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Review

Telomere length and health outcomes: An umbrella review of systematic reviews and meta-analyses of observational studies

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ABSTRACT

The aim of the present study was to map and grade evidence for the relationships between telomere length with a diverse range of health outcomes, using an umbrella review of systematic reviews with meta-analyses. We searched for meta-analyses of observational studies reporting on the association of telomere length with any health outcome (clinical disease outcomes and intermediate traits). For each association, random-effects summary effect size, 95% confidence interval (CI), and 95% prediction interval were calculated. To evaluate the credibility of the identified evidence, we assessed also heterogeneity, evidence for small-study effect and evidence for excess significance bias. Twenty-one relevant meta-analyses were identified reporting on 50 different outcomes. The level of evidence was high only for the association of short telomeres with higher risk of gastric cancer in the general population (relative risk, RR = 1.95, 95%CI: 1.68–2.26), and moderate for the association of shorter telomeres with diabetes or with Alzheimer's disease, even if limited to meta-analyses of case-control studies. There was weak evidence for twenty outcomes and not significant association for 27 health outcomes. The present umbrella review demonstrates that shorter telomere length may have an important role in incidence gastric cancer and, probably, diabetes and Alzheimer's disease. At the same time, conversely to general assumptions, it does not find strong evidence supporting the notion that shorter telomere length plays an important role in many health outcomes that have been studied thus far.

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1. Introduction

Telomeres are specific DNA-protein structures at both ends of each linear chromosome that play a vital role in protecting genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion (Blackburn et al., 2015; Lu et al., 2013). The structure of telomeres was first recognized in 1938 and thought to stabilize chromosome ends to prevent them from being recognized as DNA double-strand breaks (Montpetit et al., 2014). In the past three decades, the number of studies investigating the association between telomere length, telomere shortening and health outcomes has been growing (Epel et al., 2004; Hug and Lingner, 2006; Adamson et al., 1992; Engelhardt and Martens, 1998; Mehle et al., 1994; Ohyashiki et al., 1994).

In humans, telomeres shorten throughout the life span with each cell division, therefore reflecting the overall cellular turnover within an individual (Haycock et al., 2014). Hence, telomere length is thought to be a marker of biological ageing independent of chronological age, and linked to risks of common diseases of aging as well as all-cause mortality (Lu et al., 2013). In particular, over the past 20 years, there has been a proliferation of research suggesting that shorter telomere length are associated with higher risk of cardiovascular disease (Haycock et al., 2014), biomarkers of cardiovascular disease risk (Rehkopf et al., 2016), cancer (Shay and Wright, 1996; Sun et al., 2015), diabetes (Pavanello et al., 2018), schizophrenia (Russo et al., 2018), depression and anxiety (Needham et al., 2015), decline in cognitive function (Yaffe et al., 2011) and mortality (Njajou et al., 2009). Various measures of telomere length or attrition rate have been used in different studies (Montpetit et al., 2014). In recognition of the reported deleterious outcomes of shortened telomere length, research began to explore the determinants, particularly modifiable determinants, of telomere length and telomere attrition rates (Epel et al., 2004; Latifovic et al., 2016; Shammas, 2011). Research has shown that women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women (Epel et al., 2004). In a cross-sectional study including 477 healthy volunteers aged 20–50 years it was found that smoking was related to shorter telomere length while vigorous physical activity was related to longer telomeres (Latifovic et al., 2016). Other identified determinents of telomere length include diet and obesity (Shammas, 2011).

Whilst the literature suggests that reduced telomere length may be associated with adverse outcomes, the epidemiological credibility of this evidence is still unclear. In addition, a number of nuances exist within the literature including varying definitions in the specific measures of telomere length (e.g. some capture “telomere length”, other capture “attrition rate” or “shortening” and some report “telomerase activity”) making it challenging for interpreting the data.

In order to address the breadth of the literature of complex health behaviors and outcomes, an increasing emphasis has been placed on “umbrella reviews” (Ioannidis, 2017a, 2017b). To the best of our knowledge, there are no existing umbrella reviews to capture the breadth of outcomes associated with telomere length and to assess systematically the quality and the strength of the evidence from meta-analyses of telomere length and health outcomes.

Therefore, the aim of the present paper is to assess the strength and credibility of the evidence derived from meta-analyses and systematic reviews of telomere length on health outcomes across systematic reviews with meta-analyses of observational studies. The following questions will be answered: (i) Which health outcomes are associated with telomere length? (ii) What is the epidemiological credibility of the relationship between telomere length and health outcomes?

2. Materials and methods

We conducted an umbrella review (Ioannidis, 2009a, 2009b) following a predetermined, published protocol (PROSPERO ID: CRD42018104343). Three authors (CL, JD, PS) searched the electronic databases MEDLINE/PubMed, PsycINFO, and Embase from inception to 1 st August 2018. The search terms used were (“telomere” OR “telomeres” OR “telomeric” OR “telomere length” OR “T/C ratio”) AND (Meta-Analysis[ptyp] OR metaanaly*[tiab] OR meta-analy*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab]). In addition, we hand-searched the reference lists of eligible articles and other narrative overviews of systematic reviews/meta-analyses.

2.1. Eligibility criteria

We included meta-analyses informed by systematic reviews which investigated the relationship between telomere length and any health outcome in any type of observational study (case-control, cross-sectional, cohort). We included only studies that: (i) measured telomere length directly, excluding those relying on indirect assessment of telomere length or telomere function (e.g. telomerase activity, polymorphisms of telomerase reverse transcriptase subunit), and (ii) ascertained health outcomes using self-report (e.g. depression questionnaire), observed (e.g. clinical diagnoses) or objective (e.g. biomarkers, certified mortality) criteria.

We included meta-analyses reporting any effect size including estimates for discrete (such as odds ratio (OR), relative risk (RR), hazard ratio (HR)) or continuous outcomes (such as Pearson’s coefficients, r) with their 95% confidence intervals (Cis) or such information could be inferred from the presented data.

2.2. Data extraction

Two independent investigators (CL, JD) extracted the following information for each article: (1) first author name; (2) year of publication; (3) journal; (4) the number of included studies and the total number of people included in the review; (5) the population; (6) effect sizes from the most adjusted model(s) used; (7) number of cases and controls for each study when available; (8) study design (case-control, cross-sectional, prospective); (9) the unit of comparison (continuous, longest vs. shortest category of telomere length). Any discrepancies were revoled by discussion.

We subsequently extracted the study-specific estimated associations for health outcomes (RR, OR, HR, standardized mean differences (SMDs), correlation coefficients), along with their 95% CIs. Correlation coefficients were transformed into ORs using a standard formula (Cochrane Collaboration, 2008).

When two meta-analyses were available for the same association, we included the largest in terms of number of studies.

2.3. Quality assessment

We assessed the methodological quality of the included meta-analyses using AMSTAR 2 (Shea et al., 2007). We categorized the overall AMSTAR 2 score as high: no or one non-critical weakness; moderate: more than one non-critical weakness; low: one critical flaw with or without non-critical weaknesses; critically low: more than one critical flaw with or without non-critical weaknesses (Shea et al., 2007).

2.4. Statistical analyses

We followed standard umbrella review quantitative frameworks (Ioannidis, 2009a, 2009b). We reported the results according to each health outcome. For each meta-analysis, we estimated the summary effect size and its 95% CI through random-effects models. We calculated the prediction interval and its 95% CI, which further accounts for between-study effects, and estimates the certainty of the association if a new study addresses that same association (Higgins et al., 2009). In order to estimate whether any large (very precise) studies were

available, for the largest study of each meta-analysis, we calculated the standard error (SE) of the standardized effect size. If the SE is less than 0·10 then the 95% CI would be lower than 0·20 (which is less than the magnitude of a small effect size). Between-study inconsistency was estimated with the I^2 metric, with values greater than 50% indicative of large and greater than 75% for very large heterogeneity (Higgins and Thompson, 2002).

In addition, we tested for evidence of small-study effects (i.e. whether small studies would have larger effect sizes compared to larger studies) using the regression asymmetry test (Egger et al., 1997). A p-value < 0.10 with more conservative effects in larger studies in random-effects meta-analysis was considered as indicative of small-study effects.

Finally, we applied the excess of significance test (Ioannidis, 2013). In brief, this test evaluates whether the number of studies with nominally significant results (i.e., with $p < 0{\cdot}05$) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at $\alpha = 0{\cdot}05$. The power estimate for each data set was calculated. The sum of the power estimates of each outcome provides the expected (E) number of data sets with nominal statistical significance. As described elsewhere, the number of expected 'positive' (i.e. statistically significant data sets) sets can be compared with the observed (O) number of statistically significant studies through a χ^2-based test (Ioannidis and Trikalinos, 2007). The larger the difference between O and E, the higher the degree of excess significance. All the analyses were conducted with STATA 13.0 (STATA Corp, Texas, USA).

2.5. Grading of evidence

Using the criteria mentioned above, associations that presented nominally statistically significant random effects summary estimates (i.e. $p < 0{\cdot}05$) were categorized into convicing, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields (Veronese et al., 2018; Bellou et al., 2016; Belbasis et al., 2016; Aromataris et al., 2015).

Criteria for class I (convincing) were the following: statistical significance with $p < 10^{-6}$, more than 1000 cases (or > 20,000 participants for continuous outcomes), the largest component study reported statistically significant effect ($p < 0{\cdot}05$); 95% prediction interval excluded the null; no large heterogeneity ($I^2 < 50\%$), no evidence of small study effects ($p > 0{\cdot}10$) and no excess significance bias ($p > 0{\cdot}10$); for class II (highly suggestive): statistical significance with $p < 10^{-6}$, more than 1000 cases (or > 20,000 participants for continuous outcomes), the largest component study reported statistically significant effect ($p < 0{\cdot}05$); for class III (suggestive): statistical significance with $p < 10^{-3}$, more than 1000 cases (or > 20,000 participants for continuous outcomes); for class IV (weak): the remaining statistically significant associations with $p < 0{\cdot}05$.

3. Results

3.1. Literature review

As shown in Fig. 1, we identified 257 unique papers across three major databases (Pubmed, PsychInfo, Embase). After applying the eligibility criteria, 41 articles were selected as potentially eligible and, of them, 21 systematic reviews with meta-analyses (Haycock et al., 2014; Adam et al., 2017; Darrow et al., 2016; D'Mello et al., 2015; Ennour-Idrissi et al., 2017; Forero et al., 2016a, b; Huang et al., 2018; Kachuri et al., 2016; Lee et al., 2017; Lee and Bae, 2016; Malouff and Schutte, 2017; Naing et al., 2017; Nilsonne et al., 2015; Polho et al., 2015; Ridout et al., 2016; Wang et al., 2016, 2017; Zhang et al., 2015, 2018; Zhou et al., 2018; Zhu et al., 2016) (=50 different outcomes) were finally eligible for our umbrella review.

3.2. Meta-analyses of observational studies

As reported in Table 1, the median number of studies of meta-analyses for each outcome was 6 (range 2–20), the median number of participants was 2536 (range 315–26,660), and the median number of cases was 983 (range 58–7335).

Overall these meta-analyses included 50 outcomes covering a wide spectrum of disorders. Of them, cancer and cancer-related outcomes (n = 28; 56%) were the most frequent examined. The outcomes eligible included only cohort studies (n = 21), only case-control studies in 13 outcomes, and only cross-sectional studies in 3 outcomes. The other outcomes included mixed types of studies (e.g. nested case-control and cohort studies together).

Overall, 23 (46%) out of the 50 outcomes reported nominally significant summary results ($p < 0{\cdot}05$). These included several diseases, especially the association between telomere length and incident cancer (n = 5 outcomes) and prognosis in cancer (n = 3).

Heterogeneity among studies was generally high and 43/50 outcomes (86%) had an I^2 estimates consistent with a large heterogeneity (≥50%), with 33 showing a very large heterogeneity (≥75%). Only two associations (comparison between diabetic vs. no diabetic patients and overall survival in people with lung cancer) presented 95% prediction intervals excluding the null value. Evidence for excess statistical significance was present in two outcomes and small-study effects were also seen in 10 of the outcomes. The largest study maintained its statistical significance in 20/50 outcomes (= 40%) and had a more conservative effect in 30/50 outcomes (n = 60%).

Based on the above criteria, no outcome presented convincing evidence, only one outcome presented highly suggestive evidence (class II: higher incidence of gastric cancer in the general population in 3 studies including 3726 subjects; RR = 1·95, 95%CI: 1·68–2·26, $I^2 = 14$), two (4%) outcomes presented suggestive evidence (class III: shorter telomere length in the comparison between diabetic people and people with Alzheimer's disease vs. healthy controls) (Table 1) and 20 outcomes (40%) a weak evidence. No association was found for 27 outcomes.

The majority of meta-analyses scored low or critically low (n = 20) on AMSTAR 2 and one scored moderate. (Supplementary Table 1), with all the meta-analyses included not reporting information regarding the funding source of the included studies. The outcome with highly suggestive evidence was supported by a low quality due to not sufficient information regarding the methodology used. (Supplementary Table 1).

4. Discussion

In the present umbrella review, including 21 meta-analyses and 50 outcomes, highly suggestive evidence was found for one outcome variable, as shorter telomere length was associated with a higher incidence of gastric cancer in the general population. Additionally, there was suggestive evidence for shorter telomere length in diabetic people and people with Alzheimer's disease compared to healthy controls. Finally, 20 outcomes of telomere length shortening showed only weak evidence, whilst 27 did not report any significant association between telomere length and health outcomes. These findings were derived by examining the epidemiological credibility of the evidence using a novel umbrella review approach, an emerging technique that has been applied in other fields of science (Veronese et al., 2018; Bellou et al., 2016; Belbasis et al., 2016; Aromataris et al., 2015). It is reported that researchers often use a nominal significance level $p < 0{\cdot}05$ to claim novel associations with clinical relevance. However, there is discussion that $p < 0{\cdot}05$ constitutes only weak evidence (Johnson, 2013), thus level of significance should be redefined to a more conservative value (e.g. $p < 0{\cdot}0001$) to reduce false positives or at least at 0·005 as recently suggested (Ioannidis, 2018). In the present review, for example, 23 outcomes were statistically significant taking a p-value < 0·05 as the threshold, but only 3 outcomes were deemed having evidence that was

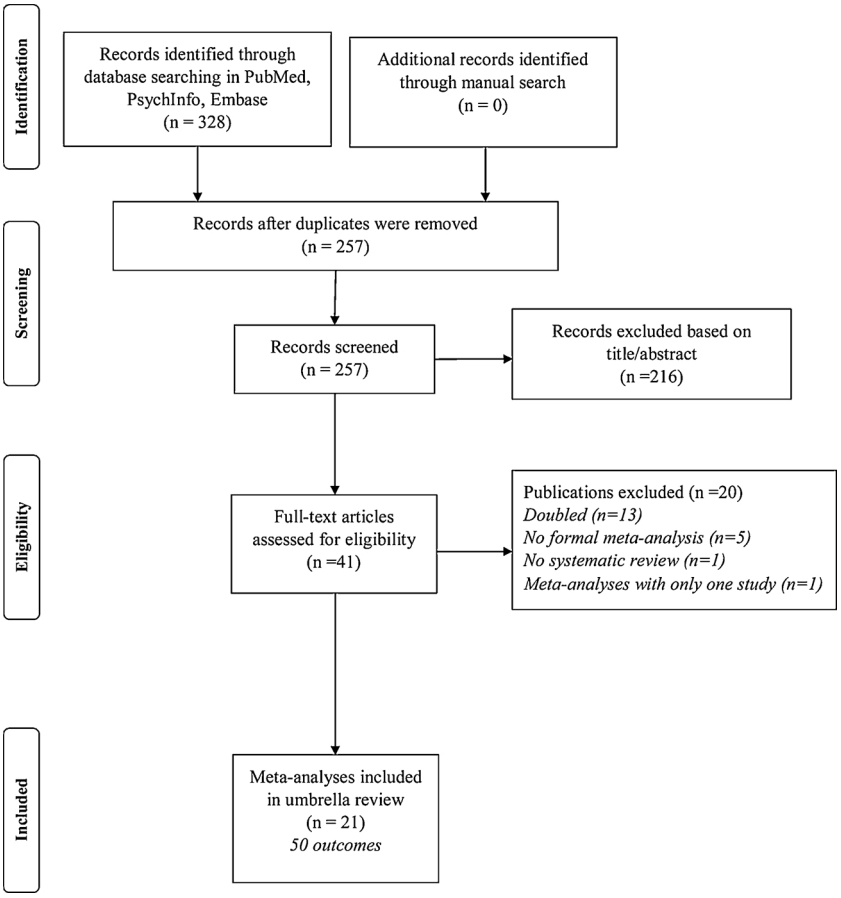

Fig. 1. PRISMA flow-chart.

highly suggestive or suggestive, and no outcome was deemed as having convincing evidence after employing the critical appraisal of the literature using the umbrella review technique.

It remains unclear if telomere length is simply a biomarker of disease or if it plays a causal role in disease processes, even if the link between telomere length and cancer may be biologicaly plausible. Cell proliferation is accompanied by telomere shortening (Allsopp et al., 1995) and this observation explains the crucial role of telomeres in maintaining the normal homeostasis, but also in influencing cell senescence and carcinogenesis (Aragona et al., 2000; Harley et al., 1992). A hallmark of cancer, indeed, is represented by its intrinsic capacity of uncontrolled proliferation. To this aim, cancer cells have developed the ability to maintain telomere length, activating a pathway known as telomere maintenance mechanism. In the majority of cancers, telomeric DNA is provided by telomerase (Robinson, 2000), but some cancers (e.g. sarcomas) can use other processes to achieve telomere maintenance, such as the so called ALT ("alternative lengthening of telomeres) (De Vitis et al., 2018). Given this complex telomere landscape, we focused only on telomere length in our study. After having confirmed that the presence of short telomeres is associated with an increased risk of several cancers (even if we found only a weak evidence for many of them), we found an important highly suggestive association with incident gastric cancer. Possible reasons of this interesting finding may reside in the fact that the epithelium of the stomach undergoes massive replications, since the frequency of cellular turn-over in this area is one of the highest in the human body. Alterations in telomere maintenance, thus, may be amplified in these kind of cells with an intensified basal rate of cellular division.

Although supported by weak evidence, an inverse association was found for other cancers, including melanoma and prostate cancer, where longer telomeres were associated with a lower risk of developing such cancers. In melanoma, this association may indicate that shorter telomere length is protective against the carcinogenetic process of melanocytic cells, probably triggering the onset of a senescent stage as late event and cooperating with important senescent effectors, like p16 in this cancer (D'Arcangelo et al., 2017). Of interest is also the observation of Sanchez-Esperidion et al., which showed that patients with lung squamous cell carcinoma had shorter telomeres than controls, whereas the contrary has been observed for patients with lung adenocarcinoma, for which telomeres were longer than those of controls (Sanchez-Espiridion et al., 2014).

These findings, also in the light of the heterogeneous results of our umbrella-review, may suggest that telomere length could influence cancer risk based on histology, further pointing to the peculiar roles of telomeres biology in cancer biology and development.

The present review found suggestive evidence for shorter telomere length in those with diabetes compared to healthy controls, even though these findings are limited only to case-control studies. Type II diabetes is characterized by insulin resistance and relative insulin deficiency (American Diabetes A, 2010). The literature suggests that telomere length in those with type II diabetes is likely influenced by oxidative stress. A shortening of telomere length increases the risk of β-cell injury and apoptosis, leading to a decline in islet cell functioning and diabetes development and progression. However, the exact role of telomere length in predicting diabetes should be better examined in longitudinal studies, since in a meta-analysis investigating diabetes as an incident outcome (D'Mello et al., 2015), the association with telomere length was only weak, mainly due to high heterogeneity (Brownlee, 2001; Tentolouris et al., 2007).

Suggestive evidence was found for shorter telomere length and Alzheimer disease. Similar to the previously discussed health outcomes, the exact link between shorter telomere length and AD is elusive. In AD

Table 1
Health outcomes and evidence class reported in included meta-analyses of observational studies.

Outcome	Population	Study design	Unit of comparison	Type of metric	N of studies	Mean ES (95%CI)	P [a]	I^2	p-value Egger	Small study effect	Excess significance bias	Largest study significant	Cases	Controls	Sample size	Level of evidence[b]
Gastric cancer (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	3	1·95 (1·68 − 2·26)	$7·53 e^{-19}$	14	0·86	no	no	yes	1832	1894	3726	**II**
AD (Forero et al., 2016b)	–	Case-control	NA	SMD	13	−0·98 (−1·43; −0·54)	0·00001	92	0·07	yes	no	yes	748	1808	2536	**III**
Diabetes (Wang et al., 2016)	–	Case-control	NA	SMD	18	−3·41 (−4·02; −2·81)	$3·63 e^{-28}$	99	0·001	yes	NA	yes	5575	6389	11964	**III**
Disease-free survival in CLL (Zhang et al., 2015)	CLL patients	Cohort	Longest vs· shortest TL	RR	6	1·79 (1·25; 2·55)	0·001	61	0·003	yes	NA	NA	NA	NA	NA	**IV**
Esophageal cancer (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	3	2·07 (1·59; 2·69)	$6·66 e^{-08}$	0	0·72	no	no	yes	440	701	1141	**IV**
Head and neck cancer (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	4	1·86 (1·23; 2·82)	0·003	70	0·06	no	yes	yes	509	1156	1665	**IV**
Overall survival in glioma (Zhang et al., 2015)	Glioma patients	Cohort	Longest vs· shortest TL	RR	2	1·51 (1·20; 1·89)	0·0005	0	NA	NP	NP	yes	NA	NA	330	**IV**
Overall survival in lung cancer (Kachuri et al., 2016)	Lung cancer patients	Cohort	Longest vs· shortest TL	RR	4	2·52 (1·73; 3·67)	$1·69 e^{-06}$	0	0·16	no	no	yes	58	106	315	**IV**
Prostate cancer (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	3	0·85 (0·74; 0·97)	0·01	0	0·35	no	no	no	1646	2047	3693	**IV**
Skin cancer - basal cell carcinoma (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	5	1·98 (1·06; 3·69)	0·03	93	0·01	yes	no	no	1467	3234	4701	**IV**
Skin cancer - melanoma (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	5	0·52 (0·30; 0·89)	0·02	89	0·02	yes	no	yes	1484	1787	3271	**IV**
OSA (Huang et al., 2018)	–	Case-control	NA	MD	7	−0·04 (−0·07; −0·001)	0·046	86	0·54	no	NP	yes	1024	1234	3745	**IV**
RA (Lee and Bae, 2016)	–	Case-control	NA	SMD	9	−0·83 (−1·33; −0·33)	0·001	89	0·25	no	no	no	388	362	750	**IV**
Anxiety (various) (Malouff and Schutte, 2017)	–	Cross-sectional	NA	R to OR	17	0·95 (0·92; 0·97)	0·00007	61	0·14	no	NP	yes	NA	NA	16424	**IV**
Depressive Disorders (Darrow et al., 2016)	–	Case-control	NA	SMD	11	−0·55 (−0·92; −0·18)	0·003	96	0·38	no	NA	yes	2227	3142	5369	**IV**

(*continued on next page*)

Table 1 (*continued*)

Outcome	Population	Study design	Unit of comparison	Type of metric	N of studies	Mean ES (95%CI)	P [a]	I^2	p-value Egger	Small study effect	Excess significance bias	Largest study significant	Cases	Controls	Sample size	Level of evidence[b]
PTSD (Darrow et al., 2016)	–	Case-control	NA	SMD	5	−1·27 (−2·11; −0·43)	0·003	94	0·22	no	NA	no	217	2888	3105	**IV**
Anxiety (Darrow et al., 2016)	–	Case-control	NA	SMD	3	−0·53 (−1·06; −0·008)	0·047	97	0·31	no	NA	yes	1599	2268	3867	**IV**
SLE (Lee et al., 2017)	–	Case-control	NA	SMD	12	−0·84 (−1·29; −0·38)	0·0003	89	0·33	no	NA	yes	472	365	837	**IV**
Depression (Ridout et al., 2016)	–	Cohort/ nested case control	NA	MD	10	−0·23 (−0·40; −0·06)	0·008	69	0·02	yes	NA	no	597	3644	4827	**IV**
Stroke (D'Mello et al., 2015)	General population	Cohort/ case control	Longest vs· shortest TL	RR	10	1·21 (1·06; 1·38)	0·004	62	0·34	no	no	yes	2993	7083	10076	**IV**
Myocardial Infarction (D'Mello et al., 2015)	General population	Cohort/ case control	Longest vs· shortest TL	RR	6	1·24 (1·04; 1·47)	0·02	68	0·14	no	no	no	1627	21183	22810	**IV**
T2DM (D'Mello et al., 2015)	General population	Cohort/ case control	Longest vs· shortest TL	RR	7	1·37 (1·10; 1·71)	0·005	91	0·19	no	no	no	5132	7625	12757	**IV**
CHD (Haycock et al., 2014)	General population	Cohort/ nested case control	Longest vs· shortest TL	RR	20	1·54 (1·31; 1·83)	$4·31\ e^{-07}$	64	< 0·0001	yes	NA	NA	NA	NA	5566	**IV**
All-cause mortality in breast cancer (Ennour-Idrissi et al., 2017)	Breast cancer patients	Cohort	Longest vs· shortest TL	HR	4	0·54 (0·20; 1·44)	0·22	96	0·05	yes	NA	NP	NA	NA	NA	**NS**
Bladder cancer (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	3	1·36 (0·63; 2·97)	0·43	86	0·25	no	no	yes	382	420	802	**NS**
Breast cancer (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	8	0·96 (0·77; 1·19)	0·70	83	0·13	no	no	no	4270	4896	9139	**NS**
Cancer recurrence in breast cancer (Ennour-Idrissi et al., 2017)	Breast cancer patients	Cohort	Longest vs· shortest TL	HR	2	0·49 (0·14; 1·69)	0·26	76	NA	NA	NA	NA	NA	NA	NA	**NS**
Cancer-specific mortality in breast cancer (Ennour-Idrissi et al., 2017)	Breast cancer patients	Cohort	Longest vs· shortest TL	HR	3	1·21 (0·64; 2·28)	0·55	75	0·36	no	NA	NA	NA	NA	NA	**NS**

(*continued on next page*)

Table 1 (*continued*)

Outcome	Population	Study design	Unit of comparison	Type of metric	N of studies	Mean ES (95%CI)	P [a]	I^2	p-value Egger	Small study effect	Excess significance bias	Largest study significant	Cases	Controls	Sample size	Level of evidence[b]
Colorectal cancer (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	8	1·27 (0·97; 1·65)	0·08	83	0·49	no	no	yes	5022	8033	13055	**NS**
Disease-free survival in colorectal cancer (Wang et al., 2017)	Colorectal cancer patients	Cohort	Longest vs· shortest TL	HR	3	3·44 (0·78; 15·09)	0·10	71	0·22	no	NA	NA	NA	NA	NA	**NS**
Hepatocellular carcinoma (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	2	0·29 (0·06; 1·42)	0·13	96	NA	NP	no	yes	380	520	902	**NS**
Lung cancer (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	9	0·96 (0·68; 1·36)	0·80	90	0·09	no	no	no	2917	2920	5834	**NS**
Lymphoma - Hodgkin's lymphoma (Zhu et al., 2016)	General population	Cohort	Longest vs· shortest TL	OR	3	1·59 (0·22; 11·3)	0·65	90	0·29	no	no	no	561	561	1122	**NS**
Ovarian cancer (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	2	1·63 (0·56; 4·79)	0·37	89	NA	NP	no	no	1010	1047	2057	**NS**
Overall survival in bladder cancer (Zhang et al., 2015)	Bladder cancer patients	Cohort	Longest vs· shortest TL	RR	3	1·51 (0·79; 2·89)	0·21	77	0·24	no	NP	NA	NA	NA	NA	**NS**
Overall survival in CLL (Zhang et al., 2015)	CLL patients	Cohort	Longest vs· shortest TL	RR	9	1·14 (0·59; 2·18)	0·70	91	0·002	yes	NP	NA	NA	NA	NA	**NS**
Overall survival in colorectal cancer (Wang et al., 2017)	Colorectal cancer patients	Cohort	Longest vs· shortest TL	HR	7	1·26 (0·76; 2·08)	0·38	83	0·22	no	NP	yes	NA	NA	334	**NS**
Overall survival in esophageal cancer (Adam et al., 2017)	Esophageal cancer patients	Cohort	Longest vs· shortest TL	HR	3	0·84 (0·39; 1·80)	0·65	83	0·06	no	NP	yes	NA	NA	490	**NS**
Overall survival in ovarian cancer (Adam et al., 2017)	Ovarian cancer patients	Cohort	Longest vs· shortest TL	HR	3	1·25 (0·63; 2·52)	0·52	84	0·92	no	NP	yes	NA	NA	321	**NS**
Progression-free survival in lung cancer (Kachuri et al., 2016)	Lung cancer patients	Cohort	Longest vs· shortest TL	HR	3	1·87 (1·34; 2·60)	0·002	0	0·81	no	yes	no	232	405	714	**NS**
Renal cell carcinoma (Zhu et al., 2016)	General population	Cohort/ case control	Longest vs· shortest TL	OR	4	0·98 (0·79; 1·20)	0·81	27	0·7	no	no	no	1132	1336	2468	**NS**

(*continued on next page*)

Table 1 (*continued*)

Outcome	Population	Study design	Unit of comparison	Type of metric	N of studies	Mean ES (95%CI)	P [a]	I^2	p-value Egger	Small study effect	Excess significance bias	Largest study significant	Cases	Controls	Sample size	Level of evidence[b]
Frailty (Zhou et al., 2018)	–	Cross-sectional/ case control	NA	MD	6	0·006 (−0·02; 0·14)	0·12	86	0·45	no	no	no	728	1305	3268	**NS**
Psychotic Disorders (Darrow et al., 2016)	–	Case-control	NA	SMD	6	−0·23 (−0·68; 0·21)	0·30	91	0·27	no	no	yes	772	763	1535	**NS**
Bipolar Disorder (Darrow et al., 2016)	–	Case-control	NA	SMD	7	−0·26 (−0·76; 0·23)	0·30	92	0·05	yes	no	yes	474	337	811	**NS**
Hippocampus Volume (Nilsonne et al., 2015)	–	Cross-sectional	NA	R to OR	7	1·12 (0·90; 1·40)	0·32	80	0·99	no	NA	yes	NA	NA	2107	**NS**
Parkinson Disease (Forero et al., 2016a)	–	Case-control	NA	SMD	8	0·36 (−0·25; 0·96)	0·25	97	0·52	no	no	no	956	1284	2240	**NS**
Depression (Ridout et al., 2016)	–	Cross-sectional	NA	MD	16	−0·06 (−0·13; 0·01)	0·11	67	0·29	no	NA	no	7335	16482	26660	**NS**
Schizophrenia (Polho et al., 2015)	–	Case-control	NA	SMD	7	0·34 (−0·05; 0·73)	0·09	91	0·08	yes	no	yes	883	865	1748	**NS**
AF (Zhang et al., 2018)	–	Case-control	NA	SMD	3	−0·11 (−0·29; 0·07)	0·24	77	0·47	no	NA	NP	NA	NA	NA	**NS**
AF (incident) (Zhang et al., 2018)	General population	Cohort	Longest vs· shortest TL	HR	4	1·36 (0·92; 2·02)	0·12	50	0·51	no	NA	NA	NA	NA	NA	**NS**
					Median = 6								**Median = 983**	**Median = 1562**	**Median = 2536**	

Abbreviations: AD= Alzheimer's disease; AF= atrial fibrillation; CHD= coronary heart disease; CLL= Chronic lymphocytic leukemia; ES= effect size; HR= hazard ratio; MD= mean difference; OSA= obstructive sleep apnea; PTSD= post traumatic stress disorder; RA= rheumatoid arthritis; RR= relative risk; SLE= lupus erythematosus;SMD= standardized mean difference; T2DM= Type 2 Diabetes Mellitus;OR= odds ratio.

[a] P value of summary random effects estimate.

[b] Evidence class criteria: class I (convincing): statistical significance with $P < 10^{-6}$, more than 1000 cases (or > 20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P < 0·05); 95% prediction interval excluded the null; no large heterogeneity ($I^2 < 50\%$), no evidence of small study effects (P > 0·10) and excess significance bias (P > 0·10); class II (highly suggestive): statistical significance with $P < 10^{-6}$, more than 1000 cases (or > 20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (P < 0·05); class III (suggestive): statistical significance with $P < 10^{-3}$, more than 1000 cases (or > 20,000 participants for continuous outcomes); class IV (weak): the remaining statistically significant associations with P < 0.05.

patients, the shortest telomeres have been associated with high levels of the proinflammatory cytokine tumor necrosis factor-α (Panossian et al., 2003) and there is evidence that markers of oxidative stress are associated with telomere shortening (Eitan et al., 2014). Moreover, perceived stress and lower physical activity are risk factors for AD and are both associated with shorter telomeres (SN and MJ, 2016; Mundstock et al., 2015).

Whilst this umbrella review indicated there may be some highly/suggestive and weak evidence for a number of the aforementioned outcomes, it also transpires that most health outcomes (more than half) were not supported by any evidence. This finding of a large number of null relationships may help direct the field in the search for outcomes associated with telomere length, indicating this should turn towards the associations supported by suggestive evidence. For instance, our data provide no evidence on several outcomes related to cancer or several psychiatric conditions and future studies investigating this may not be helpful use of resources. The large proportion of null findings in our review also suggests that telomere length may not be as an important marker for health as once thought. However, some of the null associations may be explained by limitations in the original studies and meta-analyses, such as small studies, low number of cases and other inherent biases and accounting for these may yeild future contradicotry results.

The present review focused on associations between telomere length and health outcomes. It should also be noted there is a growing body of literature that suggests lifestyle has an important role in telomere dynamics. Indeed, research has shown that smoking, stress, and poor diet are associated with shorter telomeres whereas physical activity participation and a balanced diet are associated with longer telomeres (Epel et al., 2004; Latifovic et al., 2016; Shammas, 2011). Importantly, engaging in healthy behaviors may mitigate the effect of harmful behaviors on telomere length.

The present umbrella review is the first of its kind investigating the relationship between telomere length and all researched health outcomes. The data should, however, be interpreted in light of its limitations. First, except for cancer-related outcomes, several outcomes reported a comparison between people with a condition vs. controls, possibly introducing a reverse causation. Moreover, meta-analyses contained studies that differed in their design, population and other characteristics. To account for this, we used an $I^2 < 50\%$ as one of the criteria for class I evidence (convincing) in order to assign the best evidence grade only to robust associations and without any suspect of bias. Unfortunately a large part of the outcomes included reported a high or very high heterogeneity. Observational studies are susceptible to confounding bias and uncertainty. However, credibility assessment criteria was employed that was based on established tools for observational evidence (Li et al., 2017). Meta-analyses per se have limitations (Ioannidis, 2016) and results will depend on decisions relating to which estimates are selected from each primary study and how to apply them in the meta-analysis. It is important to note that telomere length should not be compared with the activity of an enzyme (telomerase) as it does not represent the actual length of telomeres, but only a possible index of the status of the telomeres (hypothesis exist of a direct correlation, but only in some cell types and in some specific moments of the cell life) (Januszkiewicz et al., 2003). Therefore, meta-analyses that looked at only telomerease were excluded during the screening process. We excluded outcomes where meta-analyses were not available, such as coronary artery calcium (Hunt et al., 2015; Kark et al., 2013; Kroenke et al., 2012; Mainous et al., 2010). Such studies may have helped clarify if shortened telomere length is a prognostic biomarker for the early identification of participants at high risk of developing CVD before symptoms appear. Finally, the majority of meta-analyses included in the present review scored low or critically low on AMSTAR 2. This calls for clearer reporting of meta-analyses in this field and to better standardize methods of telomeres measurement.

In conclusion, the present umbrella review of the top tier of evidence from systematic reviews with meta-analyses suggests that shorter telomere length has a weak association with heightened risks in a range of health outcomes. However, there was some highly suggestive association with incidence of gastric cancer and suggestive evidence with diabetes and Alzeimar's disesae risks. Therefore, the present umbrella review does not provide strong evidence to support an association between telomere length and a range health outcomes. Nevertheless, the present review does suggest shorter telomere length is associated with incident gastric cancer, diabetes and Alzheimer's disease.

Declarations of interest

None.

Contributors

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Appendix A. Supplementary data

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