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ASSOCIATION AMONG STATIN, TELOMERE LENGTH AND CARDIOVASCULAR DISEASES

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ABSTRACT

***Background**: Recent evidence has shown associations between cardiovascular diseases (CVDs) and telomere length (TL). Many factors affect telomerase activity (TA) and TL, and statin was recently found to be associated with TA and TL. This systematic review and meta-analysis was conducted to summarize the evidence on the effect of statin on TA and TL, and update the knowledge of association between TL and CVDs. Primary objective is to determine the effect of statin on TA and TL; Secondary objective, to assess the associations between TL and CVDs.*
***Methods:** The MEDLINE and Scopus databases were searched to identify eligible studies and extracted data. Meta-analysis was done to see effects of statin on TA/TL [i.e., standardized/unstandardized mean difference (SMD/USMD)] and TL on CVDs using random-effects and fixed-effects model according to heterogeneity assessed by Q test and I^2.*
***Results:** Five and 18 studies were selected for the primary and secondary objectives, respectively. Pooled TA showed effect of statin on TA with SMD [95% confidence interval (CI)] of 1.90 (1.16, 2.64) TA. However, no significant effect on TL was seen. Increased risk of CHD among participants with shorter TL was estimated by a pooled risk ratio of 1.58 (1.19, 2.09). However, pooled hazard ratios (HRs) for CHD and stroke were non-significant; but shorter TL was significantly increased risk for unspecified CVDs with pooled HR of 1.33 (1.04, 1.70).*
***Conclusions:** Our study showed association between statin and TA, but not for TL. In addition, shorter TL is more likely to be higher risk for CHD and unspecified CVDs. However, results were still inconclusive based on different pooled parameters. More studies are required to confirm the association of statin with TL, possibly to elucidate its protective effect on CVDs.*

***Key words**: Telomere, Telomerase, Statin, Cardiovascular diseases*

INTRODUCTION

Cardiovascular diseases (CVDs) comprise diseases of the heart, blood vessels and the vascular diseases of the brain, and coronary heart disease (CHD) and stroke represent approximately 80% of the CVDs [1]. Apart from many risk factors of CVDs [2], recent evidence has shown the association of shorter telomere length (TL) with CVDs [3].

Telomeres located at the ends of eukaryotic chromosomes provide chromosomal stability, whereas telomerase maintains the telomere length [4]. Apart from many factors maintaining TL and telomerase activity (TA) [5], recent evidence suggested statin to be one factor [6-10].

In 2014, a systematic review and meta-analysis by Haycock et al. showed inverse association between leucocyte TL and risk of CHD independent of vascular risk factors [11]. A recent meta-analysis in 2018 by Jin et al. reported the inverse association between TL and stroke [12]. Few studies have been done to determine statin's effect on TL and TA, and a systematic review and meta-analysis has not been conducted yet.

Therefore, a systematic review and meta-analysis was conducted with 2 objectives: primary objective, to see the treatment effects of statin on TA and TL; and secondary objective, to update on the previous knowledge of TL's relationship with CVDs.

METHODOLGY

Selection of studies

This study was reported according to PRISMA statement guidelines for systematic review and meta-analysis [13]. Studies were identified from MEDLINE and Scopus databases, and reference lists from inception to December 31st, 2018. The search strategy was presented in Table 1.

Two reviewers independently selected studies using following inclusion criteria: studied in humans, either reported association effect of statin on TA or TL, or effect of TL on CVDs (e.g., CHD, stroke, and unspecified CVDs). Multiple publications of the same original research, studies with insufficient data for pooling, or publications which the reviewers could not translate were excluded.

A total of 612 articles for the primary objective and 3706 for the secondary objective were identified from MEDLINE and Scopus. Five and 18 studies were selected for the primary and secondary objectives, respectively (Fig. 1 and 2).

Among primary objective studies, 2 were randomized controlled trials (RCTs) and 3 were cross-sectional studies. Two studies each assessed effect of statin on TL and TA, however one study assessed effect on both TL and TA (see Table 2).

Secondary objective studies consisted of 16 cohort and 2 case-control studies. There were 9, 4, and 9 CHD, stroke, and unspecified CVDs outcomes, respectively, with different outcome measures (see Table 3).

Table 1. Search strategy in MEDLINE via PubMed and Scopus

Domain(s)	**MEDLINE via PubMed**		**Scopus**	
	Search number	**Search terms**	**Search number**	**Search terms**
Primary objective				
Exposure	#1	"Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]	#1	"Hydroxymethylglutaryl-COA reductase inhibitor"
	#2	"Hydroxymethylglutaryl-CoA Reductase Inhibitors"	#2	"HMG COA reductase inhibitor"

Domain(s)		MEDLINE via PubMed		Scopus
	#3	"Hydroxymethylglutaryl-CoA Reductase Inhibitor"	#3	*statin
	#4	"HMG CoA Reductase Inhibitor"	#4	statins
	#5	"HMG CoA Reductase Inhibitors"	#5	#1 OR #2 OR #3 OR #4
	#6	Search*statin		
	#7	statins		
	#8	atorvastatin		
	#9	simvastatin		
	#10	fluvastatin		
	#11	lovastatin		
	#12	pravastatin		
	#13	pitavastatin		
	#14	rosuvastatin		
	#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14		
Outcomes	#16	telomer*	#6	"Telomer*"
	#17	"chromosome length"	#7	"chromosome length"
	#18	"chromosomal length"	#8	"chromosomal length"
	#19	"T/C ratio"	#9	"T/S Ratio "
	#20	"T/C ratios"	#10	"T/C Ratio"
	#21	"T/S ratio"	#11	#6 OR #7 OR #8 OR #9 OR #10
	#22	"T/S ratios"		
	#23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22		
Exposure and outcomes	#24	#15 AND #23	#12	#5 AND #11
Secondary objective				
Exposure	#1	telomer*	#1	"Telomer*"
	#2	"chromosome length"	#2	"chromosome length"
	#3	"chromosomal length"	#3	"chromosomal length"
	#4	"T/C ratio"	#4	"T/S Ratio "
	#5	"T/C ratios"	#5	"T/C Ratio"
	#6	"T/S ratio"	#6	#1 OR #2 OR #3 OR #4 OR #5
	#7	"T/S ratios"		
	#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7		
Outcomes	#9	"cardiovascular diseases"[MeSH Terms]	#7	Cardiovascular
	#10	"cardiovascular diseases"	#8	Myocardial

Domain(s)		MEDLINE via PubMed		Scopus
	#11	"cardiovascular disease"	#9	Coronary
	#12	myocardial	#10	Hypertension
	#13	coronary	#11	"Heart attack"
	#14	"coronary artery disease"	#12	Stroke
	#15	stroke	#13	Cerebrovascular
	#16	hypertension	#14	"Brain vascular accident"
	#17	"heart attack"	#15	"Brain Ischemia"
	#18	cerebrovascular	#16	"Brain Ischaemia"
	#19	"cerebrovascular disorders"[MeSH Terms]	#17	"Ischemic Encephalopathy"
	#20	"brain vascular accident"	#18	"Ischaemic Encephalopathy"
	#21	"brain ischemia"	#19	Apoplexy
	#22	"brain ischaemia"	#20	"Intima media thickness"
	#23	"ischaemic encephalopathy"	#21	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
	#24	"ischemic encephalopathy"		
	#25	apoplexy		
	#26	"intima media thickness"		
	#27	#9 #10 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR#26		
Exposure and outcomes	#28	#8 AND #27	#22	#6 AND #21

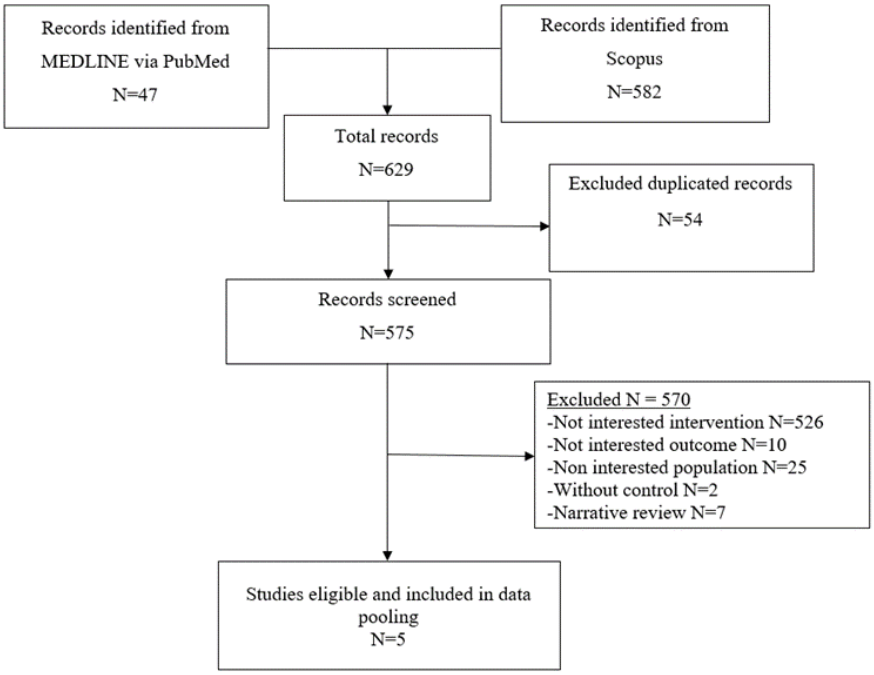


Figure 1. Flow chart of study selection for primary objective

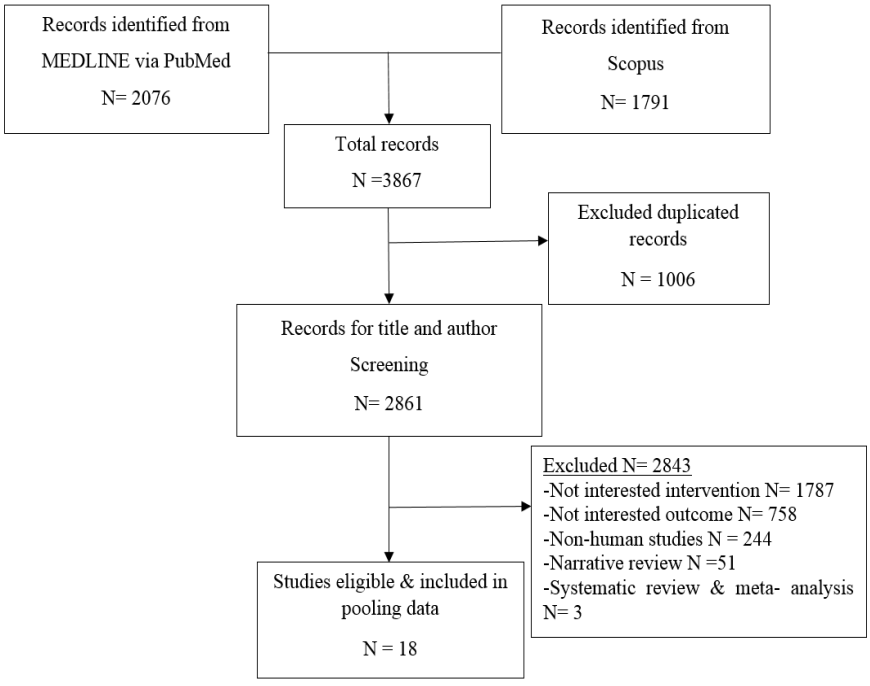


Figure 2. Flow chart of study selection for secondary objective

Table 2. Characteristics of included studies for primary objective

Author (Year)	Country	Setting	NOS Quality	Cochrane RoB 2.0 Assessment	Study Design	No. of Participants	Outcome	Mean Age (years)	Male %
Saliques [8] (2011)	France	Hospital	Good	n/a	Cross-sectional	278	TL,TA	65.05	75.18
Boccardi [6] (2013)	Italy	Hospital	Good	n/a	Cross-sectional	230	TL	64	54.34
Strazhesko [9] (2016)	Russia	Community	n/a	Low RoB	RCT	82	TA	55.58	32.92
Janic [7] (2016)	Slovenia	Hospital	n/a	Low RoB	RCT	50	TA	-	100
Tran [10] (2018)	USA	Community	Good	n/a	Cross-sectional	3496	TL	54.66	48.42

NOS, Newcastle-Ottawa scale; RoB, Risk of Bias.

Table 3. Characteristics of studies for secondary objective

Author (Year)	Country	Setting	NOS quality	Study Design	No. of Participants	Outcome	Cut-Off	Mean Age (yrs.)	Male %
Carty [14](2015)	USA	Community	Poor	Case control	1525	CHD	S vs L Quartile	64.4	0
Cawthon [15] (2003)	USA	Community	Fair	Cohort	143	CHD	25th Centile	-	50.34
Brouliette [16] (2007)	Scotland	Community	Fair	Case-control	1542	CHD	S vs L Tertile	56.76	100
Stefler [17] (2018)	Russia	Community	Good	Cohort	1144	CHD, Stroke, Uns. CVD	S vs L Tertile	57.50	46.5
Madrid [18] (2016)	Denmark	Community	Good	Cohort	62966	CHD	S vs L Quartile	57.28	44.75
Mwasongwe [19] (2017)	USA	Community	Good	Cohort	2518	CHD, Stroke	S vs L Quartile	55.25	38.36
Osthus [20] (2017)	Norway	Community	Good	Cohort	995	CHD	S vs L Tertile	70.9	51.79
Ye [21] (2013)	USA	Community	Poor	Cohort	1917	CHD	S vs L Tertile	46.53	49

Author (Year)	Country	Setting	NOS quality	Study Design	No. of Participants	Outcome	Cut-Off	Mean Age (yrs.)	Male %
Weischer [22] (2012)	Denmark	Community	Good	Cohort	19838	CHD	S vs L Quartile	57.60	51.88
Fitzpatrick [23] (2011)	USA	Community	Good	Cohort	1136	Stroke	S vs L Quartile	-	39.5
Ellohoj [24] (2016)	Denmark	Community	Good	Cohort	1397	Stroke, Uns. CVD	S vs L Tertile	44	53
Williet [25] (2010)	Italy	Community	Good	Cohort	800	Uns. CVD	S vs L Tertile	62.7	49.4
Epel [26] (2008)	USA	Community	Fair	Cohort	236	Uns. CVD	S vs L Half	73.7	49.15
Martin-Ruiz [27] (2005)	Netherlands	Community	Fair	Cohort	598	Uns. CVD	S vs L Tertile	89.73	27.09
Yuan [28] (2018)	Sweden	Hospital	Good	Cohort	247	Uns. CVD	S vs L Tertile	70.8	100
Baragetti [29] (2015)	UK	Hospital	Good	Cohort	768	Uns. CVD	Median		39.84
Hammadah [30] (2017)	USA	Hospital	Poor	Cohort	566	Uns. CVD	25th percentile	63	76
Needham [31] (2015)	USA	Community	Good	Cohort	3091	Uns. CVD	S vs L Quartile	-	52

NOS, Newcastle-Ottawa scale; Uns. CVD, Unspecified CVD; S vs L, shortest vs longest.

Data extraction and risk of bias assessment

Data extraction was performed independently by 2 reviewers using a standardized data extraction form. Statin as the exposure could be atorvastatin, pitavastatin, pravastatin, rosuvastatin, lovastatin, simvastatin, or fluvastatin with any dosage and duration. TL and TA outcomes could be in any unit. Shorter and longer TL, as categorical data, were extracted as reported by the primary studies. The CVD outcomes were categorized as CHD and stroke, or unspecified CVDs when CHD or stroke was not specified or both were combined. Risk of bias was assessed using Newcastle Ottawa Scale (NOS) for cohort [32], case-control [33], and cross-sectional studies [34], and revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [35]. Disagreements were resolved after discussion with the advisors of this study (A.T., S.R., and K.T.).

Statistical analysis

Direct meta-analysis was done using fixed-effect model when there was low heterogeneity; otherwise random-effects model was used. Cochrane Q test and I^2 statistic were used to assess the heterogeneity of each pooling, which was considered low when *P* from Cochrane Q test was <0.1 and I^2 was <25%. For primary objective, unstandardized mean difference (USMD) in kilobase for TL outcome [36] and standardized mean difference (SMD) for TA in different units between statin users and non-users were estimated using random-effects model. For secondary objective, risk ratios (RR) and hazard ratios (HR) of shorter TL (compared to longer TL) for CHD and unspecified CVDs were pooled using random-effects

model, and HRs for stroke were pooled using fixed–effect model. Publication bias was assessed by funnel plot and Egger's test, and contour-enhanced funnel plot if necessary.

All analyses were performed using Stata version 15.0. Two-sided $P<0.05$ was considered statistically significant, except for heterogeneity where $P<0.1$ was used.

RESULTS

Effect of Statin on TL and TA

The 2 RCTs had low risk of bias and all the 3 cross-sectional studies were of good quality by NOS (see Table 2). No effect of statin on TL was seen, whereas higher TA [SMD (95% confidence interval): 1.90 (1.16, 2.64)] was observed in statin users (see Fig. 3 and Table 4).

Table 4. Summary of direct meta-analysis results (mean difference) of statin's effect on TL and TA

Outcome (statin users vs non-users)	No. of studies pooled	Mean difference	95% CI lower limit	95% CI upper limit
USMD in TL(kb)	3	-0.001	-0.048	0.047
SMD in TA	3	1.898	1.156	2.641

Mean difference indicates the pooled unstandardized or standardized mean difference as described in the outcome column.

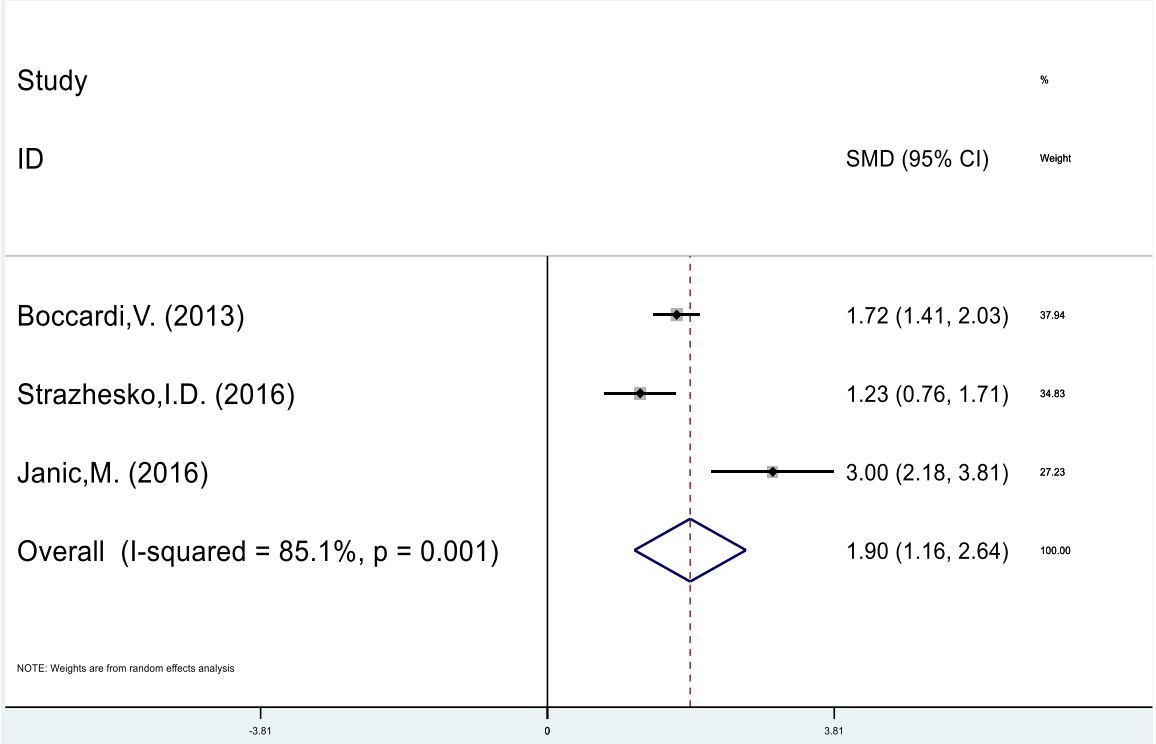


Figure 3. Forest plot of studies showing statin's effect on TA

Association between TL and CVDs

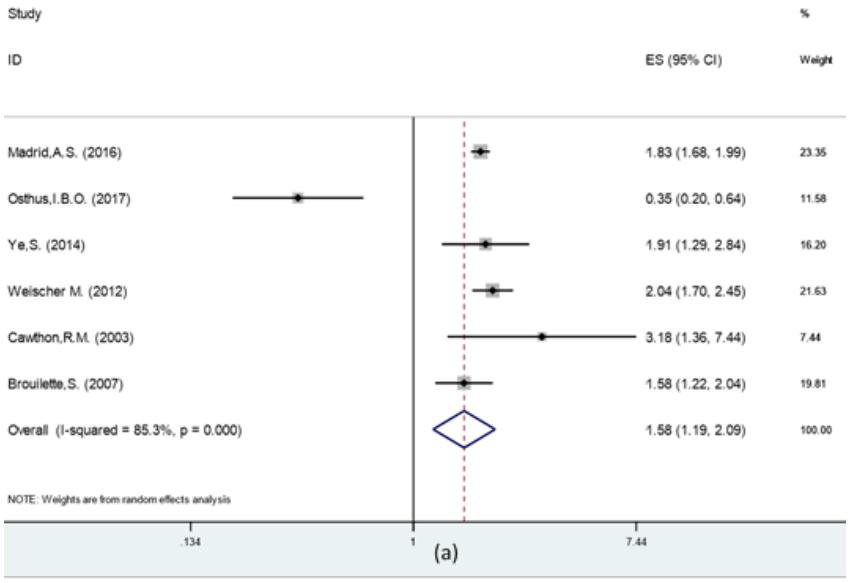
The majority (69%) of the cohort studies had good quality, whereas 3 [15, 26, 27] and 2 [21, 30] studies had fair and poor quality, respectively. One [16] of the 2 case-control studies was of fair and the other [14] was of poor quality (see Table 3).

Increased risk of CHD by 58% was observed in participants with shorter TL compared to longer TL [RR: 1.58 (1.19, 2.09)]. Meanwhile, pooled HRs for CHD and stroke were non-significant. In addition, increased risk of unspecified CVDs was observed among people with shorter TL compared to longer TL [HR: 1.33 (1.04, 1.70)] (see Fig. 4 and Table 5). Publication bias was absent in all poolings.

Table 5. Summary of direct meta-analysis results (RR/HR/OR) of association between telomere length and cardiovascular diseases

Outcome	Point estimate	95% CI lower limit	95% CI upper limit
Risk for CHD			
RR [shorter vs longer TL(R)]	1.578	1.193	2.087
HR [shorter vs longer TL(R)]	1.070	0.870	1.310
Risk for stroke			
HR [shorter vs longer TL(R)]	1.255	0.961	1.640
Risk for unspecified CVDs			
HR [shorter vs longer TL(R)]	1.329	1.040	1.697

(R), reference group. Point estimate indicates the pooled RR or HR as specified in the outcome column.



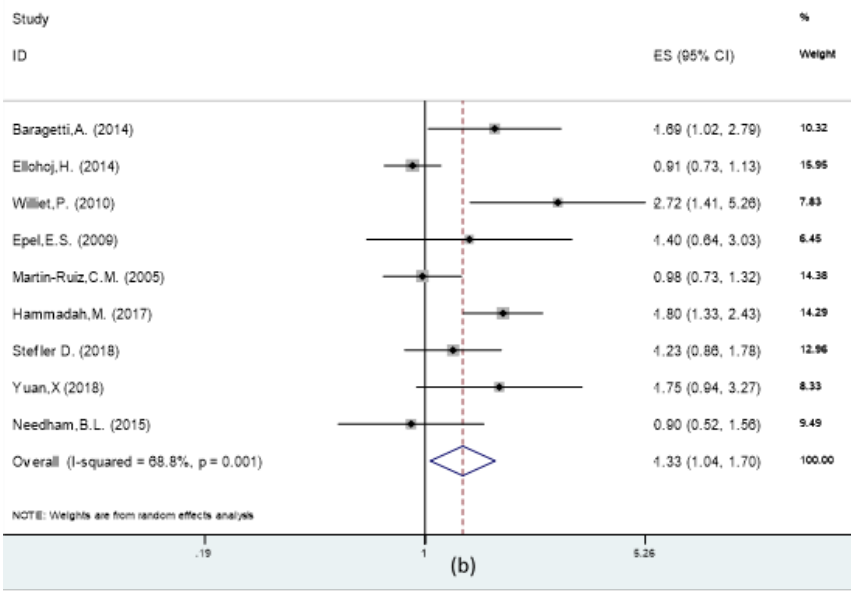


Figure 4. Forest plot of study outcomes in participants with shorter TL; (a) CHD (RRs) and (b) unspecified CVDs(HRs)

DISCUSSION

Reactive oxygen species can harm telomeres causing shortening of TL [37, 38]. Statin has been found to maintain TA [6, 7, 9], which in turn preserves TL [38-41]. Our study showed significant effect of statin on TA, but not on TL. Thus, the relationships among statin, TA, and TL might not be straightforward and other factors might also be involved. However, as we were only able to pool 3 studies for each of the TL and TA outcomes, future studies should help to contribute more to this knowledge of effects of statin on TL and TA.

For TL and CVDs, shorter TL was shown in our study to be associated with CHD and unspecified CVDs, but not with stroke. The association between shorter TL and CHD was consistent with the report by Haycock et al. in 2014 [3], but the non-significant pooled HR between shorter TL and stroke found in our study was inconsistent with the significant pooled odds ratio (OR) from the meta-analysis by Jin et al. in 2018 [12]. This was probably due to the different designs of studies as well as different measures of association (i.e., HR vs OR) used in each meta-analysis.

Our results provided insights into the associations between statin, TL, and CVDs, and may contribute to the prevention of CVDs. However, there were only 4 laboratories certified in measuring TL for the public in USA by 2017. Apart from the rare telomere syndromes, shorter TL has only been found to be related to greater risk for CVDs and it is not clear how the TL of an individual means to his/her health [42]. Thus, it may be too early to consider TL as a predictor for CVDs.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis to study the effect of statin on TL or TA. The effect of shortened TL on unspecified CVDs from our study also adds to the findings on CHD from previous systematic reviews. The fact that the effect of statin on TA was pooled from different study

designs, and that TA was measured in different units necessitating the pooling of data based on SMD, which was difficult to interpret, were our limitations.

CONCLUSION

Our study has shown the effect of statin on TA, but not on TL. In addition, shorter TL has been found to be associated with higher risk for CHD and unspecified CVDs. However, the results were still inconclusive based on different pooled parameters. Due to the small number of studies used in meta-analysis, further studies are required to clarify the association of statin with TL, as well as the utility of TL in predicting CVDs in clinical practice.

CONFLICT OF INTEREST: none

REFERENCES

1. *Global atlas on cardiovascular disease prevention and control*. 2011.
2. Mendis, S., P. Puska, and B. Norrving, *Global atlas on cardiovascular disease prevention and control*. 2011: World Health Organization.
3. Haycock, P.C., et al., *Leucocyte telomere length and risk of cardiovascular disease: Systematic review and meta- Analysis.* BMJ (Online), 2014. **349**.
4. Blackburn, E.H., *Switching and signaling at the telomere.* Cell, 2001. **106**(6): p. 661-673.
5. Fyhrquist, F., O. Saijonmaa, and T. Strandberg, *The roles of senescence and telomere shortening in cardiovascular disease.* Nat Rev Cardiol, 2013. **10**(5): p. 274-83.
6. Boccardi, V., et al., *A new pleiotropic effect of statins in elderly: modulation of telomerase activity.* Faseb j, 2013. **27**(9): p. 3879-85.
7. Janic, M., et al., *Low-Dose Fluvastatin and Valsartan Rejuvenate the Arterial Wall Through Telomerase Activity Increase in Middle-Aged Men.* Rejuvenation Res, 2016. **19**(2): p. 115-9.
8. Saliques, S., et al., *Circulating leukocyte telomere length and oxidative stress: a new target for statin therapy.* Atherosclerosis, 2011. **219**(2): p. 753-60.
9. Strazhesko, I.D., et al., *Atorvastatin Therapy Modulates Telomerase Activity in Patients Free of Atherosclerotic Cardiovascular Diseases.* Front Pharmacol, 2016. **7**: p. 347.
10. Tran, P.T., A.K. Meeker, and E.A. Platz, *Association between statin drug use and peripheral blood leukocyte telomere length in the National Health and Nutrition Examination Survey 1999-2002: a cross-sectional study.* Ann Epidemiol, 2018.
11. Haycock, P.C., et al., *Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis.* Bmj, 2014. **349**: p. g4227.
12. Jin, X., et al., *Relationship between short telomere length and stroke: A meta-analysis.* Medicine (Baltimore), 2018. **97**(39): p. e12489.
13. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Annals of internal medicine, 2009. **151**(4): p. 264-269.
14. Carty, C.L., et al., *Leukocyte telomere length and risks of incident coronary heart disease and mortality in a racially diverse population of postmenopausal women.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2015. **35**(10): p. 2225-2231.
15. Cawthon, R.M., et al., *Association between telomere length in blood and mortality in people aged 60 years or older.* Lancet, 2003. **361**(9355): p. 393-5.
16. Brouilette, S.W., et al., *Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study.* Lancet, 2007. **369**(9556): p. 107-114.
17. Stefler, D., et al., *Leukocyte telomere length and risk of coronary heart disease and stroke mortality: prospective evidence from a Russian cohort.* Scientific reports, 2018. **8**(1): p. 16627.
18. Madrid, A.S., et al., *Short telomere length and ischemic heart disease: Observational and genetic studies in 290 022 individuals.* Clinical Chemistry, 2016. **62**(8): p. 1140-1149.
19. Mwasongwe, S., et al., *Leukocyte telomere length and cardiovascular disease in African Americans: The Jackson Heart Study.* Atherosclerosis, 2017. **266**: p. 41-47.
20. Osthus, I.B.O., et al., *Association of Telomere Length With Myocardial Infarction: A Prospective Cohort From the Population Based HUNT 2 Study.* Prog Cardiovasc Dis, 2017. **59**(6): p. 649-655.
21. Ye, S., et al., *Relation between leukocyte telomere length and incident coronary heart disease events (from the 1995 Canadian Nova Scotia Health Survey).* American Journal of Cardiology, 2013. **111**(7): p. 962-967.
22. Weischer, M., et al., *Short telomere length, myocardial infarction, ischemic heart disease, and early death.* Arterioscler Thromb Vasc Biol, 2012. **32**(3): p. 822-9.
23. Fitzpatrick, A.L., et al., *Leukocyte telomere length and mortality in the cardiovascular health study.* Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 2011. **66 A**(4): p. 421-429.
24. Ellehoj, H., L. Bendix, and M. Osler, *Leucocyte Telomere Length and Risk of Cardiovascular Disease in a Cohort of 1,397 Danish Men and Women.* Cardiology (Switzerland), 2016. **133**(3): p. 173-177.

25. Willeit, P., et al., *Cellular aging reflected by leukocyte telomere length predicts advanced atherosclerosis and cardiovascular disease risk.* Arterioscler Thromb Vasc Biol, 2010. **30**(8): p. 1649-56.
26. Epel, E.S., et al., *The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men.* Aging (Albany NY), 2008. **1**(1): p. 81-8.
27. Martin-Ruiz, C.M., et al., *Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: A population-based study.* Aging Cell, 2005. **4**(6): p. 287-290.
28. Yuan, X., et al., *Longitudinal changes in leukocyte telomere length and mortality in elderly Swedish men.* Aging (Albany NY), 2018. **10**(10): p. 3005.
29. Baragetti, A., et al., *Telomere shortening over 6 years is associated with increased subclinical carotid vascular damage and worse cardiovascular prognosis in the general population.* Journal of Internal Medicine, 2015. **277**(4): p. 478-487.
30. Hammadah, M., et al., *Telomere shortening, regenerative capacity, and cardiovascular outcomes.* Circulation Research, 2017. **120**(7): p. 1130-1138.
31. Needham, B.L., et al., *Leukocyte Telomere Length and Mortality in the National Health and Nutrition Examination Survey, 1999-2002.* Epidemiology, 2015. **26**(4): p. 528-535.
32. Wells, G., et al., *Newcastle-Ottawa quality assessment scale cohort studies*. 2014.
33. Wells, G., et al., *NewCastle–Ottawa quality assessment scale—case control studies*. 2017.
34. *NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE(adapted for cross sectional studies).*
35. Higgins, J., et al., *Revised Cochrane risk of bias tool for randomized trials (RoB 2.0)*. 2016, Version.
36. Cawthon, R.M., *Telomere measurement by quantitative PCR.* Nucleic acids research, 2002. **30**(10): p. e47-e47.
37. Shammas, M.A., *Telomeres, lifestyle, cancer, and aging.* Current opinion in clinical nutrition and metabolic care, 2011. **14**(1): p. 28.
38. Wang, Z., et al., *Characterization of oxidative guanine damage and repair in mammalian telomeres.* PLoS genetics, 2010. **6**(5): p. e1000951.
39. Haendeler, J., et al., *Antioxidants Inhibit Nuclear Export of Telomerase Reverse Transcriptase and Delay Replicative Senescence of Endothelial Cells.* Circulation Research, 2004. **94**(6): p. 768-775.
40. Chen, J.-w., S.-b. Zhou, and Z.-m. Tan, *Aspirin and pravastatin reduce lectin-like oxidized low density lipoprotein receptor-1 expression, adhesion molecules and oxidative stress in human coronary artery endothelial cells.* Chinese medical journal, 2010. **123**(12): p. 1553-1560.
41. Puccetti, L., et al., *Effects of atorvastatin and rosuvastatin on thromboxane-dependent platelet activation and oxidative stress in hypercholesterolemia.* Atherosclerosis, 2011. **214**(1): p. 122-128.
42. Elissa Epel , E.B. *Background Information and Our Views onTelomere Dynamics and Measurement*. 2017; Available from: http://www.amecenter.ucsf.edu/telomeretesting.