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Gender and telomere length: Systematic review and meta-analysis ☆

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☆ Précis: There is an association between gender and telomere length, with females having longer telomeres than males.

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ABSTRACT

Background: It is widely believed that females have longer telomeres than males, although results from studies have been contradictory.
Methods: We carried out a systematic review and meta-analyses to test the hypothesis that in humans, females have longer telomeres than males and that this association becomes stronger with increasing age. Searches were conducted in EMBASE and MEDLINE (by November 2009) and additional datasets were obtained from study investigators. Eligible observational studies measured telomeres for both females and males of any age, had a minimum sample size of 100 and included participants not part of a diseased group. We calculated summary estimates using random-effects meta-analyses. Heterogeneity between studies was investigated using sub-group analysis and meta-regression.
Results: Meta-analyses from 36 cohorts (36,230 participants) showed that on average females had longer telomeres than males (standardised difference in telomere length between females and males 0.090, 95% CI 0.015, 0.166; age-adjusted). There was little evidence that these associations varied by age group ($p = 1.00$) or cell type ($p = 0.29$). However, the size of this difference did vary by measurement methods, with only Southern blot but neither real-time PCR nor Flow-FISH showing a significant difference. This difference was not associated with random measurement error.
Conclusions: Telomere length is longer in females than males, although this difference was not universally found in studies that did not use Southern blot methods. Further research on explanations for the methodological differences is required.

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1. Introduction

Telomeres are nucleoprotein complexes at chromosome ends, where the DNA component is a repetitive stretch of (TTAGGG), which caps and protects the end of the chromosome. Some studies have found that shorter telomeres are associated with obesity (Nordfjall et al., 2008a), gender (Bekaert et al., 2007), lower socioeconomic position (Cherkas et al., 2008), smoking (Valdes et al., 2005) and mortality (Cawthon et al., 2003). Hence telomere length has been proposed as a useful index of biological age (Hunt et al., 2008), although this has been called into question (von Zglinicki, 2012). The present study focuses on the association with gender.

In the literature there are inconsistencies in the association between gender and telomere length. Some studies (Nawrot et al., 2004; Bekaert et al., 2007; Fitzpatrick et al., 2007) have found white blood cell telomeres to be longer in women than men. Several hypotheses have been postulated to explain this association (Nawrot et al., 2004; Mayer et al., 2006; Barrett and Richardson, 2011). One is the action of oestrogen (Mayer et al., 2006). An oestrogen-responsive element is present in telomerase reverse transcriptase (hTERT) (Nawrot et al., 2004), hence oestrogen might stimulate telomerase to add telomere repeats to the ends of chromosomes. Furthermore, telomeres are particularly sensitive to oxidative stress (von Zglinicki, 2002) and women produce fewer reactive oxygen species than men (Nawrot et al., 2004). It has been suggested that women might also metabolise reactive oxygen species better because of oestrogen (Nawrot et al., 2004), due to its antioxidant properties (Carrero et al., 2008). However, other studies have found that it is not always the case that telomere length is longer in females than males (Hunt et al., 2008; Shiels et al., 2011) or even the reverse (Adams et al., 2007). At birth, one study found that there was little difference in telomere length between the sexes (Okuda et al., 2002), but another study found that female newborns had longer telomeres than males (Aubert et al., 2012). In another study, (Hunt et al., 2008) no difference was detected in the telomere length of women and men in the younger Bogalusa Heart Study cohort (19–37 years), but in the older Family Heart Study cohort (30–93 years) telomeres were longer in women than men. Hence the association between gender and telomere length might vary by age. Whilst telomere length is inversely related to chronological age in humans (Shiels et al., 2011), there are concerns about how robust telomere length is as a biomarker of ageing (Shiels, 2010; Shiels et al., 2011).

Existing studies of the association of gender and telomere length in humans have a number of limitations. For example, some of the studies are small e.g. (Benetos et al., 2001) and hence may not have sufficient power to detect gender differences in telomere length. Furthermore, there are methodological differences between assay methods (Aviv et al., 2006), with Southern Blot providing a mean terminal restriction length for DNA fragments containing the telomeric DNA stretch plus sub-telomeric regions of variable length and sequence composition and real-time PCR measuring actual telomere -repeat length relative to a reference gene (Aviv et al., 2006). The most frequent cell types used in studies on telomere length are either whole blood (leukocytes made up of lymphocytes, monocytes and granulocytes) or peripheral blood mononuclear cells (PBMCs made up of lymphocytes and monocytes). In adults, lymphocytes have shorter telomeres than granulocytes (Aviv et al., 2006), hence it is important to assess whether the association between gender and telomere length varies by cell type. A literature search and qualitative meta-analysis (Barrett and Richardson, 2011) found that at a qualitative level, males tended to have shorter telomeres than females. However, no systematic review of the literature has been done to examine the association between gender and telomere length.

We carried out a systematic review and meta-analyses to test the hypothesis that in human populations females have longer telomeres than males and that this association becomes stronger with increasing age. Furthermore, we also investigated whether the association between gender and telomere length varied by method of measurement of telomere length or cell type. Our study has several advantages over the earlier review: (a) our study is a systematic review and meta-analysis; (b) has standardised effect estimates; (c) has more rigorous methodology including exploration of sources of heterogeneity. We hypothesised that there would be an association between gender and telomere length, with females having longer telomeres than males and that this association would become stronger with increasing age.

2. Methods

We undertook a systematic review of the published literature following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al., 2000) and the PRISMA statement (Moher et al., 2009) and we include a completed PRISMA checklist (Supplementary Data 1). Full review protocol is available in Supplementary Data 2.

2.1. Selection criteria

Eligible observational studies had a minimum number of 100 participants and measures of telomere length for both males and females.

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