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Telomere length and frailty in older adults—A systematic review and meta-analysis

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ABSTRACT

Telomere shortening has been proposed as a potentially useful biomarker of human ageing and age-related morbidity and mortality. We performed a systematic review and meta-analysis to summarize results from individual studies on the telomere length according to the frailty status and frailty index in older adults. We searched the PubMed, SCOPUS and Web of Science databases to identify studies that evaluated the telomere length in frail and non-frail older adults and the relationship between telomere length and frailty index score. We used the base pairs (bp) as a measure of the telomere length. Summary estimates were calculated using random-effects models. Nine studies were included in the present systematic review and a total of 10,079 older adults were analyzed. We found that the frail older adults (n = 355) had shorter telomeres than the non-frail (n = 1894) (Standardized Mean Difference [SMD] -0.41; 95% CI -0.73 to -0.09; P = 0.01; I^2 = 82%). Significant differences in telomere length between frail and non-frail older adults were identified in Hispanic (SMD -1.31; 95% CI -1.71 to -0.92; P < 0.0001; I^2 = 0%) but not in Non-Hispanic countries (SMD -0.13; 95% CI -0.26 to 0.00; P = 0.06; I^2 = 0%). Similar results were found in the adjusted meta-analysis (SMD -0.56; 95% -1.12 to 0.00; P = 0.05; I^2 = 85%). A significant but weak relationship was found between telomere length and frailty index analyzing 8244 individuals (SMD -0.06; 95% IC -0.10 to 0.01; P = 0.01; I^2 = 0%). The current available evidence suggests that telomere length may be not a meaningful biomarker for frailty. Because the potential influence of ethnicity in shortening of telomeres and decline in physiologic reserves associated with aging, additional multiethnic studies are needed.

1. Introduction

Telomeres are specific DNA–protein structures that cap chromosomal ends and protect them from being recognized and processed as DNA double-strand breaks (Rhodes et al., 2002). Because DNA replication machinery is unable to copy the extreme ends of chromosomes during mitosis, telomeres will steadily shorten with each cell division unless new repetitive nucleotide sequences are added by telomerase, a reverse transcriptase enzyme essential for telomere maintenance (Feng and Koh, 2013; Kim et al., 1994; Pallis et al., 2010; Wang et al., 2018). Thus, telomere length can reflect the growth rate or remaining replicative potential of a population of cells (Sanders and Newman, 2013; Shammas, 2011).

As telomere maintenance has a significant impact during cell division, ageing has long been considered as a source for telomere dysfunction through increasing numbers of cell divisions in the absence of sufficient telomerase activity, along with genetic, epigenetic make-up and environmental influences (Gilley et al., 2008). The progressive shortening of telomeres is recognized by the cell rather like a form of DNA damage leading to apoptosis or growth arrest and is termed replicative senescence (Akbar and Henson, 2011). Telomere shortening resulting from the absence of telomerase activity has been proposed as a potentially reliable biomarker of human aging and age-related morbidity and mortality (Akbar and Henson, 2011; Hornsby, 2007; von Zglinicki and Martin-Ruiz, 2005; Wang et al., 2018; Yu et al., 1990). Moreover, a number of studies have suggested that individuals with

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shorter leukocyte telomeres have higher mortality rates (Mons et al., 2017; Wang et al., 2018), but the magnitude effect decreases with increasing age, though retaining a significant association through to age 90 years (Zhan et al., 2018).

Although telomere shortening has been associated with ageing-related markers of inflammation (O'Donovan et al., 2011), oxidative stress (Demissie et al., 2006), functional disability (Risques et al., 2010) and sarcopenia (Marzetti et al., 2014), evidence on the association between telomere shortening and frailty is sparse. Frailty can be described as a geriatric multidimensional condition characterized by decreased physiological reserve and diminished resistance to stressors, and results from cumulative cellular damage over the life-course. (Collard et al., 2012; Morley et al., 2013; Rockwood et al., 1999; Serra-Prat et al., 2017; Speechley and Tinetti, 1991). Because chronic inflammation has been suggested as an underlying mechanism for frailty (Barzilay et al., 2007; Leng et al., 2007; Soysal et al., 2016) and may be associated with telomerase/telomere dysfunction (Jose et al., 2017; Kordinas et al., 2016), the potential relationship between telomere shortening and frailty should be investigated.

During the last few years, two complementary instruments have been widely used to assess frailty in older people, the Fried's Frailty Phenotype (Fried et al., 2001) and the Frailty Index of Accumulative Deficits (Mitnitski et al., 2001). The frailty phenotype constitutes a common reference frame in many geriatric studies and includes measures of slowness, exhaustion, physical activity, weight loss, and weakness (Fried et al., 2001). This physical frailty model is often applied at the first contact with the subject and may serve for the initial risk stratification according to different profiles (i.e. robust, pre-frail and frail) (Cesari et al., 2014). In turn, frailty index has been operationalized as a risk index by counting the number of deficits accumulated over time, including disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes (i.e. falls, delirium, and urinary incontinence) (Howlett et al., 2014; Mitnitski et al., 2001; Searle et al., 2008), and should be used after a comprehensive geriatric assessment (Cesari et al., 2014). Although the phenotypic and deficit accumulation approaches to evaluate frailty are different, it is noteworthy that each approach has shown overlap in identifying frail individuals with convergent predictive validity (Rockwood et al., 2007).

Frailty is a concept with utility for geriatricians, health-care services and broader society (Nicholson et al., 2017). From a clinical perspective, frailty is important because it constitutes a condition of greater risk of adverse health outcomes, such as falls, reduced mobility, less independence, hospitalization, disability, and death (Collard et al., 2012; Morley et al., 2013). Moreover, understanding how components of immune aging interact and are associated with the physiological decline and increased vulnerability to stressors is crucial for the development of effective therapies to prevent frailty development or progression. The aim of this systematic review and meta-analysis was to summarize the results from individual studies on the telomere length according to the frailty status and frailty index in older adults.

2. Methods

This study was conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement (Stroup et al., 2000). Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

2.1. Research question and eligibility criteria

The present study focused on the following question: Is there a difference in telomere length according to the frailty status and frailty index in older adults? Studies were considered eligible if they satisfied the following criteria: (i) they were a case-control or cohort (either prospective or retrospective) study, or nested design; (ii) participants were aged 60 years or older; (iii) telomere length was measured in peripheral or whole blood leukocytes; (iv) and assessed frailty status using the physical phenotype model (Fried et al., 2001) or frailty index using the cumulative deficit model (Howlett et al., 2014; Mitnitski et al., 2001; Searle et al., 2008). Studies using other criteria for frailty assessment and those with insufficient data on telomere length were excluded.

Frailty status was based on a set of five criteria including shrinking (non-intentional weight loss), poor endurance or exhaustion (reduced energy level), weakness (low handgrip strength), slowness (gait speed), and low physical activity. Participants were classified as non-frail if none of these components were present; as pre-frail if one or two components were present, and as frail if three or more components were present (Fried et al., 2001).

The frailty index was based on accumulation of deficits – including symptoms, signs, blood markers, disabilities and diseases – and indicated the likelihood that frailty was present. The index was expressed as ratio of accumulated deficits observed for any individual to the total number of deficits considered (Howlett et al., 2014; Mitnitski et al., 2001; Searle et al., 2008). For example, if 30 medical variables were used for the construction of frailty index and 18 of the 30 deficits were present, the individual's frailty index was 18/30 = 0.60. Because the continuous nature of the frailty index score, studies using arbitrary cut-off points to define frailty were excluded.

2.2. Search strategy

A systematic search using the PubMed, Scopus and Web of Science databases was performed to identify studies that evaluated the telomere length according to the frailty status and frailty index in older people. A grey-literature search was conducted using Google Scholar and OpenThesis. The first 100 results of Google Scholar were registered. The search was performed in November 2018, without language restrictions. For studies published in languages other than English, native speakers of the languages were sought from the authors' affiliated institutions for assistance with data extraction. The list of all eligible studies and reviews was manually scanned to identify additional studies for inclusion. The full electronic search strategy is illustrated in eTable 1 (Supplement).

2.3. Study selection

Two independent investigators (A.C.A.C. and M.L.T.M.) screened the searched studies based on each paper's title and abstract. Relevant studies were read in full-text and selected according to the eligibility criteria. Disagreements between the two reviewers were resolved by consensus or by a third reviewer (P.R.S.M.-F.).

2.4. Data extraction and risk of bias assessment

Two independent investigators (A.C.A.C. and M.L.T.M.) extracted data from the published reports using a predefined protocol. Information regarding the study design, eligible population, age and gender distribution, inclusion and exclusion criteria, frailty status, frailty index score and laboratory analysis of telomere length were checked. Corresponding authors were contacted for missing data.

For studies evaluating the frailty status, means and standard deviations (SD) of telomere length were obtained for each study group (frail, pre-frail, and non-frail). Where data were not presented in table or text and authors could not be reached, data were extracted using WebPlotDigitizer (Web Plot Digitizer, V.3.11. Texas, USA: Ankit Rohatgi, 2017). If the means and standard deviations were not directly reported in the publication, indirect methods of extracting estimates were used (Hozo et al., 2005; Wan et al., 2014).

To evaluate the relationship between telomere length and frailty index, correlation and regression coefficients were extracted and

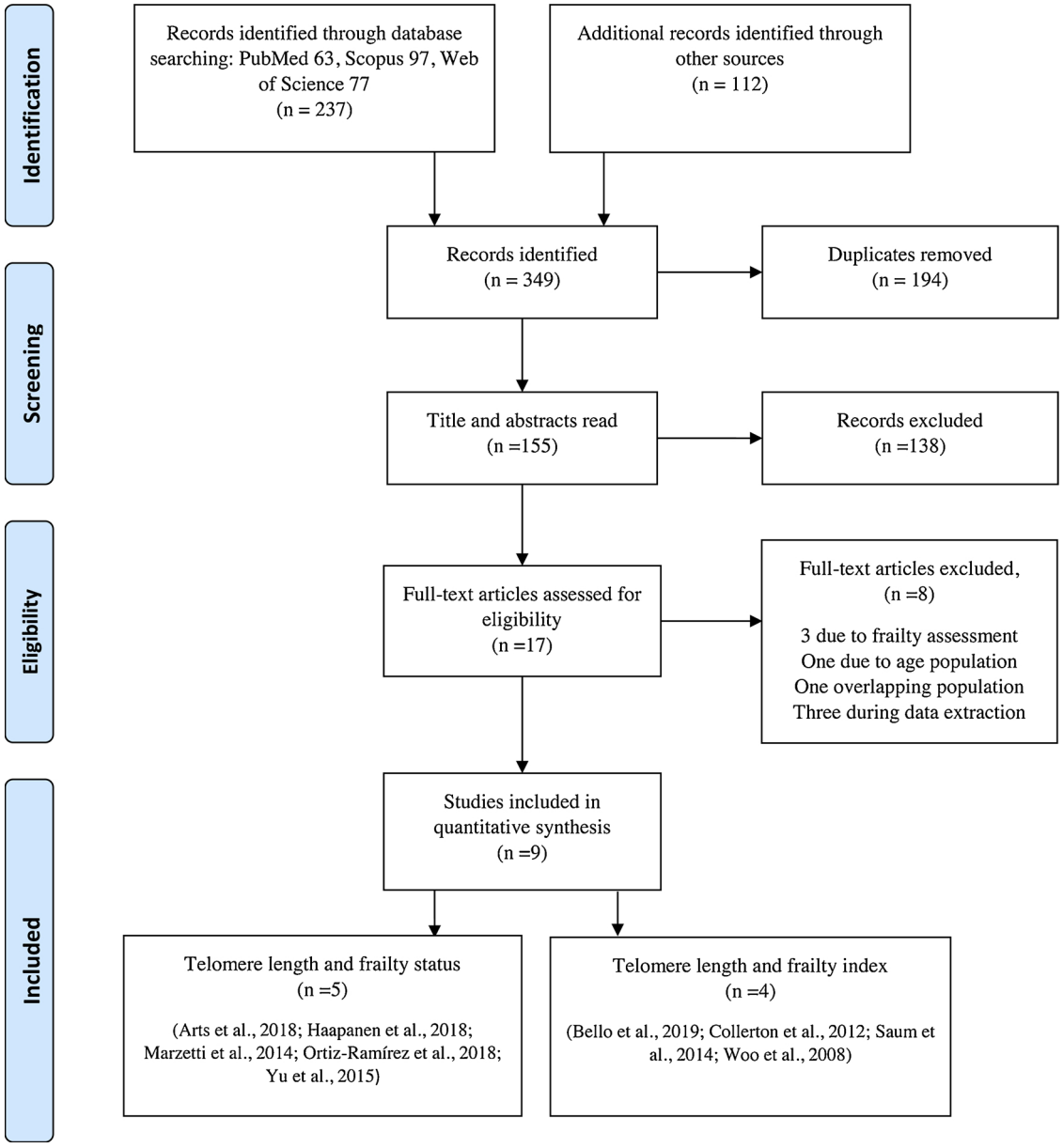

Fig. 1. Flow chart of the search process.

converted to standardized mean difference (SMD) using the following formulas:

$$SMD = 2r/\sqrt{1 - r^2}$$

Or:

$$SMD = \beta/\sqrt{n \times SE}$$

where r is the correlation coefficient; β is the regression coefficient; and SE is the standard error.

For the present systematic review, we used absolute telomere length measurements expressed in base pairs (bp). Results reported in Telomere/Single Copy Gene (T/S) ratio were converted to bp by means of the following formula:

$$bp = 3274 + 2413 \times ((T/S - 0.0545)/1.16)$$

(Park et al., 2015).

Information on the relationship between telomere length and frailty included both unadjusted and adjusted data. Adjusted data estimates with 95% confidence intervals (CIs) that had been adjusted for one or more potential confounders were extracted. For studies that applied regression or multilevel modeling, adjusted data from the most fully identified model were used in the meta-analysis. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (NIH) (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to grade the quality of each individual study.

2.5. Data analysis

Meta-analyses were conducted using the inverse-of-variance method and random-effects model assuming that the true value of the effect size of each study is sampled from a probability distribution rather than being identical. The random-effects meta-analysis is the most common approach to combine study results into a single summary estimates in the medical literature. In several clinical settings it may not be realistic to assume that effect sizes are invariant to study settings. Differences in study characteristics (study design, population, etc) together with other reasons (different ethnicity, geographical variation, etc) lead to assume

Table 1
Characteristics of included studies.

Author	Year	Country	N	Age (y)	Population	Telomere length assessment				Frailty model
						Sample	Cell Type	Laboratory analysis	Description	
Arts	2018	Netherlands	292	65+	Elderly on mental health care institutes or general practice	Peripheral blood	Leukocyte	PCR	bp	Fried phenotype
Bello	2019	United States	1890	60+	Community-dwelling elderly. Sample from National Health and Nutrition Examination Survey (NHANES)	Peripheral blood	Leukocyte	PCR	T/S ratio	Frailty index*
Collerton	2012	United Kingdom	811	85+	Community-dwelling and institutionalized elderly. Sample from Newcastle 85 + Study	Peripheral blood	Leukocyte	PCR	bp	Fried phenotype and frailty index
Haapanen	2018	Finland	1078	70+	Community-dwelling elderly. Sample from Helsinki Birth Cohort Study	Peripheral whole blood	Leukocyte	PCR	T/S ratio	Fried phenotype
Marzetti	2014	Italy	142	65+	Community-dwelling elderly. Sample from the Teaching Hospital "Agostino Gemelli", Catholic University of the Sacred Heart	Peripheral blood	Leukocyte	PCR	T/S ratio	Fried phenotype and frailty index
Ortiz-Ramírez	2018	Mexico	323	60+	Community-dwelling elderly. Sample from Cohort of Obesity, Sarcopenia and Frailty of Older Mexican Adults	Peripheral blood	Leukocyte	PCR	bp	Fried phenotype
Saum	2014	Germany	3537	60+	Sample from ESTHER Cohort Study	Whole blood	Leukocyte	PCR	T/S ratio	Frailty index
Woo	2008	Hong Kong	2006	65+	Community-dwelling elderly. Sample from Mr. OS and Ms. OS Cohort Study	Peripheral blood	Leukocyte	PCR	T/S ratio	Frailty index
Yu	2015	Hong Kong	2006	65+	Community-dwelling elderly. Sample from Mr. OS and Ms. OS Cohort Study	Peripheral blood	Leukocyte	PCR	bp	Fried phenotype

PCR, polymerase chain reaction; bp, base pairs; Telomere/Single Copy Gene ratio, T/S ratio.
* Frailty index computing the proportion of laboratory test biomarkers/physiological parameters (FI-LAB).

that studies will not share a common effect size and should be analyzed using a random-effects model as presented in this meta-analysis (Nikolakopoulou et al., 2014; Riley et al., 2011; Serghiou and Goodman, 2019). The results were expressed as SMD and an effect size of 0.2 was considered a small effect, a value of 0.5 a medium effect, and a value of 0.8 a large effect (Cohen, 1988). A negative effect size indicated that frail older adults had shorter telomere compared to non-frail.

Forest plots were used to present the pooled estimates in graphical form. P values lower than 0.05 were regarded as statistically significant. Heterogeneity was investigated using the Cochran Q test with a cut-off of 10% for significance (Cochran, 1954) and quantified using the I^2 index [100% x (Q-df)/Q] (Higgins et al., 2003). A subgroup analysis was performed to explore differences in telomere length in the frail and non-frail older people according to ethnicity (the chosen categories being Hispanic and Non-Hispanic). A complementary analysis included comparisons between pre-frail status and other phenotypes.

Publication bias was assessed by inspecting the funnel plot. Visual inspection of the funnel plot yields an indication of publication bias when larger and smaller studies are non-symmetrically distributed across the combined effect size. "Leave-one-out" sensitivity analysis was conducted by omitting one study at a time and examining the influence of each individual study on the pooled effect size. Analyzes were performed using the R statistical programming language version 2.10.13 (R Core Team, 2013) and the Review Manager version 5.3 (Cochrane IMS, Copenhagen, Denmark).

3. Results

3.1. Study selection

The initial search located 349 references, 63 of which were collected from PubMed, 97 from Scopus, 77 from Web of Science, 100 from Google Scholar, eight from OpenThesis, and four via a hand-search. From 155 non-duplicate references, 17 studies were found to be potentially relevant and were analyzed in full. After a complete reading, eight studies were excluded: three because of the frailty assessment (Compté et al., 2015, 2013; Goldeck et al., 2016), three during data extraction (Brault et al., 2014; Breitling et al., 2016; Fernández-Eulate et al., 2018), one due to overlapping population (Dent et al., 2018) and one due to the age population (Pathai et al., 2013). Finally, nine studies (Arts et al., 2018; Bello et al., 2019; Collerton et al., 2012; Haapanen et al., 2018; Marzetti et al., 2014; Ortiz-Ramírez et al., 2018; Saum et al., 2014; Woo et al., 2008; Yu et al., 2015) satisfied the eligibility criteria and were included in the present systematic review and meta-analysis. A flowchart depicting the selection process of references at each stage is provided in the Fig. 1.

3.2. Study characteristics

The included studies were conducted in England (Collerton et al., 2012), Italy (Marzetti et al., 2014), The Netherlands (Arts et al., 2018), Germany (Saum et al., 2014), Finland (Haapanen et al., 2018), Hong Kong (Woo et al., 2008; Yu et al., 2015), the United States (Bello et al., 2019), and Mexico (Ortiz-Ramírez et al., 2018). Eight studies presented a nested design reporting cross-sectional results from the following cohorts: Mr. OS and Ms. OS Cohort Study (Woo et al., 2008; Yu et al., 2015), Cohort of Obesity, Sarcopenia and Frailty of Older Mexican Adults (Ortiz-Ramírez et al., 2018), Helsinki Birth Cohort Study (Haapanen et al., 2018), Newcastle 85+ Study (Collerton et al., 2012), ESTHER Cohort Study (Saum et al., 2014), National Health and Nutrition Examination Survey (NHANES) (Bello et al., 2019), and Netherlands Study of Depression in Older People (NESDO) (Arts et al., 2018). One study had a cross-sectional design and was conducted with outpatient older people (Marzetti et al., 2014).

Clinical data and blood specimens from 10,079 older adults were

evaluated (292 from the NESDO cohort; 1890 from the NHANES Study; 811 from the Newcastle 85+ Study; 1078 from the Helsinki Birth Cohort Study; 142 from the Teaching Hospital "Agostino Gemelli", Catholic University of the Sacred Heart; 323 from the Cohort of Obesity, Sarcopenia and Frailty of Older Mexican Adults; 3537 from the ESTHER Cohort Study; and 2006 from the Mr. OS and Ms. OS Cohort Study. The clinical phenotype of frailty was analyzed in four studies (Arts et al., 2018; Haapanen et al., 2018; Ortiz-Ramírez et al., 2018; Yu et al., 2015) and the frailty index in three studies (Bello et al., 2019; Saum et al., 2014; Woo et al., 2008). Two studies used both frailty models (Collerton et al., 2012; Marzetti et al., 2014). Genomic DNA was extracted from leukocytes and amplified using polymerase chain reaction (PCR). In five studies, telomere length was measured according to the T/S ratio (Bello et al., 2019; Haapanen et al., 2018; Marzetti et al., 2014; Saum et al., 2014; Woo et al., 2008); in four studies, data were presented in bp (Arts et al., 2018; Collerton et al., 2012; Ortiz-Ramírez et al., 2018; Yu et al., 2015). The primary characteristics of the studies are listed in Table 1.

3.3. Risk of bias assessment

Studies included in this systematic review stated the research question, clearly described information related to the eligibility criteria, and had a low risk of selection bias. Most studies used representative samples to strengthen the observational evidence on the relationship between telomere length and frailty and had a low risk for attrition bias. Although studies clearly described the frailty diagnosis and assessment of telomere length, there was potential for performance bias and uncontrolled confounding (eTable 2 in the Supplement).

3.4. Telomere length and frailty status

3.4.1. Unadjusted meta-analysis

Five studies (Arts et al., 2018; Haapanen et al., 2018; Marzetti et al., 2014; Ortiz-Ramírez et al., 2018; Yu et al., 2015) included in this systematic review provided sufficient data to compare telomere length between frail and non-frail older people. A total of 2249 older adults were analyzed: 355 classified as frail and 1894 as non-frail. The overall result of this meta-analysis showed that the frail older people had shorter telomeres than non-frail with a mild to moderate effect size (SMD -0.41; 95% CI -0.73 to -0.09; P = 0.01; I^2 = 82%). There is no potential for publication bias (eFig. 1 in the Supplement).

Of the five studies included in this meta-analysis, four (Arts et al., 2018; Haapanen et al., 2018; Marzetti et al., 2014; Yu et al., 2015) were conducted in Non-Hispanic countries (Netherlands, Finland, Italy, and Hong Kong) and one (Ortiz-Ramírez et al., 2018) in a Hispanic country (Mexico). Significant differences in telomere length between the frail and non-frail older adults were identified in Hispanic (SMD -1.31; 95% CI -1.71 to -0.92; P < 0.0001; I^2 = 0%) but not in Non-Hispanic countries (SMD -0.13; 95% CI -0.26 to 0.00; P = 0.06; I^2 = 0%) (Fig. 2).

3.4.1.1. Complementary analysis. The results of meta-analysis with 1592 pre-frail older adults (Haapanen et al., 2018; Ortiz-Ramírez et al., 2018; Yu et al., 2015) showed no differences in telomere length compared to those with frailty (SMD -0.35; 95% CI -0.80 to 0.09; P = 0.12; I^2 = 90%) and non-frailty status (SMD -0.03; 95% CI -0.12 to 0.06; P = 0.47; I^2 = 26%). However, significant differences in telomere length between frail and pre-frail older adults were identified in Hispanic but not in Non-Hispanic countries (eFig. 2 in the Supplement). Similar results were found in the subgroup analysis comparing pre-frail and non-frail older adults (eFig. 3 in the Supplement).

3.4.2. Adjusted meta-analysis

Three studies (Arts et al., 2018; Marzetti et al., 2014; Ortiz-Ramírez et al., 2018) provided adjusted data for the relationship between telomere length and frailty status. The number of adjusted confounders differed across studies, but all of them adjusted their estimates for age, gender, tobacco consumption, and comorbidities. In the adjusted meta-analysis, differences in telomere length were also found between frail and non-frail older adults (SMD -0.56; 95% CI -1.12 to 0.00; P = 0.05; I^2 = 85%) and similar findings were identified in the subgroup analysis (Fig. 3).

3.5. Telomere length and frailty index

Four studies (Bello et al., 2019; Collerton et al., 2012; Saum et al., 2014; Woo et al., 2008) reported data on the relationship between telomere length and frailty index for 8244 older people. A significant but weak relationship was found between telomere length and accumulation of deficits (SMD -0.06; 95% CI -0.10 to -0.01; P = 0.01). No between-study heterogeneity was found (I^2 = 0%) (Fig. 4) and there is no potential for publication bias (eFig. 4 in the Supplement).

4. Discussion

Frailty has been recognized as a multidimensional and multifactorial syndrome associated with functional impairment and increased susceptibility to disease, disability and mortality. Latent human herpes virus infections, comorbidities (such as cardiovascular disease, diabetes), low socioeconomic status and activity of daily living disability have been associated with frailty among older adults (Araújo Carvalho et al., 2018; Espinoza and Fried, 2007; Silva da and Almeida de, 2018; Vaes et al., 2017). In addition, there is emerging evidence of the effects of shortening of telomeres on health outcomes in the elderly. This systematic review and meta-analysis analyzed the current evidence on the association between telomeres shortening and frailty in older adults. The overall results of this study suggested a weak relationship between telomere length and frailty, but the magnitude of the effect seems to be ethnicity-dependent.

Telomere length has been associated with increased incidence of age-related diseases and decreased lifespan in humans (Müezzinler et al., 2013). It has been found that during cell division, telomeres shorten by about 30 to 200bp because of the inability of DNA polymerase to fully replicate the 3′ end of the DNA strand (Aubert and Lansdorp, 2008). This is known as the end replication problem and results in a gradual decline in telomere length over time (Cesare and Reddel, 2010). In addition, it is known that cell division may occur 50–70 times before the telomere reaches a critically short length (Hayflick limit), in which the telomere becomes too close to the coding DNA region and the loop structures cannot hold the telomere structure together (Shay and Wright, 2000). Telomeres that are too short are no longer afforded the protection of the telosome, a six-subunit protein complex associate with telomeric DNA to confer telomere protection and length regulation (Lim et al., 2017). The ensuing DNA damage response leads to either cell death through apoptosis or a halt to cell division referred to as cellular senescence which may be associated with poor clinical outcomes in the elderly (Lundblad, 2012).

In addition to the end replication problem, shortening of telomeres can occur as a consequence of oxidative stress and inflammation that causes DNA damage with the potential for loss of large telomeric parts during cell division (Sahin and Depinho, 2010). However, as telomere length is both heritable and modifiable by environmental factors, studies have suggested that progressive shortening of telomeres can affect the pace of aging and onset of age-associated diseases (Adler and Stewart, 2010; López-Otín et al., 2013; Shammas, 2011; Soares et al., 2014). Therefore, improvements in the quality of life may lead to reduction of the cell division rate and thereby generating a more natural aging process by maintaining the telomere integrity for longer and consequently fewer adverse outcomes in older people (Langie et al., 2012). Interestingly, the subgroup analysis carried out in the present

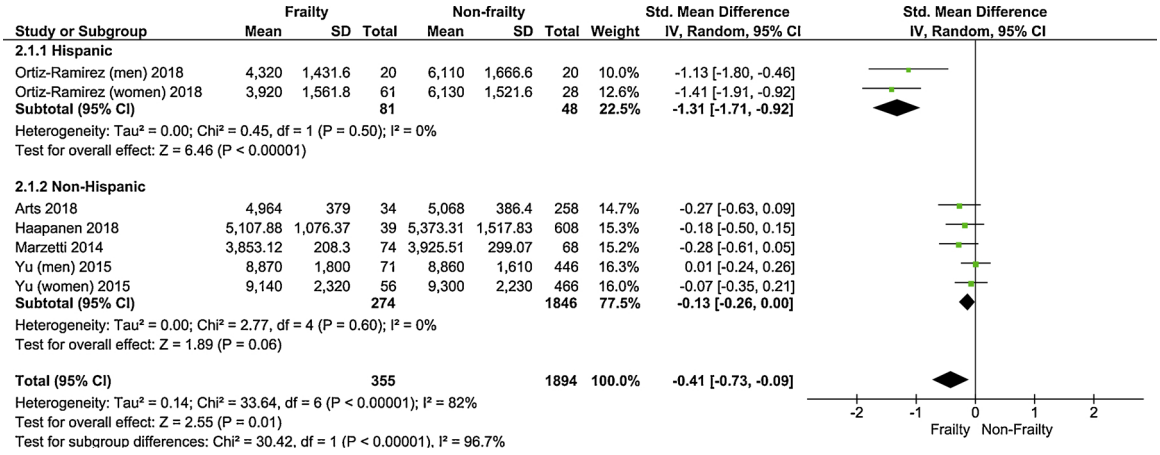

Fig. 2. Forest plot showing unadjusted analysis of telomere length in frail and non-frail older adults.

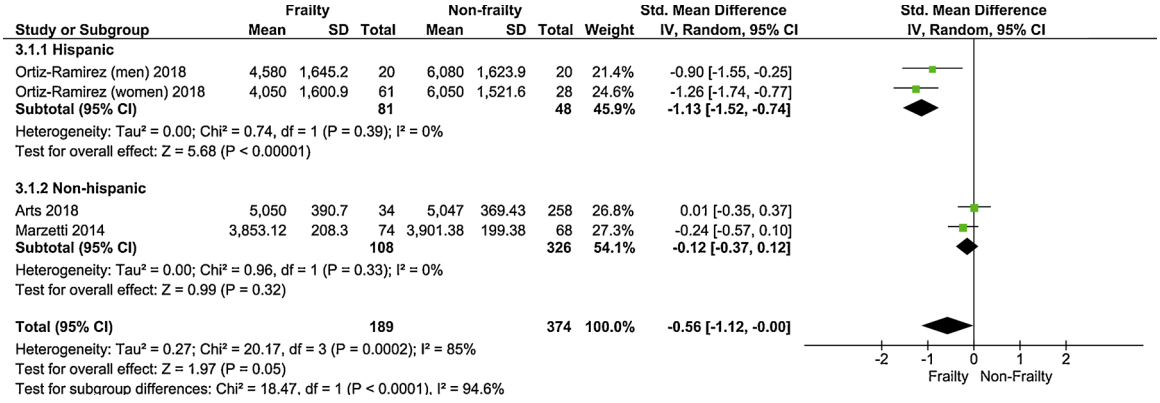

Fig. 3. Forest plot showing adjusted analysis of telomere length between frail and non-frail older adults.

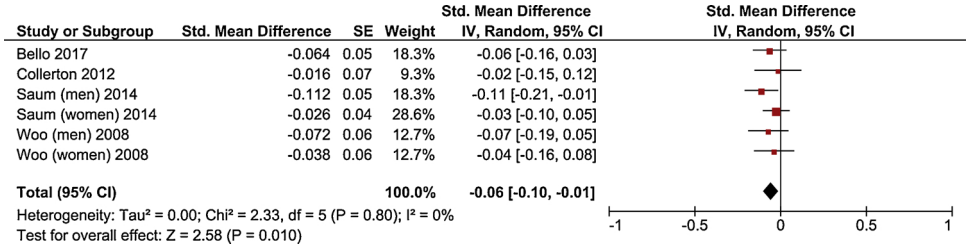

Fig. 4. Forest plots showing the relationship between telomere length and frailty index.

study showed an important influence of ethnicity on the overall results of the meta-analysis. Significant differences in telomere length between frail and non-frail people were identified in Hispanic but not in Non-Hispanic countries. Although contrasting results were found on the relationship between telomere length and health outcomes in multi-ethnic studies (Diez Roux et al., 2009; Lynch et al., 2016; Zhao et al., 2017), ethnic differences in telomere length may be related to the cumulative burden of differential exposure to oxidative stress in some populations (Diez Roux et al., 2009). The findings of the present meta-analysis support the hypothesis that the shortening of telomeres and decline in physiologic reserves associated with aging may reflect the impact of lifestyle, social demographics and environmental stressors on health over the course of life. In the Hispanic study (Ortiz-Ramírez et al., 2018), it was found an association between oxidative stress-related factors and telomere shortening in older adults. However, despite studies have shown that lifestyle and racial/ethnic differences in morbidity and mortality are associated to socioeconomic status (Assari, 2017; Colen et al., 2018; Hayward et al., 2000), the results of this exploratory analysis should be interpreted with caution. Lifestyle and socioeconomic differences often do not explain all health differences since many studies are designed under a common biomedical and social epidemiological paradigm that implicitly views race/ethnicity or socioeconomic group as risk factors (Geronimus et al., 2015). It is important to consider the potential for interpreting the relationship between race/ethnicity and socioeconomic status that are either additive in their effects or potential confounders of each other.

Some studies have suggested that the shortening of telomeres in the frail people may be the result of the influence of several stressors that act throughout the individual's life and are not necessarily a risk factor for frailty (Yu et al., 2015). This mechanism can be explained by the fact that chronic diseases, such as cardiovascular disease, produce oxidative stress that causes an inhibition of telomerase activity and consequently damage to GGG triplets in telomeric DNA (Goglin et al., 2016). Thus, the shortening of telomeres can be considered to be a weak biomarker of the aging process with a low predictability compared to accumulated deficits such as cardiovascular problems (Sanders and Newman, 2013). Corroborating this idea, determining the causal relationship between telomeres shortening and frailty in older adults

can be a challenge, as aging increases the incidence of certain diseases and disorders. In addition, the association between telomere length and frailty may be driven by an unmeasured confounder such as underlying chronic inflammation (Wong et al., 2014). Recently, it has been proposed that frailty may lead to premature apoptosis in cells with normal length telomeres, rather than apoptosis occurring as a result of replicative shortening of telomeres, and by the time frailty is clinically observable, cells with shorter telomeres have already undergone cell senescence (Dent et al., 2018). Further longitudinal studies are needed to verify the bidirectional causal relationship between telomere shortening and frailty as a vicious cycle in which one feeds the development of the other.

Our findings should be interpreted with caution. Despite all studies having used blood sample-based PCR assay to evaluate telomere length, genomic DNA was derived from multiple subsets of leukocytes. It has been shown that telomere length may vary in different peripheral blood cell types (Lin et al., 2010) and the exposure to chronic stress or infection can alter the number and proportion of leukocyte types (Dent et al., 2018), which can lead to heterogeneous results. Furthermore, the results of the present study were based on cross-sectional reports, which is a key limitation for demonstrating a causal inference between telomere length and frailty in the elderly. However, cross-sectional results may provide valuable preliminary data to justify the synthesis of available evidence and indicate the need for further epidemiologic investigation. Finally, there appear to be variations in telomere shortening depending on the ethnicity of the population under analysis. Due to limited number of studies, prospective multi-ethnic cohort studies are needed to confirm our findings. These major limitations need to be taken into consideration when evaluating the validity of our results.

5. Conclusion

The results of this meta-analysis showed that the frail older people had shorter telomeres than non-frail with a mild to moderate effect size. In addition, a significant but weak relationship was found between telomere length and accumulation of deficits. Therefore, the current available evidence suggests that telomere length may be not a meaningful biomarker for frailty. Because the potential influence of ethnicity in shortening of telomeres and decline in physiologic reserves associated with aging, additional multiethnic studies are needed.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100914.

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