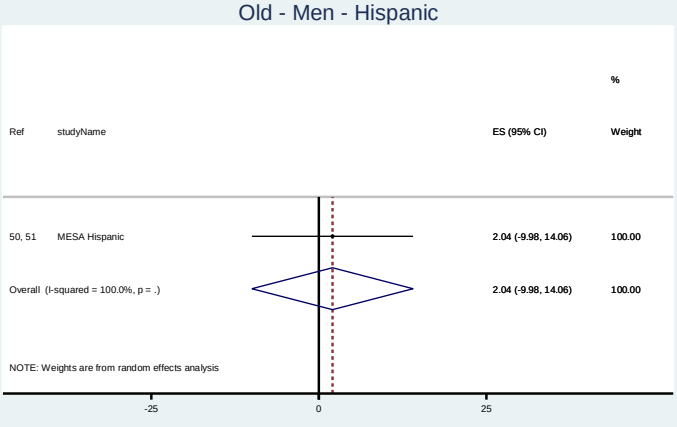
Young - Men - Hispanic



Middle - Men - Hispanic



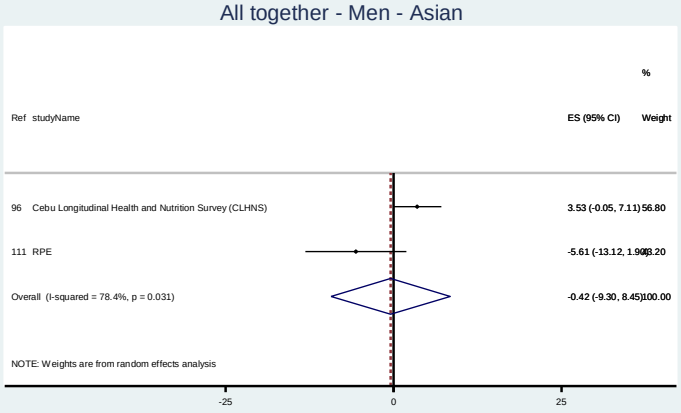
Old - Men - Hispanic



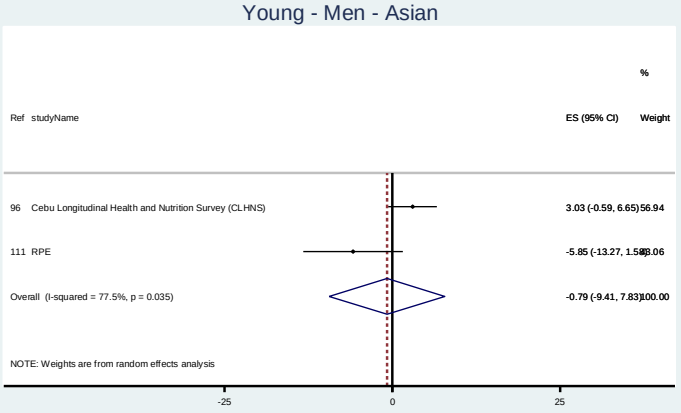
Relative telomere length (T/S ratio):

Men - Asian

All together - Men - Asian

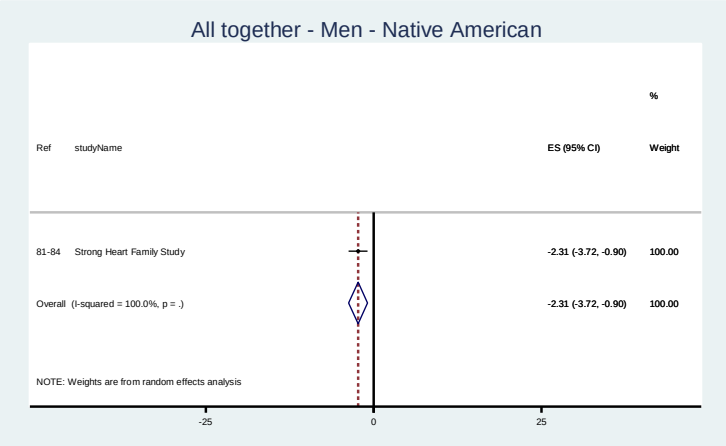


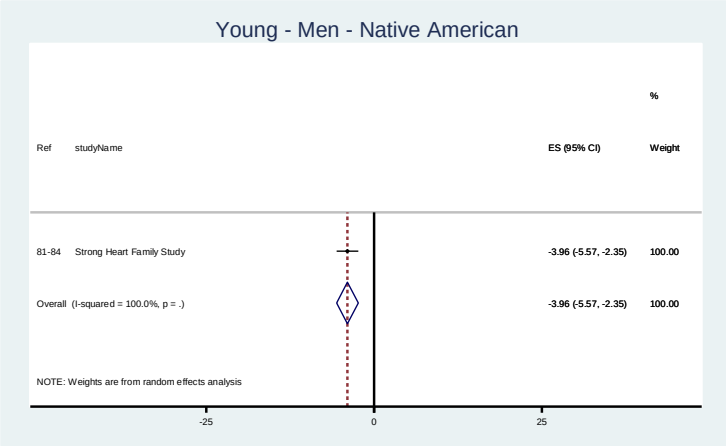
Young - Men - Asian

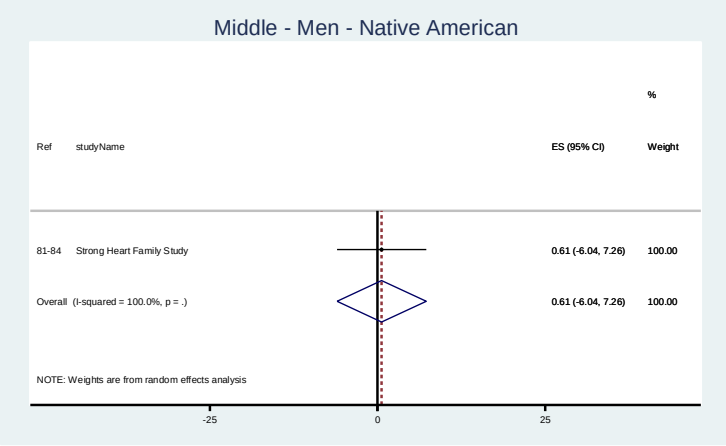


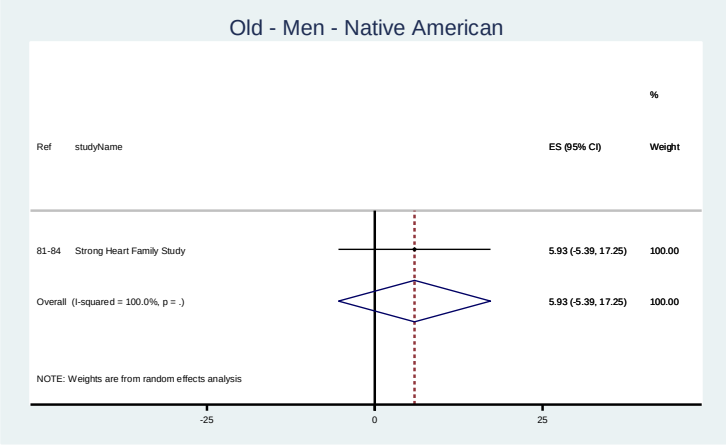
Relative telomere length (T/S ratio):

Men – Native American





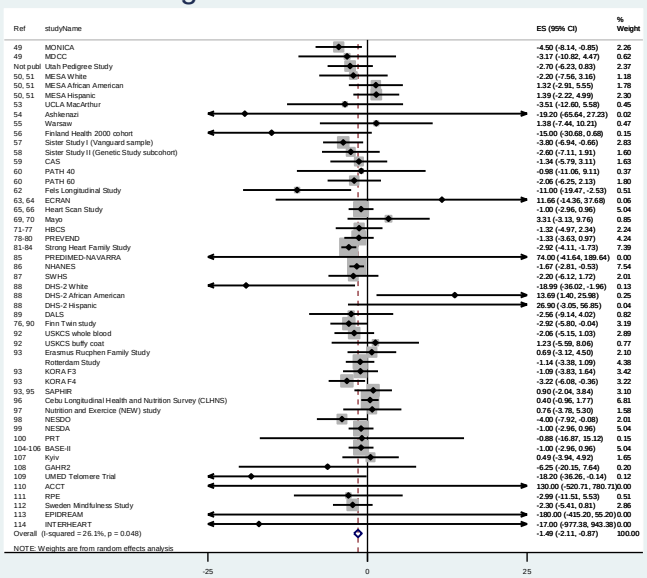




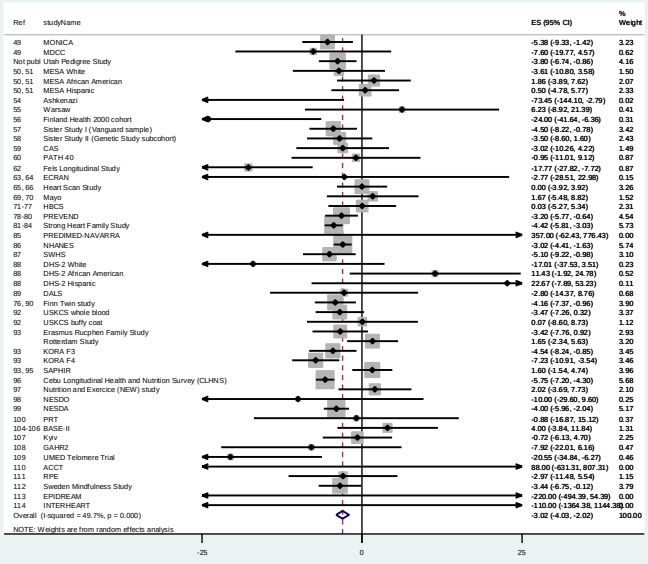
Online Supporting Material

Relative telomere length (T/S ratio): Women - Overall

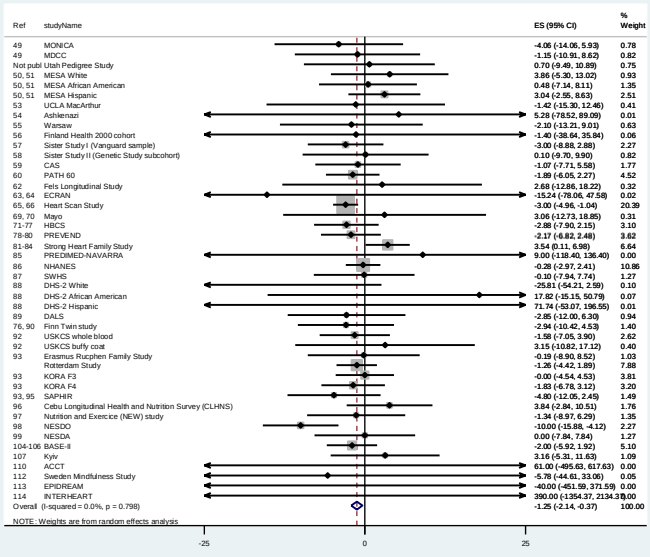
All together - Women - Overall



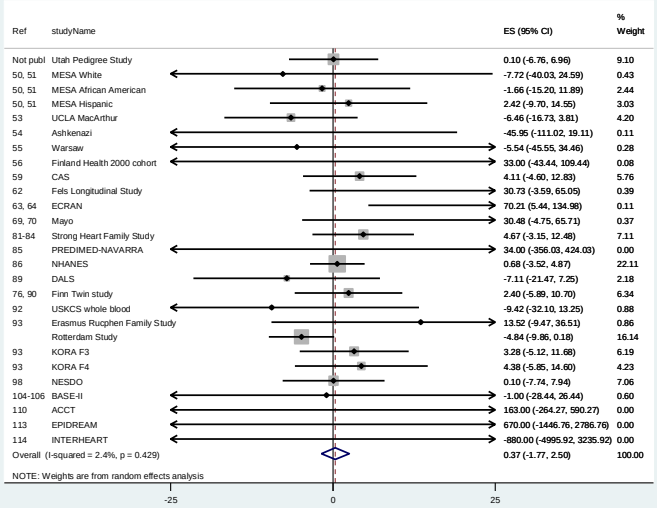
Young - Women - Overall



Middle - Women - Overall



Old - Women - Overall

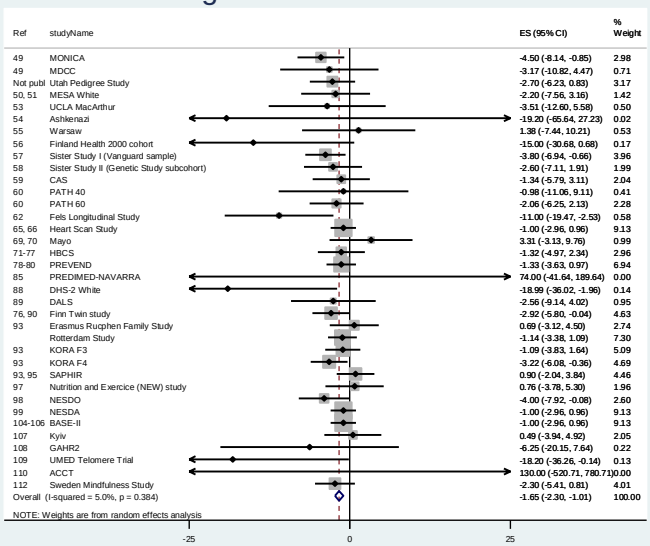


Online Supporting Material

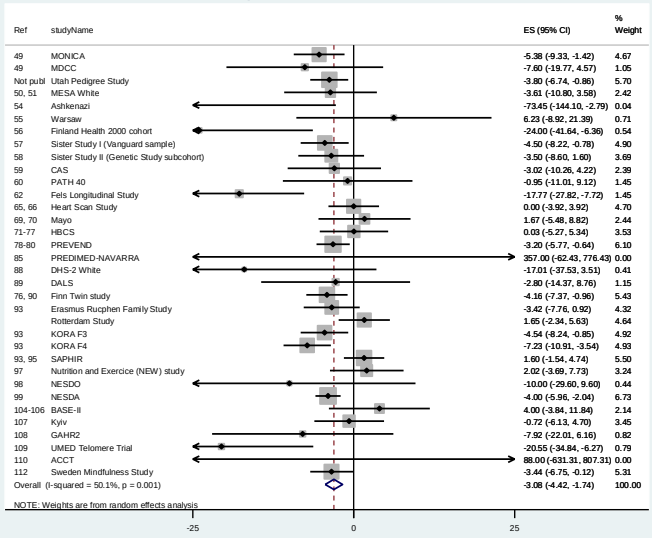
Relative telomere length (T/S ratio):

Women - white

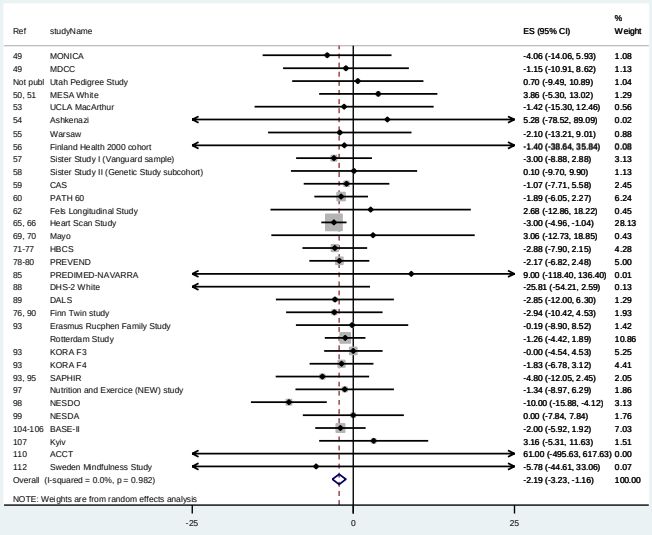
All together - Women - white



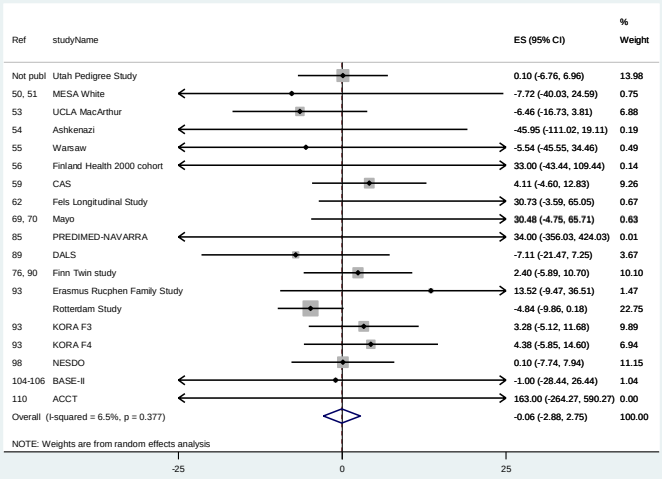
Young - Women - white



Middle - Women - white



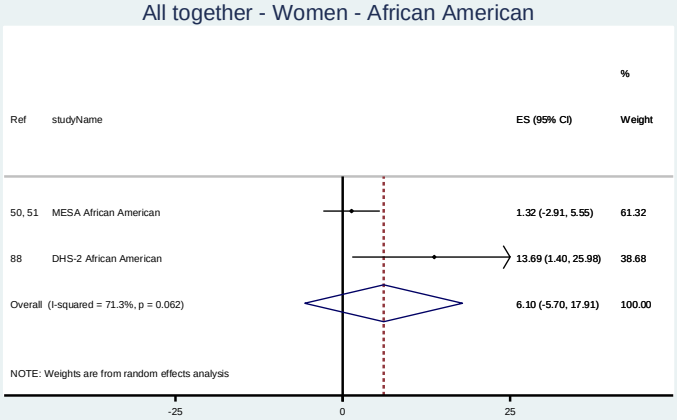
Old - Women - white



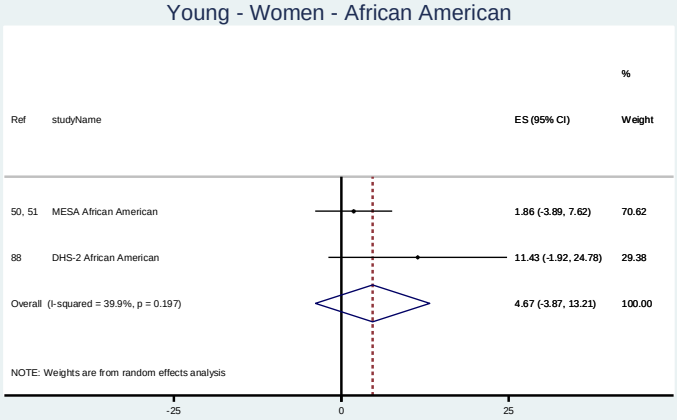
Relative telomere length (T/S ratio):

Women – African American

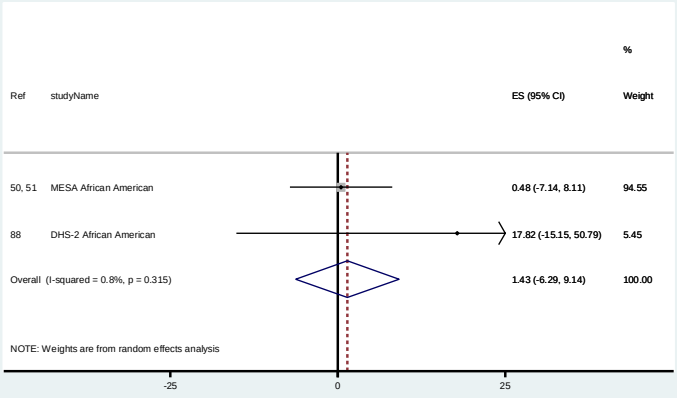
All together - Women - African American



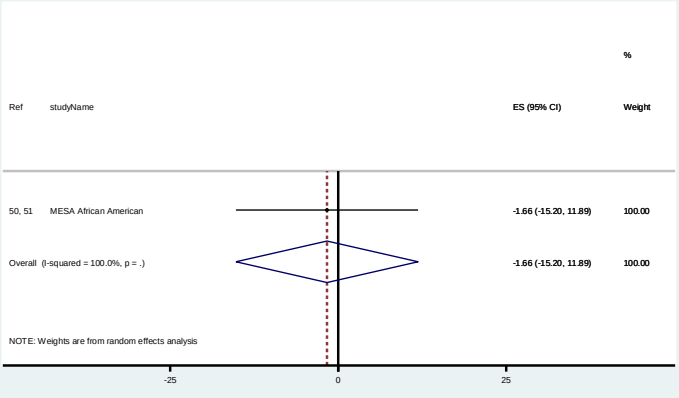
Young - Women - African American



Middle - Women - African American



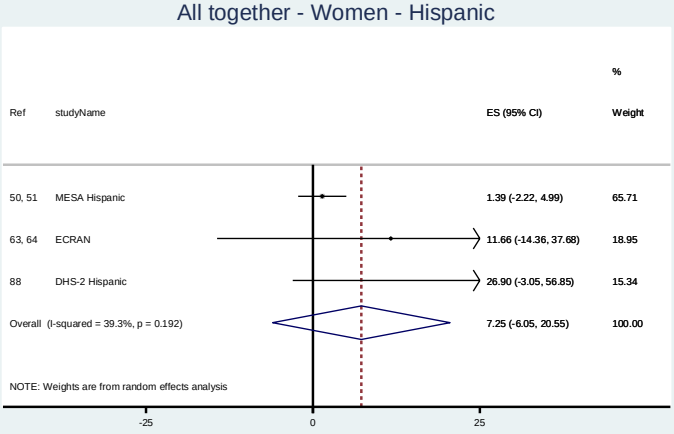
Old - Women - African American



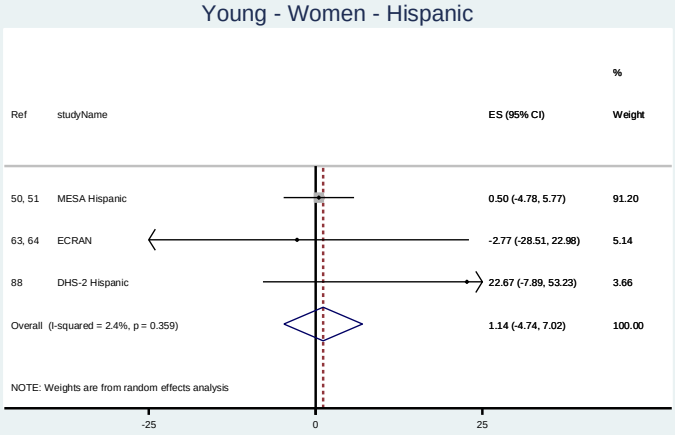
Relative telomere length (T/S ratio):

Women - Hispanic

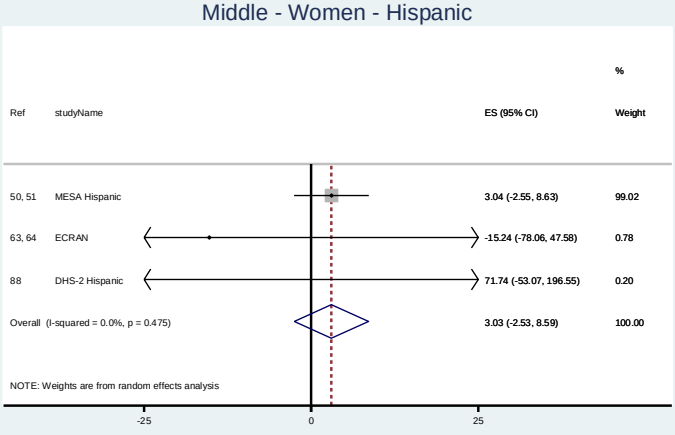
All together - Women - Hispanic



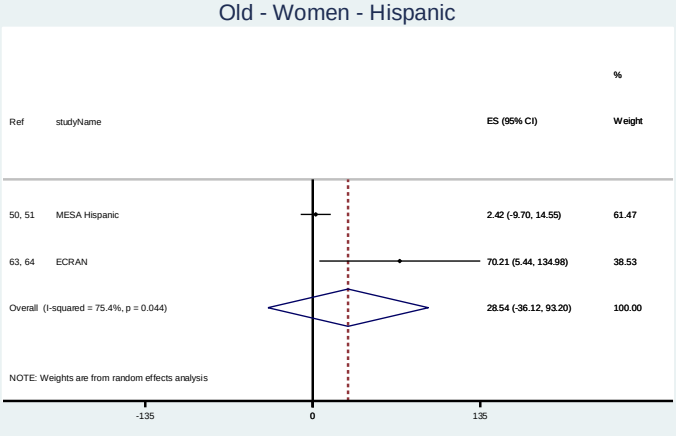
Young - Women - Hispanic



Middle - Women - Hispanic



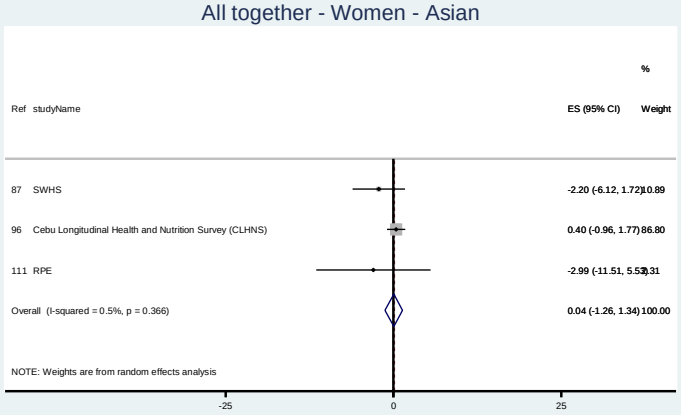
Old - Women - Hispanic



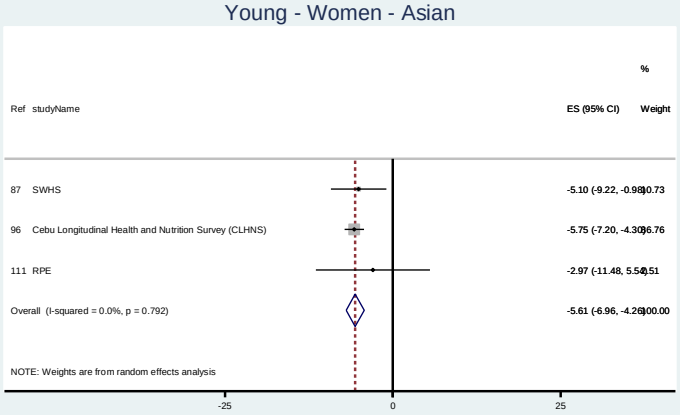
Relative telomere length (T/S ratio):

Women - Asian

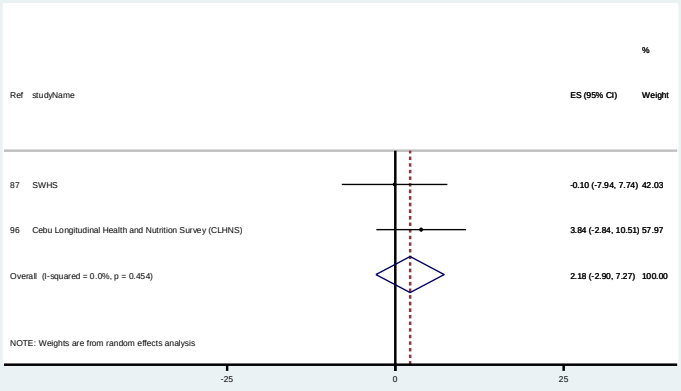
All together - Women - Asian



Young - Women - Asian



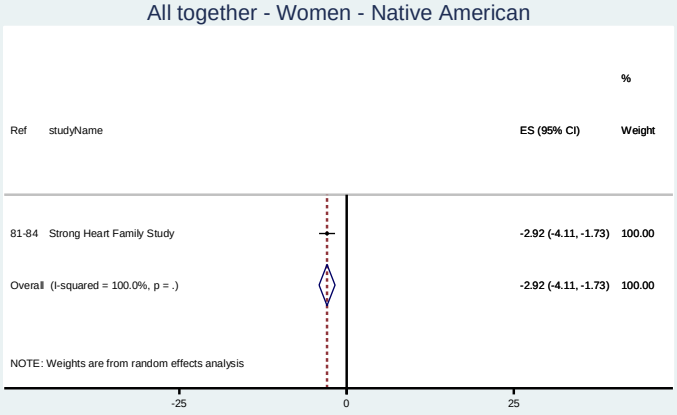
Middle - Women - Asian



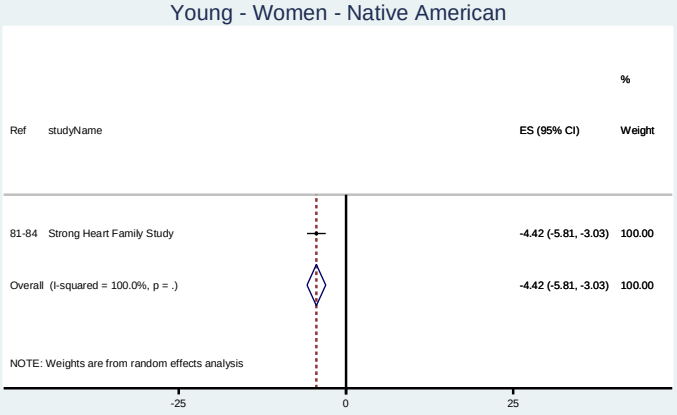
Relative telomere length (T/S ratio):

Women – Native American

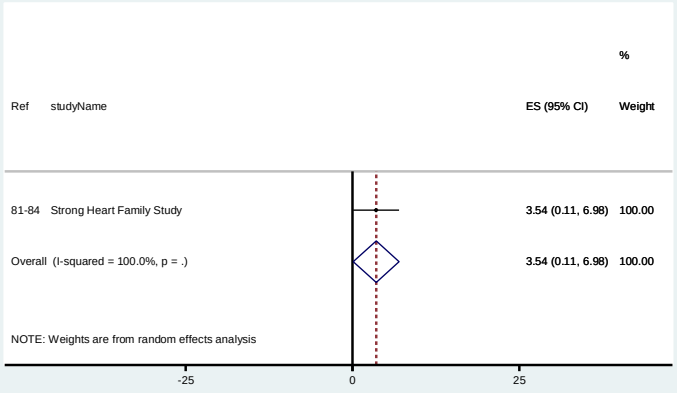
All together - Women - Native American



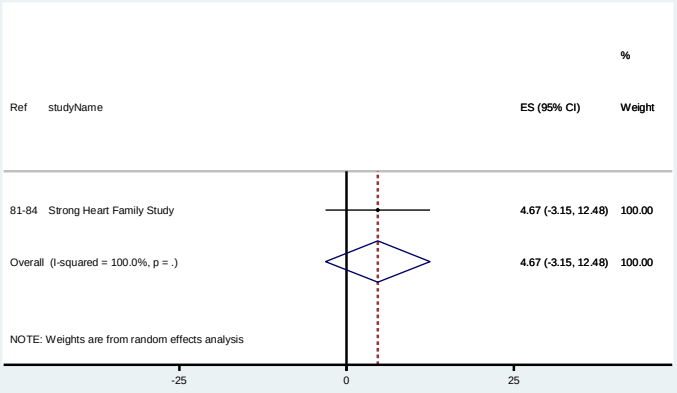
Young - Women - Native American



Middle - Women - Native American



Old - Women - Native American



Online Supporting Material

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STUDY PROTOCOL FOR PARTICIPATING PIs

Version August 2014
Note. A third search is performed in January 2016 and a fourth search in November 2017.

TELOMAAS study

Is BMI associated with shorter telomere length? A meta-analysis of observational studies
Marij Gielen, Maurice P. Zeegers

Background
Shorter telomeres are associated with age-related diseases such as type 2 diabetes and cardiovascular disease. Obesity, in which oxidative stress and chronic inflammation plays a role, is a precursor for these diseases. Increased oxidative stress and chronic inflammation are also negatively associated with telomere length (TL). Although many studies have collected information on obesity and TL, few have published on the association between TL and obesity with conflicting results. To resolve whether BMI is truly associated with TL a meta-analysis is set up. We hypothesize that BMI is associated with shorter TL independent of age.

Objectives
Our main objective is to set-up a large scale powerful international study to conduct a comprehensive investigation into the effect of BMI on TL.

Study design
This will be a pooled analysis of data collected from observational studies which collected BMI and TL of adult individuals.

Analysis
Study specific age- and sex-adjusted betas will be combined using a random-effects pooling. Absolute TL (kilo base pairs; kbp) or relative TL (T/S ratio) is outcome measure and BMI (kg/m^2; continuous) is independent variable.
As potential sources of heterogeneity at study level are considered: (1) general factors: ethnicity, (2) factors related to TL measurement: cell type in which telomere length is determined, the technique of telomere length measurement, storage of DNA and (3) factors related to BMI: self reported or measured.
Additionally stratified analysis will be performed by sex and by three age categories (younger than 60 years; between 60 and 75 years; older than 75 years of age). This means that a total of 12 betas will be estimated. For a complete list of variables please see below.
Between study heterogeneity will be estimated by Q and I^2 statistics. Potential sources of heterogeneity will be investigated by meta-regression analysis and via sensitivity analyses.

Outcome measures
The primary outcome will be a pooled estimation of the decrease in kbp TL or T/S ratio per unit BMI.

Time-schedule
By the end of this year we would like to present the first draft.
A first search has taken place in 2011.
A second search is performed in summer 2014.
To be included in the meta-analysis we need the summary statistics or raw data. See next page for information.

Co-authorship
Because of the long list of co-authors, we have decided to include 1 co-author per participating study. This co-author will represent the study group of the participating study and will be recorded as

"name co-author" on behalf of "name group". In pubmed and on the CV this will be regarded as a regularly co-authorship for all members of the group. The names of the members of the study group will be published online.

Betas (and standard errors (SE) and number of individuals (n))

	Both	Male	Female
All	1	2	3
Age <= 60 years	4	5	6
Age > 60 years and <= 75 years	7	8	9
Age > 75 years of age	10	11	12

X= BMI (kg/m^2)
Y= TL (kbp) or T/S ratio if kbp is not available

Confounders:
Analysis 1: corrected for sex (male/female) and age (years)
Analyses 2 and 3: corrected for age (years)
Analysis 4, 7 and 10: corrected for sex (male/female)

If the design is a(n)
Case-control study: only raw data or summary statistics of the controls is needed.
Intervention study: only raw data or summary statistics at baseline of participants is needed.

List of variables
If you prefer to send the raw data, please include the variables listed below.
If you prefer to send the summary statistics, please indicate how the variables mentioned below are collected in your study.

TL	Absolute TL length kilo base pairs kbp T/S ratio if absolute TL length not available	
BMI	kg/m^2	
BMI report	0= measured; 1= self reported	
Age continuous	years	
Age categories	0= <= 60 years 1= > 60 years and <= 75 years 2= above 75 years of age	
Sex	0= male 1= female	
Ethnicity	Summary statistics: Percentage White Percentage Black Percentage Asian Percentage Hispanic	Raw data: 0= White 1= Black 2= Asian 3= Hispanic
Cell type	0= Leucocytes/whole blood/buffy coat 1= PBMC (Peripheral Blood Mononuclear cells) 2= Lymphocytes 3= Granulocytes 4= Monocytes	
TL measure	0= Southern Blood RF 1= Real time PCR 2= Flow Fish 3=fluorescent 4= other	

DNA	0= stored before TL measurement 1= not stored before TL measurement
Study ID	Please provide the name/acronym under which your study should be quoted in manuscript or table.