THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 8, 1069–1073
doi:10.1093/gerona/glw053
Advance Access publication April 18, 2016

OXFORD

Research Article

Meta-analysis of Telomere Length in Alzheimer's Disease

Diego A. Forero,[1] Yeimy González-Giraldo,[2] Catalina López-Quintero,[3] Luis J. Castro-Vega,[4] George E. Barreto,[2,5] and George Perry[6]

[1]Laboratory of Neuropsychiatric Genetics, Biomedical Sciences Research Group, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia. [2]Departamento de Nutrición y Bioquímica, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá, Colombia. [3]Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing. [4]INSERM, UMR970, Paris-Cardiovascular Research Center, France. [5]Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile, Santiago, Chile. [6]College of Sciences, University of Texas at San Antonio.

Address correspondence to Diego A. Forero, MD, PhD, Laboratory of NeuroPsychiatric Genetics, School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia. E-mail: diego.forero@uan.edu.co

Received October 7, 2015; Accepted March 1, 2016

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Alzheimer's disease (AD) is a common and severe neurodegenerative disorder. Human telomeres are fundamental for the maintenance of genomic stability and play prominent roles in both cellular senescence and organismal aging. Regulation of telomere length (TL) is the result of the complex interplay between environmental and genetic factors. Alterations in TL are increasingly being studied as a possible risk factor for AD, and published studies on TL in AD show discrepant results, highlighting the need for a meta-analysis.

Methods: In the current study, we carried out a meta-analysis of published studies of TL in AD patients and healthy controls. PubMed, Web of Science and Google Scholar databases (from inception to September 2015) were used to identify relevant articles reporting TL in humans with AD, from which we retrieved data such as sample size, experimental methods, and mean TL for cases and controls. A random-effects model was used for meta-analytical procedures.

Results: The meta-analysis included 13 primary studies and demonstrated a significant difference in TL between 860 AD patients and 2,022 controls, with a standardized mean difference of −0.984 (confidence interval: −1.433 to −0.535; *p* value: <.001).

Conclusions: Our results show a consistent evidence of shorter telomeres in AD patients and highlight the importance of the analysis of epigenomic markers associated with neurodegeneration and with the risk for common and severe neurological diseases, such as AD.

Keywords: Dementia—Epigenomics—Telomeres—Alzheimer's disease—Meta-analysis

Introduction

Alzheimer's disease (AD) is a common and severe neurodegenerative disorder (1). Genomic studies have identified several causal genes for hereditary subtypes of AD (such as *APP*, *PSEN1*, and *PSEN2*) and susceptibility genes for its multifactorial forms (such as *APOE*, *CLU*, and *CR1*) (1,2). Several theories about the etiology and pathophysiology of AD have been developed, which highlight the importance of mechanisms involved in the response to cell-intrinsic and cell-extrinsic stresses and of alterations in neural plasticity (1,3).

Human telomeres are ribonucleoprotein structures that consist of a repetitive DNA sequence (TTAGGG) and a core of associated proteins called shelterin. The capping function of telomeres at the extremities of chromosomes is fundamental for the maintenance of genomic stability (4). Compelling evidence has shown that telomere shortening leads to cellular senescence and is also present with aging in several organisms. In fact, alterations in telomere length (TL) have been reported as critical factors in age-related diseases, including cancer and neurodegenerative disorders (4). Regulation of TL is the result of the interplay between multiple environmental and genetic factors. For instance, it has been suggested that telomere maintenance mechanisms play an important role in the response and plasticity of postmitotic neurons to oxidative and genomic stress (4,5). TL is increasingly being studied as a possible epigenomic marker associated with several neuropsychiatric disorders, such as AD, Parkinson's disease, vascular dementia, unipolar depression, bipolar disorder, and schizophrenia, among others (6).

Results from published studies for TL in AD are contradictory (7,8), highlighting the need for a meta-analysis. In the current study, we carried out a meta-analysis of published studies for TL, which compared DNA samples of AD patients with samples from healthy controls.

Methods

We followed the recommendations of the PRISMA statement (9) for reporting of meta-analyses (Supplementary Figure S1). There was no previously published review protocol. We searched for original studies analyzing TL in AD patients and control participants in the PubMed, Web of Science, and Google Scholar databases (from inception to September 2015). We combined disease search terms "Alzheimer's disease" and "telomere." In addition, we searched reference lists of relevant review and original papers to identify additional papers not covered by the electronic search of abstracts.

We included articles published in English in peer-reviewed journals that described results from case–control studies analyzing the association of TL with AD in different ethnic populations. Exclusion criteria were as follows: lack of control groups, analysis of other types of dementia, or studies of telomerase activity.

We extracted the following information from each one of the included studies: year, country, sample size, age and gender distributions, criteria used for AD diagnosis, disease severity and duration, cell types used for DNA extraction, methodologies used for the analysis of TL, and TL data (mean and *SD*) for patient and control groups. In cases of missing data, we contacted the corresponding authors to ask TL data that were not available in the main text of the articles or in the Supplementary Material. Quality assessment of included studies was carried out with a modified version of the Newcastle-Ottawa Quality Assessment Scale, as proposed by Colpo and coworkers (10) for meta-analyses of case–control studies of TL. This scale evaluates three dimensions (selection, comparability, and exposure), for a possible maximum of seven points. Study selection and data extraction and synthesis were performed and checked by two independent investigators.

For the meta-analysis procedures, we used the freely available Meta-Analyst program (11). It is a cross-platform software that allows the analysis of case–control association studies and other advanced approaches (eg, implementation of random-effects models, sensitivity analysis, and generation of forest plots). Following recommendations in the area, we used random-effects models and calculated the I^2 statistic for heterogeneity (12). Standardized mean differences were used as the main index of effect sizes in these meta-analyses. Subgroup analyses were carried out for age at examination of the samples, for methods used for TL measurement, and for cell types employed for DNA extraction (Supplementary Table S1); a sensitivity analysis was carried out with the leave-one-out method.

Results

Thirteen primary studies were included in the current meta-analysis for AD (7,8,13–21). It was not possible to include two additional studies, which did not provide TL data (22,23) (Supplementary Figure S1). The majority of the studies used the NINCDS-ADRDA criteria for the diagnosis of AD and few reported data for disease duration and severity. A quality assessment of included studies showed that several articles did not report information on selection of participants and their comparability (Supplementary Table S2). No studies were excluded due to the results of the quality assessment. Details of included studies are provided in Table 1 and

Table 1. Details of the Original Studies Included in the Meta-analysis for Telomere Length and Alzheimer's Disease

Author, Year	PMID	Country	Sample Size	% Male	Mean Ages	Tissue	Method	TL Patients	TL Controls	Finding
Tedone, 2015	26402514	Italy	31/20	32/50	81/79	PBMC	Flow citometry	2.1 ± 0.5	2.3 ± 0.4	Similar
Kota, 2015	25541866	India	57/55	49/47	65/65	Leukocytes	qPCR multiplex	0.6 ± 0.58	1.0 ± 0.6	Shorter
Mathur, 2014	24121960	Canada	41/41	46/46	76/74	Buccal cells	3D QFISH	6.227 ± 0.743	7.590 ± 0.165	Shorter
Guan, 2012	21912072	Japan	40/59	48/51	70/70	Leukocytes	TRF	8.09 ± 1.34	8.93 ± 2.24	Similar
Takata, 2012	22016362	Japan	74/35	32/40	79/80	Leukocytes	qPCR multiplex	0.754 ± 0.13	0.793 ± 0.13	Similar
Hochstrasser, 2012	22178633	Austria	18/14	22/46	75/72	Monocytes	TRF	6.6 ± 0.2	7.3 ± 0.2	Shorter
Movérare-Skrtic, 2012	22210159	Sweden	32/20	47/50	75/75	Leukocytes	qPCR monoplex	NR	NR	Similar
Honig, 2012	22825311	United States	314/1,469	26/33	84/77	Leukocytes	qPCR monoplex	6.13 ± 0.79	6.43 ± 0.86	Shorter
Zekry, 2010	20709332	Switzerland	80/204	NR	NR	Lymphocytes	Flow citometry	NR	NR	Similar
Lukens, 2009	19896585	United States	29/22	27/50	80/80	Cerebellum	qPCR monoplex	0.799 ± 0.21	0.736 ± 0.33	Similar
Thomas, 2008-1	18242664	Australia	54/26	30/42	80/69	Leukocytes	qPCR monoplex	77.3 ± 32.4	110.3 ± 28.2	Shorter
Thomas, 2008-2	18242664	Australia	54/26	30/42	80/69	Buccal cells	qPCR monoplex	27.4 ± 27.7	40.6 ± 19.2	Shorter
Thomas, 2008-3	18242664	Australia	13/9	38/67	76/74	Brain	qPCR monoplex	176.9 ± 44.4	118.7 ± 49.6	Longer
Franco, 2006	19595878	United States	8/7	38/86	75/70	Neurons	QFISH	0.259 ± 0.048	0.468 ± 0.013	Shorter
Panossian, 2003	12493553	United States	15/15	100/73	73/70	PBMC	TRF	6.22 ± 0.23	7.15 ± 0.37	Shorter

Note: AD = Alzheimer's disease; NR = not reported; PBMC = peripheral blood mononuclear cells; QFISH = quantitative fluorescent in situ hybridization; qPCR = quantitative polymerase chain reaction; TL = telomere length; TRF = terminal restriction fragment method. TL data for AD patients and controls were provided as kilobases (mean and *SD*) for studies based on TRF and as T/S ratios (mean and *SD*) for studies based on qPCR.

Supplementary Table S1, and data for 860 AD patients and 2,022 controls were analyzed. Sample sizes for the AD patient groups in the different studies ranged from less than 20 to more than 300. An important fraction of the studies used genomic DNA extracted from leukocytes and quantitative polymerase chain reaction–based methods for analysis of TL.

We applied random-effects meta-analyses to the available data and a significant difference in TL between AD patients and controls, with a standardized mean difference of −0.984 (confidence interval: −1.433 to −0.535; p value: <.001; Figure 1). There was evidence of heterogeneity (I^2: 91.8%) and a sensitivity analyses (using a leave-one-out method) showed that no single study was responsible for the pooled result of the meta-analysis (Figure 2). A subgroup analysis showed that studies with younger patients (Supplementary Figure S2) and that employed terminal restriction fragment methods (Supplementary Figure S3) showed preliminary evidence for a possible larger effect on shorter telomeres in AD patients and that the significant association was more evident in studies carried out with DNA from leukocytes (Supplementary Figure S4).

Discussion

Although TL has been evaluated as a possible biomarker for AD in several publications, no meta-analysis has been conducted so far to assess the relative importance of such results (6,24). In the current study, we performed a meta-analysis for 13 published studies and found consistent and significant evidence of shorter telomeres in samples from AD patients (p value: <.001). A sensitivity analysis showed that no single study was responsible for those findings and a subgroup analysis showed that the finding of shorter telomeres in AD patients was more evident in studies that were carried out with DNA from leukocytes. This finding from the available cumulative evidence (standardized mean difference of −0.984) is consistent with results from individual studies that reported shorter telomeres in AD patients (7,8,14,17,18,20,21).

Several studies used DNA extracted from leukocytes, taking into account its broad and easy availability for large samples of living patients (25). It will be important to include in future studies DNA extracted from matched pairs of affected and healthy brain tissues. It is possible that the interstudy variability in the TL data shown in Table 1 is given by the use of different approaches for normalization of quantitative polymerase chain reaction results (26). We did not find studies on TL and AD in African, South Eastern Asian, or Latin American countries, populations that have a large burden of neurodegenerative disorders and particular genetic and environmental features (27).

It has been suggested that telomere maintenance mechanisms play an important role in the response and plasticity of postmitotic neurons to oxidative and genomic stress (5,28). It has been shown that the third generation of knockout mice for the telomerase RNA component TERC (G3Terc−/−, which display short telomeres) have reduced neurogenesis in the dentate gyrus, in addition to neuronal loss in hippocampus and frontal cortex and short-term memory dysfunction (29). On other hand, telomere shortening reduced the number of amyloid plaques and reactive microgliosis in APP23 transgenic mice (29). There is also evidence showing that newly generated neurons and mature neurons have low telomerase levels and are more susceptible to the effects of DNA damage (30), that the antidepressant-effect of telomerase overexpression is possibly associated to adult neurogenesis mechanisms (31), and that lithium normalizes telomerase activity (32). As oxidative stress and inflammation are increased in aged individuals, these mechanisms could be related to telomere shortening (6). In AD patients, the shortest telomeres have been associated with high levels of the proinflammatory cytokine tumor necrosis factor-α (8) and there is evidence that markers of oxidative stress are associated with telomere shortening (6). There is evidence showing that microglial cells, rather than postmitotic neurons, undergo replicative senescence. The microglial activation could contribute with the inflammatory microenvironment ultimately promoting disease progression (6).

Finally, emerging evidence suggests that perceived stress and lower physical activity, known risk factors for AD, are associated with shorter telomeres (33,34). King and coworkers (35) identified a significant correlation between leukocyte TL and volume of total brain and specific regions, such as hippocampus. An inverse correlation between leukocyte TL and hippocampal volume was found

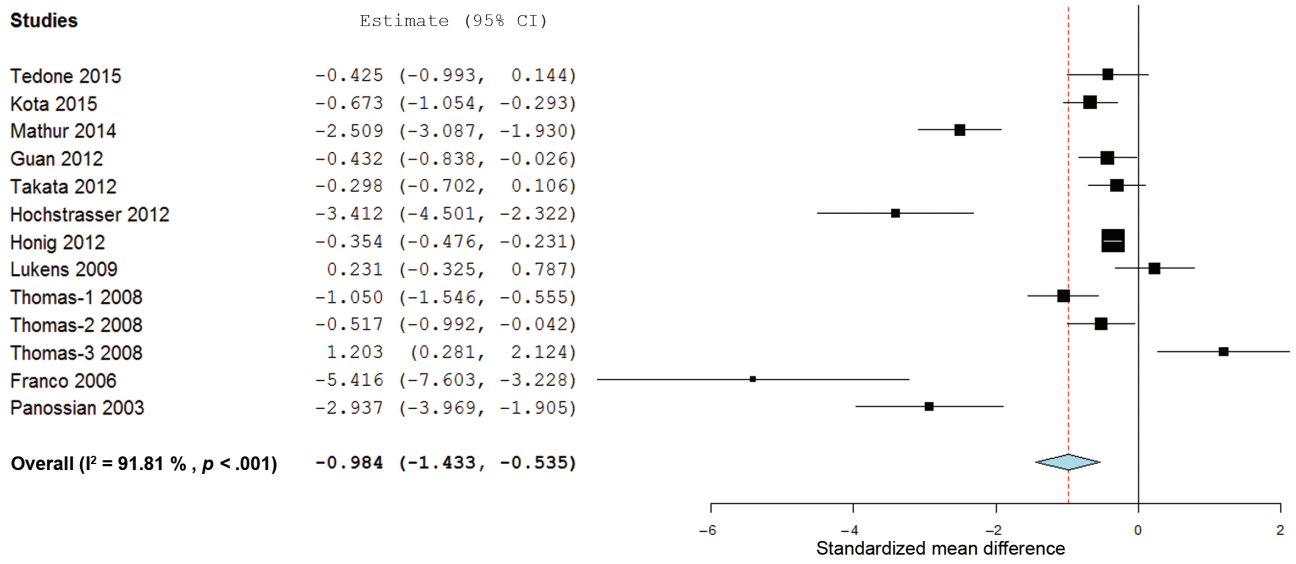

Figure 1. Forest plot for the meta-analysis of telomere length and Alzheimer's disease (AD). p value: <.001, for a random-effects Model. A standardized mean difference below zero means shorter telomeres in AD patients, in comparison with control subjects.

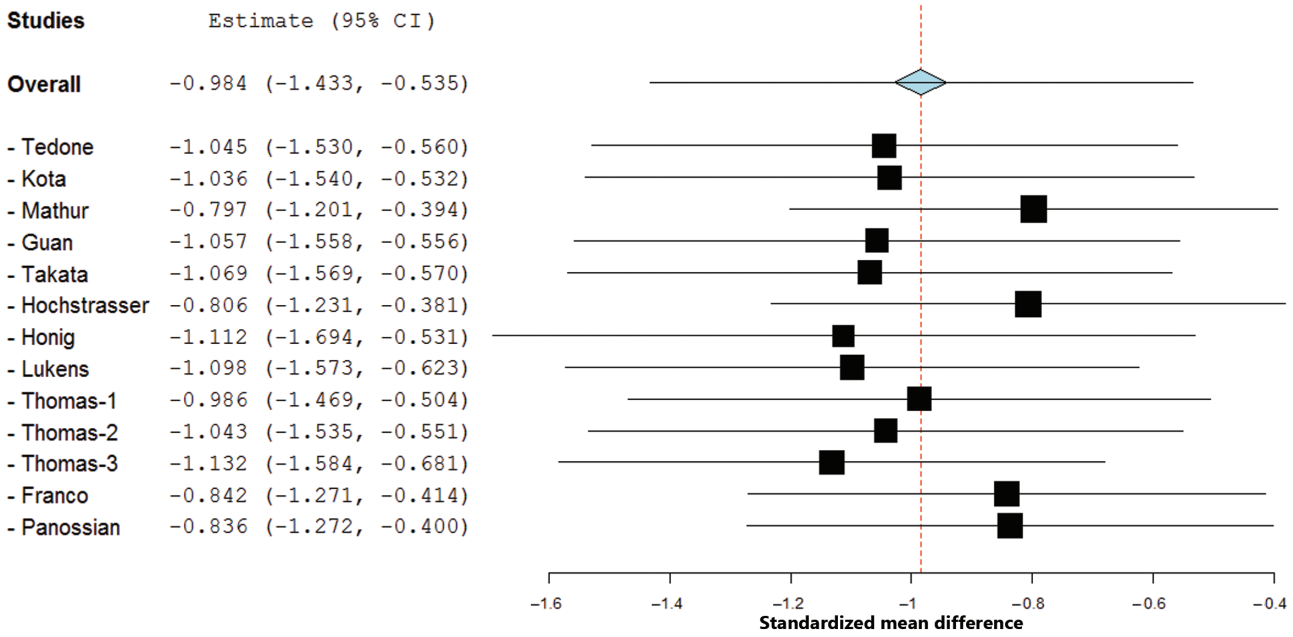

Figure 2. Sensitivity analysis for the meta-analysis of telomere length and Alzheimer's disease.

in nondemented individuals that were *APOE* 3/3 carriers (but not in *APOE* 4 carriers), and it was also found that *APOE* 4 carriers had longer telomeres and a higher attrition rate (36). *APOE* 4 carriers with longer telomeres were associated with worse performance on episodic memory tasks (37). A number of epigenetic factors, such as modifications of DNA methylation in the promoter region of the catalytic subunit of the telomerase enzyme and several noncoding RNAs, are known to have an effect on telomere dynamics (38) and could be related to shorter telomeres in AD patients.

Limitations of the current study include the retrospective nature of our meta-analysis, the inclusion of study-level data, and being underpowered for the subgroup analyses. The strengths of our study involve the inclusion of all published studies with available data for TL and AD and the use of state of the art biostatistical methods for meta-analyses.

Future studies using high-throughput approaches, such as next-generation sequencing, could identify novel genetic and epigenetic factors (39) that influence TL in AD patients and in its presymptomatic stages (40). It would be important to carry out longitudinal studies for TL and AD in multiethnic populations that control for genetic and environmental variables and that include quantitative markers of disease progression.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

Funding

D.A.F. is supported by research grants from Colciencias and VCTI-UAN (grants # 20131079 and 20131080). Y.G.-G. is supported by a PhD fellowship from Centro de Estudios Interdisciplinarios Básicos y Aplicados (CEIBA; Rodolfo Llinás Program). C.L.-Q. is supported by the National Institute on Drug Abuse (grant # T32DA021129, PI: J. Anthony). G.E.B. work is supported by Pontificia Universidad Javeriana. G.P. is supported by a National Institutes of Health grant (G12-MD007591).

Acknowledgments

We thank corresponding authors who contributed with additional data from primary studies that were not available in the original articles.

References

1. Karch CM, Cruchaga C, Goate AM. Alzheimer's disease genetics: from the bench to the clinic. *Neuron*. 2014;83:11–26. doi:10.1016/j.neuron.2014.05.041
2. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39:17–23. doi:10.1038/ng1934
3. Forero DA, Casadesus G, Perry G, Arboleda H. Synaptic dysfunction and oxidative stress in Alzheimer's disease: emerging mechanisms. *J Cell Mol Med*. 2006;10:796–805. doi:10.1111/j.1582-4934.2006.tb00439.x
4. Lindqvist D, Epel ES, Mellon SH, et al. Psychiatric disorders and leukocyte telomere length: underlying mechanisms linking mental illness with cellular aging. *Neurosci Biobehav Rev*. 2015;55:333–364. doi:10.1016/j.neubiorev.2015.05.007
5. Zhang P, Dilley C, Mattson MP. DNA damage responses in neural cells: focus on the telomere. *Neuroscience*. 2007;145:1439–1448. doi:10.1016/j.neuroscience.2006.11.052
6. Eitan E, Hutchison ER, Mattson MP. Telomere shortening in neurological disorders: an abundance of unanswered questions. *Trends Neurosci*. 2014;37:256–263. doi:10.1016/j.tins.2014.02.010
7. Kota LN, Bharath S, Purushottam M, et al. Reduced telomere length in neurodegenerative disorders may suggest shared biology. *J Neuropsychiatry Clin Neurosci*. 2015;27:e92–e96. doi:10.1176/appi.neuropsych.13100240
8. Panossian LA, Porter VR, Valenzuela HF, et al. Telomere shortening in T cells correlates with Alzheimer's disease status. *Neurobiol Aging*. 2003;24:77–84. doi:10.1016/S0197-4580(02)00043-X
9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. doi:10.1371/journal.pmed.1000097

10. Colpo GD, Leffa DD, Köhler CA, Kapczinski F, Quevedo J, Carvalho AF. Is bipolar disorder associated with accelerating aging? A meta-analysis of telomere length studies. *J Affect Disord*. 2015;186:241–248. doi:10.1016/j.jad.2015.06.034
11. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol*. 2009;9:80. doi:10.1186/1471-2288-9-80
12. Sagoo GS, Little J, Higgins JP. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. *PLoS Med*. 2009;6:e28. doi:10.1371/journal.pmed.1000028
13. Tedone E, Arosio B, Colombo F, et al. Leukocyte telomere length in Alzheimer's disease patients with a different rate of progression. *J Alzheimers Dis*. 2015;46:761–769. doi:10.3233/JAD-142808
14. Mathur S, Glogowska A, McAvoy E, et al. Three-dimensional quantitative imaging of telomeres in buccal cells identifies mild, moderate, and severe Alzheimer's disease patients. *J Alzheimers Dis*. 2014;39:35–48. doi:10.3233/JAD-130866
15. Guan JZ, Guan WP, Maeda T, Makino N. Effect of vitamin E administration on the elevated oxygen stress and the telomeric and subtelomeric status in Alzheimer's disease. *Gerontology*. 2012;58:62–69. doi:10.1159/000327821
16. Takata Y, Kikukawa M, Hanyu H, et al. Association between ApoE phenotypes and telomere erosion in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2012;67:330–335. doi:10.1093/gerona/glr185
17. Hochstrasser T, Marksteiner J, Humpel C. Telomere length is age-dependent and reduced in monocytes of Alzheimer patients. *Exp Gerontol*. 2012;47:160–163. doi:10.1016/j.exger.2011.11.012
18. Honig LS, Kang MS, Schupf N, Lee JH, Mayeux R. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol*. 2012;69:1332–1339. doi:10.1001/archneurol.2012.1541
19. Lukens JN, Van Deerlin V, Clark CM, Xie SX, Johnson FB. Comparisons of telomere lengths in peripheral blood and cerebellum in Alzheimer's disease. *Alzheimers Dement*. 2009;5:463–469. doi:10.1016/j.jalz.2009.05.666
20. Thomas P, O'Callaghan NJ, Fenech M. Telomere length in white blood cells, buccal cells and brain tissue and its variation with ageing and Alzheimer's disease. *Mech Ageing Dev*. 2008;129:183–190. doi:10.1016/j.mad.2007.12.004
21. Franco S, Blasco MA, Siedlak SL, et al. Telomeres and telomerase in Alzheimer's disease: epiphenomena or a new focus for therapeutic strategy? *Alzheimers Dement*. 2006;2:164–168. doi:10.1016/j.jalz.2006.03.001
22. Movérare-Skrtic S, Johansson P, Mattsson N, et al. Leukocyte telomere length (LTL) is reduced in stable mild cognitive impairment but low LTL is not associated with conversion to Alzheimer's disease: a pilot study. *Exp Gerontol*. 2012;47:179–182. doi:10.1016/j.exger.2011.12.005
23. Zekry D, Herrmann FR, Irminger-Finger I, et al. Telomere length and ApoE polymorphism in mild cognitive impairment, degenerative and vascular dementia. *J Neurol Sci*. 2010;299:108–111. doi:10.1016/j.jns.2010.07.019
24. Cai Z, Yan LJ, Ratka A. Telomere shortening and Alzheimer's disease. *Neuromolecular Med*. 2013;15:25–48. doi:10.1007/s12017-012-8207-9
25. Aviv A, Valdes AM, Spector TD. Human telomere biology: pitfalls of moving from the laboratory to epidemiology. *Int J Epidemiol*. 2006;35:1424–1429. doi:10.1093/ije/dyl169
26. Elbers CC, Garcia ME, Kimura M, et al. Comparison between southern blots and qPCR analysis of leukocyte telomere length in the health ABC study. *J Gerontol A Biol Sci Med Sci*. 2014;69:527–531. doi:10.1093/gerona/glt121
27. Forero DA, Vélez-van-Meerbeke A, Deshpande SN, Nicolini H, Perry G. Neuropsychiatric genetics in developing countries: current challenges. *World J Psychiatry*. 2014;4:69–71. doi:10.5498/wjp.v4.i4.69
28. Spilsbury A, Miwa S, Attems J, Saretzki G. The role of telomerase protein TERT in Alzheimer's disease and in tau-related pathology in vitro. *J Neurosci*. 2015;35:1659–1674. doi:10.1523/JNEUROSCI.2925-14.2015
29. Rolyan H, Scheffold A, Heinrich A, et al. Telomere shortening reduces Alzheimer's disease amyloid pathology in mice. *Brain*. 2011;134(Pt 7):2044–2056. doi:10.1093/brain/awr133
30. Cheng A, Shin-ya K, Wan R, et al. Telomere protection mechanisms change during neurogenesis and neuronal maturation: newly generated neurons are hypersensitive to telomere and DNA damage. *J Neurosci*. 2007;27:3722–3733. doi:10.1523/JNEUROSCI.0590-07.2007
31. Zhou QG, Hu Y, Wu DL, et al. Hippocampal telomerase is involved in the modulation of depressive behaviors. *J Neurosci*. 2011;31:12258–12269. doi:10.1523/JNEUROSCI.0805-11.2011
32. Wei YB, Backlund L, Wegener G, Mathé AA, Lavebratt C. Telomerase dysregulation in the hippocampus of a rat model of depression: normalization by lithium. *Int J Neuropsychopharmacol*. 2015;18:pyv002. doi:10.1093/ijnp/pyv002
33. Schutte NS, Malouff JM. The relationship between perceived stress and telomere length: a meta-analysis. *Stress Health*. 2014. doi:10.1002/smi.2607
34. Mundstock E, Zatti H, Louzada FM, et al. Effects of physical activity in telomere length: systematic review and meta-analysis. *Ageing Res Rev*. 2015;22:72–80. doi:10.1016/j.arr.2015.02.004
35. King KS, Kozlitina J, Rosenberg RN, Peshock RM, McColl RW, Garcia CK. Effect of leukocyte telomere length on total and regional brain volumes in a large population-based cohort. *JAMA Neurol*. 2014;71:1247–1254. doi:10.1001/jamaneurol.2014.1926
36. Wikgren M, Karlsson T, Lind J, et al. Longer leukocyte telomere length is associated with smaller hippocampal volume among non-demented APOE epsilon3/epsilon3 subjects. *PLoS One*. 2012;7:e34292. doi:10.1371/journal.pone.0034292
37. Wikgren M, Karlsson T, Nilbrink T, et al. APOE epsilon4 is associated with longer telomeres, and longer telomeres among epsilon4 carriers predicts worse episodic memory. *Neurobiol Aging*. 2012;33:335–344. doi:10.1016/j.neurobiolaging.2010.03.004
38. Koziel JE, Fox MJ, Steding CE, Sprouse AA, Herbert BS. Medical genetics and epigenetics of telomerase. *J Cell Mol Med*. 2011;15:457–467. doi:10.1111/j.1582-4934.2011.01276.x
39. Zhan Y, Song C, Karlsson R, et al. Telomere length shortening and Alzheimer disease—a Mendelian randomization study. *JAMA Neurol*. 2015;72:1202–1203. doi:10.1001/jamaneurol.2015.1513
40. Chen W, Kimura M, Kim S, et al. Longitudinal versus cross-sectional evaluations of leukocyte telomere length dynamics: age-dependent telomere shortening is the rule. *J Gerontol A Biol Sci Med Sci*. 2011;66:312–319. doi:10.1093/gerona/glq223