**TELOMERE LENGTH AND HEALTH OUTCOMES: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES OF OBSERVATIONAL STUDIES**

Lee Smith PhD,\*1 Claudio Luchini MD, PhD,\*2 Jacopo Demurtas MD,\*3 Pinar Soysal MD,4 Brendon Stubbs PhD,5 6 Mark Hamer PhD,7 Alessia Nottegar MD, PhD,8 Rita T. Lawlor MD,9 Guillermo Felipe Lopez-Sanchez PhD,10 Joseph Firth PhD,11,12 Ai Koyanagi MD,13 Justin Roberts PhD,1 Peter Willeit MD, PhD,14,15 Thomas Waldhoer T PhD,16 Mike Loosemore MD, PhD,17 Adam David Abbs MD,18 James Johnstone PhD,1 Lin Yang PhD,16 Nicola Veronese MD19,20

1. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK.

2. Department of Diagnostics and Public Health, University of Verona, Italy

3. Primary Care Department Azienda USL Toscana Sud Est, Grosseto, Italy.

4. Kayseri Education and Research Hospital, Geriatric Center, Kayseri, Turkey.

5. Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ,UK.

6. Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London,UK.

7. School Sport Exercise Health Sciences, Loughborough University, Loughborough.UK

8. Department of Surgery, Section of Pathology, San Bortolo Hospital, Vicenza, Italy

9. ARC-Net Research Center, University of Verona, Verona, Italy

10. Faculty of Sports Sciences, University of Murcia, Spain

11. NICM Health Research Institute, University of Western Sydney, Sydney, Australia.

12. Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia.

13. Parc Sanitari Sant Joan de Déu/CIBERSAM, Universitat de Barcelona, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain.

14. Department of Neurology, Medical University of Innsbruck, Austria.

15. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, UK

16. Department of Epidemiology, Center for Public Health, Medical University of Vienna, Austria.

17. University College London, Institute of Sport, Exercise and Health, UK

18. Pennine Acute Hospitals, NHS Trust, UK

19. National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy.

20. Ambulatory of Nutrition, IRCCS “S. de Bellis” National Institute of Gastroenterology-Research Hospital Castellana Grotte Bari Italy.

\*These authors share first authorship

Corresponding authors: Dr Lee Smith [lee.smith@anglia.ac.uk](mailto:lee.smith@anglia.ac.uk) and Dr Nicola Veronese [ilmannato@gmail.com](mailto:ilmannato@gmail.com)

**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 and including a total of 326 observational studies. 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.

**Key words:** Telomere length, umbrella review, observational studies,

**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.[1](#_ENREF_1),[2](#_ENREF_2) 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.[3](#_ENREF_3) In the past three decades, the number of studies investigating the association between telomere length, telomere shortening and health outcomes has been growing.[4-9](#_ENREF_4)

In humans, telomeres shorten throughout the life span with each cell division, therefore reflecting the overall cellular turnover within an individual.[10](#_ENREF_10) 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 [2](#_ENREF_2).  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,[10](#_ENREF_10) biomarkers of cardiovascular disease risk,[11](#_ENREF_11) cancer,[12](#_ENREF_12),[13](#_ENREF_13) diabetes,[14](#_ENREF_14) schizophrenia,[15](#_ENREF_15) depression and anxiety,[16](#_ENREF_16) decline in cognitive function [17](#_ENREF_17) and mortality.[18](#_ENREF_18) Various measures of telomere length or attrition rate have been used in different studies.[3](#_ENREF_3) 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.[4](#_ENREF_4),[19](#_ENREF_19),[20](#_ENREF_20) 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.4 In a cross-sectional study including 477 healthy volunteers aged 20 to 50 years it was found that smoking was related to shorter telomere length while vigorous physical activity was related to longer telomeres.19 Other identified determinents of telomere length include diet and obesity.20

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”.[21](#_ENREF_21),[22](#_ENREF_22) 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 [23](#_ENREF_23),[24](#_ENREF_24) 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 1st 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 leght) for cohort studies. 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.[25](#_ENREF_25)

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. [26](#_ENREF_26) 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. [26](#_ENREF_26)

**2.4 Statistical Analyses**

We followed standard umbrella review quantitative frameworks.[23](#_ENREF_23),[24](#_ENREF_24) 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.[27](#_ENREF_27) 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 *I2* metric, with values greater than 50% indicative of large and greater than 75% for very large heterogeneity.[28](#_ENREF_28)

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.[29](#_ENREF_29) 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.[30](#_ENREF_30) In brief, this test evaluates whether the number of studies with nominally significant results (i.e., with p<0·05) among those included in a meta-analysis is too large based on the power that these data sets have to detect effects at α=0**·**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 χ2-based test.[31](#_ENREF_31) 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**·**05) were categorized into convicing, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields. [32-35](#_ENREF_32)

Criteria for class I (convincing) were the following: statistical significance with p<10−6, more than 1,000 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 (I2<50%), no evidence of small study effects (p>0·10) and no excess significance bias (p>0·10); for class II (highly suggestive): statistical significance with p<10−6, more than 1,000 cases (or >20,000 participants for continuous outcomes), the largest component study reported statistically significant effect (p<0·05); for class III (suggestive): statistical significance with p<10−3, more than 1,000 cases (or >20,000 participants for continuous outcomes); for class IV (weak): the remaining statistically significant associations with p<0·05.

**3 Results**

**3.1 Literature review**

As shown in **Figure 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[10](#_ENREF_10),[36-56](#_ENREF_36) (=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 2,536 (range 315 to 26,660), and the median number of cases was 983 (range 58 to 7,335).

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 other 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<0·05). 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 I2 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 3,726 subjects; RR=1·95, 95%CI: 1·68-2·26, I2=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.[32-35](#_ENREF_32) It is reported that researchers often use a nominal significance level p<0·05 to claim novel associations with clinical relevance. However, there is discussion that p<0·05 constitutes only weak evidence,[57](#_ENREF_57) thus level of significance should be redefined to a more conservative value (e.g. p<0·0001) to reduce false positives or at least at 0·005 as recently suggested.[58](#_ENREF_58) 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 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[59](#_ENREF_59) and this observation explains the crucial role of telomeres in maintaining the normal homeostasis, but also in influencing cell senescence and carcinogenesis.[60](#_ENREF_60),[61](#_ENREF_61) 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[62](#_ENREF_62), but some cancers (e.g. sarcomas) can use other processes to achieve telomere maintenance, such as the so called ALT (“alternative lengthening of telomeres).[63](#_ENREF_63) 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.[64](#_ENREF_64) 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.[65](#_ENREF_65)

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.[66](#_ENREF_66) 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,[38](#_ENREF_38) the association with telomere length was only weak, mainly due to high heterogeneity.[67](#_ENREF_67),[68](#_ENREF_68)

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 patients, the shortest telomeres have been associated with high levels of the proinflammatory cytokine tumor necrosis factor-α[69](#_ENREF_69) and there is evidence that markers of oxidative stress are associated with telomere shortening.[70](#_ENREF_70) Moreover, perceived stress and lower physical activity are risk factors for AD and are both associated with shorter telomeres.[71](#_ENREF_71),[72](#_ENREF_72)

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.4, 19, 20 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 I2<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.[73](#_ENREF_73) Meta-analyses per se have limitations[74](#_ENREF_74)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).[75](#_ENREF_75) 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.[76-79](#_ENREF_76) 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.

**Declerations of Interest**

None.

**Contributors**

Contributors LS, JD, CL, PS, LY, NV prepared the first draft. LS, LY, and NV conceived the study and provided overall guidance. All other authors, reviewed results, or reviewed and contributed to the report.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-fo r-profit sectors.

**5. References**

1. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science (New York, NY)* 2015; **350**(6265): 1193-8.

2. Lu W, Zhang Y, Liu D, Songyang Z, Wan M. Telomeres-structure, function, and regulation. *Experimental cell research* 2013; **319**(2): 133-41.

3. Montpetit AJ, Alhareeri AA, Montpetit M, et al. Telomere length: a review of methods for measurement. *Nursing research* 2014; **63**(4): 289-99.

4. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States of America* 2004; **101**(49): 17312-5.

5. Hug N, Lingner J. Telomere length homeostasis. *Chromosoma* 2006; **115**(6): 413-25.

6. Adamson DJ, King DJ, Haites NE. Significant telomere shortening in childhood leukemia. *Cancer genetics and cytogenetics* 1992; **61**(2): 204-6.

7. Engelhardt M, Martens UM. The implication of telomerase activity and telomere stability for replicative aging and cellular immortality (Review). *Oncology reports* 1998; **5**(5): 1043-52.

8. Mehle C, Ljungberg B, Roos G. Telomere shortening in renal cell carcinoma. *Cancer research* 1994; **54**(1): 236-41.

9. Ohyashiki JH, Ohyashiki K, Fujimura T, et al. Telomere shortening associated with disease evolution patterns in myelodysplastic syndromes. *Cancer research* 1994; **54**(13): 3557-60.

10. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2014; **349**: g4227.

11. Rehkopf DH, Needham BL, Lin J, et al. Leukocyte Telomere Length in Relation to 17 Biomarkers of Cardiovascular Disease Risk: A Cross-Sectional Study of US Adults. *PLoS medicine* 2016; **13**(11): e1002188.

12. Shay JW, Wright WE. Telomerase activity in human cancer. *Current opinion in oncology* 1996; **8**(1): 66-71.

13. Sun B, Wang Y, Kota K, et al. Telomere length variation: A potential new telomere biomarker for lung cancer risk. *Lung cancer (Amsterdam, Netherlands)* 2015; **88**(3): 297-303.

14. Pavanello S, Angelici L, Hoxha M, et al. Sterol 27-Hydroxylase Polymorphism Significantly Associates With Shorter Telomere, Higher Cardiovascular and Type-2 Diabetes Risk in Obese Subjects. *Frontiers in endocrinology* 2018; **9**: 309.

15. Russo P, Prinzi G, Proietti S, et al. Shorter telomere length in schizophrenia: Evidence from a real-world population and meta-analysis of most recent literature. *Schizophrenia research* 2018.

16. Needham BL, Mezuk B, Bareis N, Lin J, Blackburn EH, Epel ES. Depression, anxiety and telomere length in young adults: evidence from the National Health and Nutrition Examination Survey. *Molecular psychiatry* 2015; **20**(4): 520-8.

17. Yaffe K, Lindquist K, Kluse M, et al. Telomere length and cognitive function in community-dwelling elders: findings from the Health ABC Study. *Neurobiology of aging* 2011; **32**(11): 2055-60.

18. Njajou OT, Hsueh WC, Blackburn EH, et al. Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. *The journals of gerontology Series A, Biological sciences and medical sciences* 2009; **64**(8): 860-4.

19. Latifovic L, Peacock SD, Massey TE, King WD. The Influence of Alcohol Consumption, Cigarette Smoking, and Physical Activity on Leukocyte Telomere Length. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2016; **25**(2): 374-80.

20. Shammas MA. Telomeres, lifestyle, cancer, and aging. *Current opinion in clinical nutrition and metabolic care* 2011; **14**(1): 28-34.

21. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. Br J Sports Med. England; 2017: 1456-8.

22. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ: Canadian Medical Association Journal* 2009; **181**(8): 488-93.

23. Ioannidis JPA. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *Canadian Medical Association Journal* 2009; **181**(8): 488-93.

24. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *British Journal of Sports Medicine* 2017.

25. Collaboration C. Cochrane handbook for systematic reviews of interventions: Cochrane Collaboration; 2008.

26. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007; **7**(1): 10.

27. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society Series A, (Statistics in Society)* 2009; **172**(1): 137-59.

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002; **21**(11): 1539-58.

29. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997; **315**(7109): 629-34.

30. Ioannidis JP. Clarifications on the application and interpretation of the test for excess significance and its extensions. *Journal of Mathematical Psychology* 2013; **57**(5): 184-7.

31. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clinical Trials* 2007; **4**(3): 245-53.

32. Veronese N, Solmi M, Caruso MG, et al. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *The American journal of clinical nutrition* 2018; **107**(3): 436-44.

33. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. *Parkinsonism & Related Disorders* 2016; **23**: 1-9.

34. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Medicine* 2016; **14**(1): 147.

35. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *International journal of evidence-based healthcare* 2015; **13**(3): 132-40.

36. Adam R, Diez-Gonzalez L, Ocana A, Seruga B, Amir E, Templeton AJ. Prognostic role of telomere length in malignancies: A meta-analysis and meta-regression. *Experimental and molecular pathology* 2017; **102**(3): 455-74.

37. Darrow SM, Verhoeven JE, Revesz D, et al. The Association Between Psychiatric Disorders and Telomere Length: A Meta-Analysis Involving 14,827 Persons. *Psychosomatic medicine* 2016; **78**(7): 776-87.

38. D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H, Pare G. Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. *Circulation Cardiovascular genetics* 2015; **8**(1): 82-90.

39. Ennour-Idrissi K, Maunsell E, Diorio C. Telomere Length and Breast Cancer Prognosis: A Systematic Review. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2017; **26**(1): 3-10.

40. Forero DA, Gonzalez-Giraldo Y, Lopez-Quintero C, Castro-Vega LJ, Barreto GE, Perry G. Telomere length in Parkinson's disease: A meta-analysis. *Experimental gerontology* 2016; **75**: 53-5.

41. Forero DA, Gonzalez-Giraldo Y, Lopez-Quintero C, Castro-Vega LJ, Barreto GE, Perry G. Meta-analysis of Telomere Length in Alzheimer's Disease. *The journals of gerontology Series A, Biological sciences and medical sciences* 2016; **71**(8): 1069-73.

42. Huang P, Zhou J, Chen S, Zou C, Zhao X, Li J. The association between obstructive sleep apnea and shortened telomere length: a systematic review and meta-analysis. *Sleep medicine* 2018; **48**: 107-12.

43. Kachuri L, Latifovic L, Liu G, Hung RJ. Systematic Review of Genetic Variation in Chromosome 5p15.33 and Telomere Length as Predictive and Prognostic Biomarkers for Lung Cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2016; **25**(12): 1537-49.

44. Lee Y, Jung J, Seo Y, et al. Association between shortened telomere length and systemic lupus erythematosus: a meta-analysis. *Lupus* 2017; **26**(3): 282-8.

45. Lee YH, Bae SC. Association between shortened telomere length and rheumatoid arthritis. *Zeitschrift für Rheumatologie* 2016; **77**(2): 160-7.

46. Malouff JM, Schutte NS. A meta-analysis of the relationship between anxiety and telomere length. *Anxiety, stress, and coping* 2017; **30**(3): 264-72.

47. Naing C, Aung K, Lai PK, Mak JW. Association between telomere length and the risk of colorectal cancer: a meta-analysis of observational studies. *BMC cancer* 2017; **17**(1): 24.

48. Nilsonne G, Tamm S, Mansson KN, Akerstedt T, Lekander M. Leukocyte telomere length and hippocampus volume: a meta-analysis. *F1000Research* 2015; **4**: 1073.

49. Polho GB, De-Paula VJ, Cardillo G, dos Santos B, Kerr DS. Leukocyte telomere length in patients with schizophrenia: A meta-analysis. *Schizophrenia research* 2015; **165**(2-3): 195-200.

50. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: A meta-analysis. *Journal of affective disorders* 2016; **191**: 237-47.

51. Wang J, Dong X, Cao L, et al. Association between telomere length and diabetes mellitus: A meta-analysis. *The Journal of international medical research* 2016; **44**(6): 1156-73.

52. Wang W, Zheng L, Zhou N, et al. Meta-analysis of associations between telomere length and colorectal cancer survival from observational studies. *Oncotarget* 2017; **8**(37): 62500.

53. Zhang C, Chen X, Li L, Zhou Y, Wang C, Hou S. The Association between Telomere Length and Cancer Prognosis: Evidence from a Meta-Analysis. *PloS one* 2015; **10**(7): e0133174.

54. Zhang N, Fan C, Gong M, et al. Leucocyte telomere length and paroxysmal atrial fibrillation: A prospective cohort study and systematic review with meta-analysis. *Journal of clinical laboratory analysis* 2018: e22599.

55. Zhou J, Wang J, Shen Y, et al. The association between telomere length and frailty: A systematic review and meta-analysis. *Experimental gerontology* 2018; **106**: 16-20.

56. Zhu X, Han W, Xue W, et al. The association between telomere length and cancer risk in population studies. *Scientific reports* 2016; **6**: 22243.

57. Johnson VE. Revised standards for statistical evidence. *Proceedings of the National Academy of Sciences* 2013.

58. Ioannidis JPA. The Proposal to Lower P Value Thresholds to .005. *Jama* 2018; **319**(14): 1429-30.

59. Allsopp RC, Chang E, Kashefi-Aazam M, et al. Telomere shortening is associated with cell division in vitro and in vivo. *Experimental cell research* 1995; **220**(1): 194-200.

60. Aragona M, Maisano R, Panetta S, et al. Telomere length maintenance in aging and carcinogenesis. *International journal of oncology* 2000; **17**(5): 981-90.

61. Harley CB, Vaziri H, Counter CM, Allsopp RC. The telomere hypothesis of cellular aging. *Experimental gerontology* 1992; **27**(4): 375-82.

62. Robinson MO. Telomerase and cancer. *Genetic engineering* 2000; **22**: 209-22.

63. De Vitis M, Berardinelli F, Sgura A. Telomere Length Maintenance in Cancer: At the Crossroad between Telomerase and Alternative Lengthening of Telomeres (ALT). *International journal of molecular sciences* 2018; **19**(2).

64. D'Arcangelo D, Tinaburri L, Dellambra E. The Role of p16(INK4a) Pathway in Human Epidermal Stem Cell Self-Renewal, Aging and Cancer. *International journal of molecular sciences* 2017; **18**(7).

65. Sanchez-Espiridion B, Chen M, Chang JY, et al. Telomere length in peripheral blood leukocytes and lung cancer risk: a large case–control study in Caucasians. *Cancer research* 2014.

66. American Diabetes A. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2010; **33**(Suppl 1): S62-S9.

67. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**(6865): 813-20.

68. Tentolouris N, Nzietchueng R, Cattan V, et al. White Blood Cells Telomere Length Is Shorter in Males With Type 2 Diabetes and Microalbuminuria. *Diabetes Care* 2007; **30**(11): 2909-15.

69. Panossian LA, Porter VR, Valenzuela HF, et al. Telomere shortening in T cells correlates with Alzheimer’s disease status. *Neurobiology of Aging* 2003; **24**(1): 77-84.

70. Eitan E, Hutchison ER, Mattson MP. Telomere shortening in neurological disorders: an abundance of unanswered questions. *Trends in Neurosciences* 2014; **37**(5): 256-63.

71. S. SN, M. MJ. The Relationship Between Perceived Stress and Telomere Length: A Meta-analysis. *Stress and Health* 2016; **32**(4): 313-9.

72. Mundstock E, Zatti H, Louzada FM, et al. Effects of physical activity in telomere length: Systematic review and meta-analysis. *Ageing Research Reviews* 2015; **22**: 72-80.

73. Li X, Meng X, Timofeeva M, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *Bmj* 2017; **357**.

74. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *The Milbank quarterly* 2016; **94**(3): 485-514.

75. Januszkiewicz D, Wysoki J, Lewandowski K, et al. Lack of correlation between telomere length and telomerase activity and expression in leukemic cells. *International journal of molecular medicine* 2003; **12**(6): 935-8.

76. Hunt SC, Kimura M, Hopkins PN, et al. Leukocyte telomere length and coronary artery calcium. *The American journal of cardiology* 2015; **116**(2): 214-8.

77. Kark JD, Nassar H, Shaham D, et al. Leukocyte telomere length and coronary artery calcification in Palestinians. *Atherosclerosis* 2013; **229**(2): 363-8.

78. Kroenke CH, Pletcher MJ, Lin J, et al. Telomerase, telomere length, and coronary artery calcium in black and white men in the CARDIA study. *Atherosclerosis* 2012; **220**(2): 506-12.

79. Mainous AG, 3rd, Codd V, Diaz VA, et al. Leukocyte telomere length and coronary artery calcification. *Atherosclerosis* 2010; **210**(1): 262-7.

**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 | **I2** | **p-value Egger** | **Small study effect** | **Excess significance bias** | **Largest study significant** | **Cases** | **Controls** | **Sample size** | **Level of evidence**b |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gastric cancer[56](#_ENREF_56) | 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[41](#_ENREF_41) | - | Case-control | NA | SMD | 13 | -0·98  (-1·43;  -0·54) | 0·00001 | 92 | 0·07 | yes | no | yes | 748 | 1808 | 2536 | **III** |
| Diabetes[51](#_ENREF_51) | - | 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[53](#_ENREF_53) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[53](#_ENREF_53) | 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[43](#_ENREF_43) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[42](#_ENREF_42) | - | Case-control | NA | MD | 7 | -0·04  (-0·07;  -0·001) | 0·046 | 86 | 0·54 | no | NP | yes | 1024 | 1234 | 3745 | **IV** |
| RA[45](#_ENREF_45) | - | 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)[46](#_ENREF_46) | - | 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[37](#_ENREF_37) | - | Case-control | NA | SMD | 11 | -0·55  (-0·92;  -0·18) | 0·003 | 96 | 0·38 | no | NA | yes | 2227 | 3142 | 5369 | **IV** |
| PTSD[37](#_ENREF_37) | - | Case-control | NA | SMD | 5 | -1·27  (-2·11;  -0·43) | 0·003 | 94 | 0·22 | no | NA | no | 217 | 2888 | 3105 | **IV** |
| Anxiety[37](#_ENREF_37) | - | Case-control | NA | SMD | 3 | -0·53  (-1·06;  -0·008) | 0·047 | 97 | 0·31 | no | NA | yes | 1599 | 2268 | 3867 | **IV** |
| SLE[44](#_ENREF_44) | - | Case-control | NA | SMD | 12 | -0·84  (-1·29;  -0·38) | 0·0003 | 89 | 0·33 | no | NA | yes | 472 | 365 | 837 | **IV** |
| Depression  [50](#_ENREF_50) | - | 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[38](#_ENREF_38) | 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[38](#_ENREF_38) | 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[38](#_ENREF_38) | 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[10](#_ENREF_10) | 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[39](#_ENREF_39) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[39](#_ENREF_39) | 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[39](#_ENREF_39) | 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** |
| Colorectal cancer[56](#_ENREF_56) | 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[52](#_ENREF_52) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[56](#_ENREF_56) | 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[53](#_ENREF_53) | 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[53](#_ENREF_53) | 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[52](#_ENREF_52) | 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[36](#_ENREF_36) | 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[36](#_ENREF_36) | 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[43](#_ENREF_43) | 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[56](#_ENREF_56) | 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** |
| Frailty[55](#_ENREF_55) | - | 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[37](#_ENREF_37) | - | 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[37](#_ENREF_37) | - | 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[48](#_ENREF_48) | - | 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[40](#_ENREF_40) | - | Case-control | NA | SMD | 8 | 0·36  (-0·25; 0·96) | 0·25 | 97 | 0·52 | no | no | no | 956 | 1284 | 2240 | **NS** |
| Depression[50](#_ENREF_50) | - | Cross-sectional | NA | MD | 16 | -0·06  (-0·13; 0·01) | 0·11 | 67 | 0·29 | no | NA | no | 7335 | 16482 | 26660 | **NS** |
| Schizophrenia[49](#_ENREF_49) | - | Case-control | NA | SMD | 7 | 0·34  (-0·05; 0·73) | 0·09 | 91 | 0·08 | yes | no | yes | 883 | 865 | 1748 | **NS** |
| AF[54](#_ENREF_54) | - | 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)[54](#_ENREF_54) | 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** |  |

aP value of summary random effects estimate.

bEvidence class criteria: class I (convincing): statistical significance with P<10−6, more than 1,000 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 (I2<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 1,000 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 1,000 cases (or >20,000 participants for continuous outcomes); class IV (weak): the remaining statistically significant associations with P<0.05.

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

**Figure 1. PRISMA flow-chart**

**Identification**

Records identified through database searching in PubMed, PsychInfo, Embase  
(n = 328)

Additional records identified through manual search  
(n = 0)

Records screened  
(n = 257)

Records after duplicates were removed  
(n = 257)

**Screening**

Records excluded based on title/abstract  
(n =216)

Publications excluded (n =20)

*Doubled (n=13)*

*No formal meta-analysis (n=5)*

*No systematic review (n=1)*

*Meta-analyses with only one study (n=1)*

**Eligibility**

Full-text articles assessed for eligibility   
(n =41)

Meta-analyses included in umbrella review  
(n = 21)

*50 outcomes*

**Included**

**Supplementary Table 1: AMSTAR-2 quality assessment of systematic reviews and meta-analysis.**

|  | **AMSTAR-2 items** | | | | | | | | | | | | | | | |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year**  **[Reference]** | **1** | **2\*** | **3** | **4\*** | **5** | **6** | **7\*** | **8** | **9\*** | **10** | **11\*** | **12** | **13\*** | **14** | **15\*** | **16** | **Level Of Evidences\*\*** |
| Chunli Zhang,2015 | Yes | No | Yes | No | No | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Diego A. Forero,2016a | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Critically low |
| Diego A. Forero,2016b | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Critically low |
| G.B. Polho,2015 | Yes | No | Yes | No | No | Yes | No | No | Yes | No | Yes | No | No | Yes | No | Yes | Critically low |
| Gustav Nilsonne,2015 | Yes | No | Yes | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| John M. Malouff & Nicola S. Schutte,2016 | Yes | No | Yes | No | No | No | No | Yes | Yes | No | Yes | Yes | Yes | No | No | No | Critically low |
| Jianfei Wang,2016 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Jianghua Zhou,2018 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Critically low |
| Kaoutar Ennour-Idriss,2016 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | NA | NA | Yes | Yes | NA | Yes | Low |
| Kathryn K. Ridout,2016 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Low |
| Linda Kachuri,2016 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | NA | NA | Yes | Yes | NA | Yes | Moderate |
| Matthew J.J. D’Mello,2015 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Critically low |
| Nixiao Zhang,2018 | Yes | Yes | Yes | Yes | No | Yes | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Pan Huang, 2017 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Critically low |
| Philip C Haycock,2014 | Yes | No | Yes | Yes | Yes | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Roman Adam,2017 | Yes | No | Yes | Yes | Yes | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Sabrina M. Darrow, 2016 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Wei Wang, 2017 | Yes | No | Yes | Yes | Yes | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |
| Xun Zhu,2016 | Yes | No | Yes | No | No | No | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| Y. H. Lee, 2017 | Yes | No | Yes | Yes | No | No | No | Yes | Yes | No | Yes | yes | Yes | Yes | Yes | Yes | Critically low |
| Y. H. Lee, 2018 | Yes | No | Yes | Yes | No | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Critically low |

NA: No meta-analysis conducted

AMSTAR-2 items: <https://www.bmj.com/content/358/bmj.j4008>

**\***AMSTAR 2 critical domains

**\*\*High**: No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest/ **Moderate**: More than one non-critical weakness: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review/ **Low:** One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest/ **Critically low**: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.