Journal of Affective Disorders 218 (2017) 322–326

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

The association between post-traumatic stress disorder and shorter telomere length: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
PTSD
Telomere
Aging

ABSTRACT

Objective: Post-traumatic stress disorder (PTSD) is a common psychiatric disorder, which may accelerate aging. Many study have investigated the association between telomeres length and PTSD, but results from published studies are contradictory. Therefore, Meta-analysis approaches were conducted to give more precise estimate of relationship between telomere length and PTSD.

Method: We systematically reviewed the databases of PUBMED, PsycINFO, Medline(Ovid SP) and EMBASE for all articles on the association between telomere length and PTSD. Data were summarized by using random-effects in the meta-analysis. The heterogeneity among studies were examined by using Cochrane's Q statistic and *I*-squared.

Results: Five eligible studies containing 3851 participants were included in our meta-analysis. Shorten telomere length was significantly associated with PTSD with mean difference of −0.19(95% CI: −0.27, −0.01; P < 0.001) with I-square of 96%. The results from subgroup analysis demonstrated that shorter telomere length was significantly associated with PTSD across all gender groups, with mean difference of −0.15(95% CI: −0.29, −0.01; P=0.04) for female, mean difference of −0.17(95% CI: −0.19, −0.15; P < 0.001) for male. Meanwhile, shorten telomere length was significantly associated with sexual assault(mean difference =−0.15, 95% CI: −0.29, −0.01), childhood trauma (mean difference =−0.08, 95% CI: −0.19, −0.07), but not combat (mean difference =−0.39, 95% CI: −0.83, 0.05).

Conclusion: Compared to the individuals without PTSD, individuals with PTSD have shorter telomere length, which has implications for early intervention and timely treatment to prevent future adverse health outcomes.

1. Introduction

Human telomeres are DNA protein structures, characterized by TTAGGG tandem repeats at the end of chromosomes and telomere associated proteins that regulate the cell-cycle and maintain chromosomal integrity and stability (Blackburn, 2001; Yao and Dai, 2014). Telomere length has been regarded as a biomarker of biological aging that predicts incidences of age-related diseases and mortality (Sanders and Newman, 2013). There is sufficient evidence to show that shorten telomere length is closely associated with various age-related diseases, such as coronary heart disease, type 2 diabetes mellitus, and dementia (Forero et al., 2016; Haycock et al., 2014; Zhao et al., 2013). Meanwhile, exposure to chronic psychiatric disorders has been also associated with shorter telomere length, such as schizophrenia, bipolar disorder, and major depression (Darrow et al., 2016; Polho et al., 2015; Schutte and Malouff, 2015).

Post-traumatic stress disorder (PTSD) is a common psychiatric disorder, which may occur in some persons after exposure to some potentially life-threatening traumatic events. PTSD is characterized by various biological and behavioral changes, such as intrusive thoughts, hypervigilance, and sleep disturbance, which can increase the risk of somatic illness and mortality (Boscarino, 2008; Boscarino et al., 2010; Cohen et al., 2009; Qureshi et al., 2009; Yaffe et al., 2010). Zhang et al. reported individuals with PTSD had shorter telomere length than their age-matched healthy controls(2014). In parallel, shorter telomere length was found in war veterans with current PTSD (Jergovic et al., 2014; O'Donovan et al., 2011). However, Ladwing et al. reported the association of PTSD and telomere length was not significant without

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http://dx.doi.org/10.1016/j.jad.2017.03.048
Received 4 October 2016; Received in revised form 19 March 2017; Accepted 24 March 2017
Available online 27 March 2017

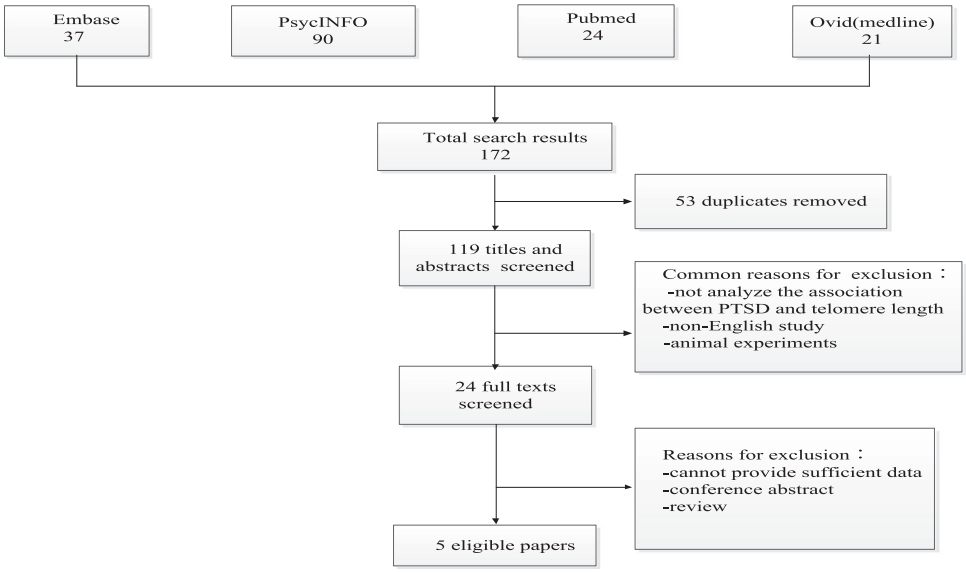

Fig. 1. Search results and study selection.

adjusting age (Ladwig et al., 2013).

Given the observed contradictory relationship between shortened telomere length and PTSD in some studies, additional investigations are needed. Our present study aimed to give more precise estimate of relationship between telomere length and PTSD through using meta-analysis according to the PRISMA guidelines. In addition, subgroup analysis was performed according to the type of trauma (e.g., combat, sexual assault) and other characters of included studies (e.g., gender, study quality).

2. Materials and methods

2.1. Search strategy and selection criteria

Our systematic review was registered at http://www.crd.york.ac.uk/PROSPERO/, with registration number of CRD42016023336. This systematic review was designed and undertaken according to guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We conducted a systematic electronic search on the databases of the PUBMED, PsycINFO, Medline(Ovid SP), EMBASE and other resources(such as Google Scholar). All databases were searched from inception to May 2016 and was updated in March 2017. MeSH terms, keywords and truncation symbol were used in the search strategy. The search strategy detail can be found in the online Supplementary material. We adjusted the search method in according with each database and used a combination of key words as well as subject terms, such as[('stress disorders') or ('traumatic') or ('post traumatic stress disorder')]and [('telomere') or ('telomere shortening') or ('telomere homeostasis') or (' telomere-binding proteins')]. We hand searched the references of eligible articles and previous reviews for studies probably suitable for inclusion criteria.

2.2. Eligibility and exclusion criteria

Studies met the following inclusion criteria: (i) studies investigating the association between telomere length and PTSD (ii) The type of study was case-control study or cross-sectional studies. Exclusion criteria are including: (i) insufficient data, (ii) review articles or conference abstracts, (iii) other language of studies, except English.

2.3. Study selection

All articles were examined independently by two authors. We primary identified relevant studies by examining title and abstract or obtaining a full text of the article if abstract was unavailable. The potentially eligible articles were re-assessed by retrieving and evaluating full text. Inter-reviewer reliability in the study selection process was determined by the Kappa test. In case of disagreement on the inclusion or the exclusion of studies, the disagreements were resolved through discussion and reexamination of the article.

2.4. Data collection process

Data were extracted by two independently reviewers. The following data were collected from the included studies: country, demographic characteristics of population, the definitions of PTSD, the study design, year of publication, the measure methods and potential sources of bias. In this study, we sent e-mails to contact authors if these articles suitable for a meta-analysis without data. Authors were asked to provide Means and standard deviations (SDs) for primary outcome. If we did not get authors' replies, we attempted to send the second request. The study was excluded from meta-analyses if the author was unable to provide additional data.

2.5. Assessment of risk of bias

Assessment of risk of bias was performed by two independent reviewers according to assessment tool that was referred to the study of Zhao et al. (2013): (1) representativeness of cases, (2) representativeness of controls, (3) ascertainment of PTSD, (4) ascertainment of controls, (5) measure method of telomere length, (6) distribution of telomeres length, (7) association assessment (Table S1). Maximum score was 13. Higher score indicated a better literature quality.

2.6. Statistical analysis

We performed a meta-analysis with studies that reported the outcomes. The chi-square test for Cochrane's Q statistic and I-squared were used to test heterogeneity, with thresholds of ≧25%, ≧50% and ≧75% indicating low, moderate and high heterogeneity, respectively. A fixed-effects meta-analysis with the mean difference (95% CIs) was conducted with RevMan 5 software (The Cochrane Collaboration) by using the inverse variance method(P≧0.05; chi-square test). In contrast, a random-effects meta-analysis was carried out. Subgroup analyses were planned by overall study quality, gender, sample size, region and the study design.