

Associations between leukocyte telomere length and gastric cancer risk: a systematic review and meta-analysis

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Abstract

Background Gastric cancer (GC) is one of the most prevalent malignancies, characterized by an abysmally poor prognosis predominantly due to late-stage detection, necessitating biomarkers for effective risk stratification and early detection. Telomere length (TL), a regulator of genomic stability and senescence, has been proposed as a potential biomarker.

Methods We searched PubMed, Scopus and the Cochrane Library for eligible studies published up to January 2025 that measured TL in peripheral blood leukocytes and reported GC risk estimates. Pooled risk estimates were calculated using a random-effects model.

Results The meta-analysis revealed a significant association between shorter telomeres and greater risk of GC, yielding a pooled odds ratio (OR) of 2.13 (95% confidence interval [CI] 1.21-3.78). Subgroup analyses suggest that this association may be stronger among individuals without *Helicobacter pylori* infection (OR 3.38, 95%CI 1.74-6.56) than those infected (OR 1.77, 95%CI 1.37-2.27), but the difference failed to reach statistical significance ($P=0.0725$). Geographical stratification indicated a stronger association in Asian populations (OR 3.09, 95%CI 1.60-5.98) than Western cohorts (OR 1.20, 95%CI 0.88-1.63). In contrast, subgroup analyses evaluating smoking status, alcohol consumption and sex revealed no significant modification of the TL-GC relationship. We investigated the potential for a non-linear, U-shaped association between TL and GC risk; however, available evidence did not substantiate this hypothesis.

Conclusions These findings indicate that TL in peripheral leukocytes may be a promising biomarker for GC risk. Further prospective, standardized studies are warranted to validate and expand our results, facilitating the integration of TL as a risk biomarker in GC.

Keywords Stomach neoplasms, telomeres, leukocytes, biomarkers

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Conflict of Interest: None

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Introduction

Gastric cancer (GC) is one of the most prevalent forms of cancer, with global estimates indicating that over 1 million new cases are identified each year, resulting in nearly 800,000 deaths [1]. These numbers are projected to rise further, driven by both population aging and growth in high-risk demographics. There are substantial geographic variations in GC incidence, the highest rates being found in East Asia, Central and Eastern Europe, and South America [2,3]. Presently, the principal treatment modalities for GC include surgery and systemic chemotherapy, with immunotherapy and targeted therapy increasingly being incorporated [4]. Early GC

is asymptomatic, leading to frequent diagnosis at advanced stages of the disease [5]. Consequently, when identified at a late stage, around 60% of individuals with GC ultimately prove unsuitable for curative therapy, mainly because of metastases or the presence of additional comorbidities, and the 5-year survival rate falls below 5% [6,7]. Hence, detecting GC at an early stage is crucial for improving patient outcomes.

The gold standard for diagnosing GC is endoscopic examination accompanied by forceps biopsies [8]. In countries with a high incidence of GC, population-based screening programs have been instituted and have successfully improved outcomes. However, endoscopic screening is not cost-effective for large-scale screening in populations with lower incidence rates, such as most Western nations [9]. Accordingly, biomarkers are critical for risk stratification, to direct screening and improve early detection and consequently survival.

In cancer, the role of telomere length (TL) is multifaceted. Telomere shortening can impede tumor progression through induction of apoptosis and senescence, but can also drive neoplastic development by increasing genomic instability [10,11]. Telomeres are nucleoprotein complexes made up of repetitive hexameric DNA sequences that serve as protective caps on eukaryotic chromosomes, thereby maintaining genomic integrity by averting terminal degradation and preventing chromosome end-fusions [12–14]. They incorporate repetitive hexameric units (5'-TTAGGG-3') spanning approximately 10–15 kilobases in human cells [12–14]. Telomeres progressively shorten after every division, ultimately triggering senescence or apoptosis once a critical threshold is reached. Telomerase activity helps sustain telomeres, and is normally detected in germline cells, stem cells and certain somatic cell populations requiring extensive proliferation, though it is generally diminished or absent in most somatic cells [15,16]. Reactivating telomerase is a pivotal step in oncogenesis, as it counteracts telomere attrition, thereby bypassing the signals for senescence and apoptosis [16,17]. However, telomere-related tumorigenesis remains a complex field, and many of the fundamental mechanisms remain only partly characterized. [10,18,19].

Beyond its mechanistic role in carcinogenesis, telomere length has increasingly been investigated as a clinically informative biomarker for cancer risk assessment, prognosis and prediction of treatment outcomes [20,21]. Leukocyte telomere length is particularly attractive for clinical translation, because it can be assessed through a minimally invasive

peripheral blood sample and may capture systemic biological processes relevant to cancer susceptibility [20–23]. Studies investigating the link between TL and cancer susceptibility show substantial variability depending on tumor type, with research demonstrating shorter telomeres correlating with a greater risk of cancer overall, and of various specific cancers, including urological, head and neck, mesothelioma and esophageal cancer [24–29]. Conversely, analyses of breast, colorectal and non-melanoma skin cancers failed to find a significant association, while longer TL has been linked to an elevated risk of lung cancer and melanoma [30–33].

The abysmal prognosis associated with the late-stage diagnosis of CG highlights the need for innovative approaches to risk stratification, and for early identification methods that can facilitate prevention and timely intervention. To our knowledge this constitutes the first systematic review and meta-analysis examining the association between TL and GC risk, aiming to elucidate its potential as biomarker.

Materials and methods

Search strategy

This study aimed to assess the link between TL and the risk of GC by conducting a systematic review and meta-analysis. The research followed the protocols outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO CRD42025639403 [34] (Supplementary Table 1).

A thorough search of the literature was performed to identify eligible studies published up to January 2025. The search encompassed major databases, including PubMed, the Cochrane Library and Scopus. The search strategy incorporated both Medical Subject Headings (MeSH) and relevant keywords focused on TL and GC risk. Specific terms, such as “telomere”, “telomere length”, “gastric cancer” and “gastric neoplasms”, were used, with Boolean operators “AND” and “OR” applied to combine them effectively. To ensure comprehensiveness, references from pertinent reviews were also examined to uncover additional studies not captured by the initial search.

Eligibility criteria

Inclusion in this meta-analysis was based on a predefined set of criteria, structured according to the Population, Intervention, Comparison, and Outcome (PICO) framework. Studies had to meet the following requirements:

Population (P): Only studies pertaining to GC were included. We excluded research focused on non-malignant or pre-malignant conditions, as well as studies involving non-human participants or cell lines. Intervention (I): To be eligible, studies needed to directly measure TL in peripheral blood leukocytes (PBL). Studies that relied on alternative biological materials or indirect methods (such as genetic risk scores)

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were excluded. Comparison (C): Eligible studies required a comparison between individuals diagnosed with GC and a healthy control group. Studies without a comparator group were excluded. Outcome (O): Studies must have reported relative risk measures, such as odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), accompanied by 95% confidence intervals (CIs), to be included in the quantitative synthesis.

Only observational designs—cohort, case-control or nested case-control—were considered, while review articles, meta-analyses, case reports, conference abstracts and dissertations were excluded. Furthermore, studies were restricted to those published in English, with no limitations based on publication date.

Selection of studies and data extraction

Upon retrieving the relevant articles, we initially screened them based on titles and abstracts to determine their eligibility. Full-text articles were subsequently reviewed for final inclusion, particularly those whose eligibility was uncertain based on abstract review alone. This process was performed independently by 2 reviewers, and any disagreements were resolved through discussion and mutual agreement.

The extraction of data was conducted independently by 2 reviewers, using a standardized extraction form to ensure consistency. Any differences in data extraction were resolved through consensus. The data extracted included: study title, name of first author, year of publication, geographic region, type of cancer, ethnic or racial composition of study population, study design, age and sex distributions for both cases and controls, number of cases and controls, methods of measuring TL, tissue source of DNA, TL categorization cutoff values, and the relative risk metrics (ORs, RRs, or HRs), along with their corresponding 95%CIs. In cases where multiple datasets from the same article were independent, they were considered separate studies. If there was overlap in participant samples between studies, the study with the largest number of cases was selected for inclusion, or in cases of similar sample sizes, the study adjusting for more covariates was preferred.

Statistical analysis

Data processing

For the meta-analysis, we standardized effect estimates across studies to ensure comparability, comparing the shortest TL with the longest TL group, consistently assigning the group with the longest TL as the reference. In those studies, namely Du *et al* [35] and Wang *et al* [36], that did not report risk estimates using the longest TL as reference, we performed re-parameterization of risk estimates. Specifically, studies that initially utilized alternative reference categories underwent logarithmic transformation of their reported risk estimates and associated 95%CIs to facilitate accurate recalibration. This re-parameterization approach involved computing

log-transformed ratios of original effect estimates relative to the category corresponding to the longest TL, accounting for variance propagation by combining standard errors appropriately via the delta method. The standard errors (SEs) were recomputed under the assumption of independence between the effect estimates when re-referencing. Given that individual studies did not provide covariance estimates between different TL categories, we assumed covariance to be zero. In studies where TL was reported as a continuous variable, the effect estimate corresponding to a decrease in TL was utilized. If a study reported multiple relative risk estimates, the one with the most comprehensive set of adjustments was selected for inclusion. Effect estimates were transformed when necessary to ensure that the longest TL served as the reference group.

Meta-analysis model

Heterogeneity across studies was assessed through Cochran's Q test, with a P-value threshold of <0.10 indicating significant heterogeneity. We quantified heterogeneity further using the I^2 statistic, where values of 25%, 50% and 75% represented low, moderate and high levels of heterogeneity, respectively [37,38]. Given the expected clinical and methodological diversity among studies, a random-effects model was employed for the meta-analysis, regardless of the statistical significance of heterogeneity. The statistical approach was refined after protocol registration using the restricted maximum likelihood (REML) method, which provides less biased variance estimates compared to traditional approaches. The Knapp-Hartung adjustment was applied to obtain more robust and conservative CIs for the pooled effect sizes. Additionally, prediction intervals were calculated to reflect the expected range of effect sizes in future studies, accounting explicitly for between-study heterogeneity. Confidence intervals for the between-study variance estimate (τ^2) were also reported. ORs were log-transformed for meta-analytic calculations, and their standard errors were used in the analysis.

Sensitivity and subgroup analyses

Subgroup analyses were carried out to explore potential sources of heterogeneity and investigate the robustness of the results. To provide a more comprehensive assessment, the subgroup analyses prespecified in the protocol were expanded to include additional clinically relevant factors. Subgroups were defined according to geographic region, sex, smoking and alcohol consumption habits, *Helicobacter pylori* (*H. pylori*) infection status and TL parameterization. To maintain methodological consistency in the pooled estimates, we excluded from the subgroup analysis any subgroups that lacked a clearly defined internal reference category. For inclusion, each subgroup had to use an internal reference for the calculation of the risk estimates. Thus, we excluded smokers from Liu *et al* [39] and Pan *et al* [40], and ever drinkers from Pan *et al* [40], since the risk estimates utilized non-smokers and non-drinkers

as reference, respectively. Since the number of studies in all subgroups in the subgroup analysis was substantially smaller than 10, the estimation of between-study variance (τ^2) when applying the Knapp–Hartung adjustment would be highly uncertain, resulting in excessively wide confidence intervals, severely limiting interpretability. Therefore, we opted to report standard (Wald-type) confidence intervals without the Knapp–Hartung adjustment for the subgroup analysis. In addition, a sensitivity analysis was performed by systematically removing each study to assess its influence on the overall effect estimate.

The statistical analyses were conducted using R software (version 4.4.1), employing the ‘meta’ and ‘metafor’ packages. Statistical significance was set at a 2-tailed P-value of <0.05, unless otherwise stated.

Publication bias assessment

To evaluate the presence of publication bias, we used funnel plots for visual inspection and performed statistical tests, including Egger’s regression test and Begg’s test [41,42]. A P-value less than 0.05 was considered suggestive of publication bias.

Quality assessment

The methodological quality of the included studies was evaluated independently by 2 reviewers using the Newcastle–Ottawa Scale (NOS), designed for observational studies. This scale assesses studies in 3 key domains: selection of participants, comparability of study groups, and ascertainment of exposure and outcomes. The maximum possible score is 9 stars, with scores of 7 or more indicating high-quality studies, scores of 5–6 indicating moderate quality, and scores below 5 indicating low quality. Any disagreements in quality assessments were resolved through discussion and consensus.

Results

Study selection

A comprehensive search across PubMed, Cochrane library and Scopus databases identified 1373 articles. After removal of duplicates, 1050 articles were screened based on their titles and abstracts, leading to the exclusion of 1019 articles that were deemed irrelevant to the research question. The full texts of the remaining 31 articles were retrieved for further review. Following a detailed assessment, 21 articles were excluded for failing to meet the predefined eligibility criteria, including the absence of a control group, use of non-human subjects, and insufficient data on TL. Finally, 10 studies met the inclusion criteria for the systematic review and meta-analysis [35,36,39,40,43–48] (Fig. 1).

Study characteristics

The key characteristics of the included studies are detailed in Table 1. The majority of the studies were conducted in China (5), with additional studies from the USA (1), Poland (1), Singapore (1), Denmark (1), and the UK (1). Participants were mostly of Chinese Han descent, though the studies also included Hispanic American and European populations. The relative risk was expressed as ORs with 95% CIs, though studies also used HRs, which were treated as equivalent to ORs [49].

Meta-analysis results

The pooled OR for the association between TL and GC across 10 studies, using the REML random-effects model with the Knapp–Hartung adjustment, was 2.13 (95%CI 1.20–3.78), indicating a significant association between shorter telomeres and a greater risk of GC ($P=0.0146$) (Fig. 2).

Subgroup analysis results

To explore the association between TL and GC risk, we conducted subgroup analyses across various factors, including geographic region, sex, smoking, alcohol consumption, *H. pylori* status and TL parameterization.

A subgroup analysis by *H. pylori* status demonstrated that shorter TL was more strongly associated with GC risk in individuals without *H. pylori* infection (OR 3.38, 95%CI 1.74–6.56) compared to those with a positive *H. pylori* status (pooled OR 1.77, 95%CI 1.37–2.27). However, the test for subgroup differences was not statistically significant ($P=0.0725$) (Fig. 3).

In subgroup analyses by smoking status, both non-smokers (OR 2.42, 95%CI 1.65–3.54) and ever smokers (OR 2.06, 95%CI 1.28–3.30) exhibited a significant association between shorter TL and increased GC risk. The test for subgroup differences was not significant ($P=0.6048$), suggesting that the effect of TL on GC risk is similar for both smokers and non-smokers (Supplementary Fig. 1).

Analysis based on alcohol consumption habits revealed a stronger association between shorter TL and GC risk among non-drinkers (OR 2.58, 95%CI 1.63–4.09) compared to ever drinkers (OR 2.42, 95%CI 1.78–3.29). Despite the difference in magnitude, the test for subgroup differences was not statistically significant ($P=0.8193$), suggesting that the effect of TL on GC risk does not substantially differ between drinkers and non-drinkers (Supplementary Fig. 2).

The association between shorter TL and GC risk was similar in both males (OR 2.19, 95%CI 1.07–4.50) and females (OR 2.30, 95%CI 1.16–4.54). The test for subgroup differences showed no significant effect between males and females ($P=0.9262$), indicating that the TL–GC association is consistent across sex (Supplementary Fig. 3).

In subgroup analyses based on geographic location, a notable difference was observed in the strength of the

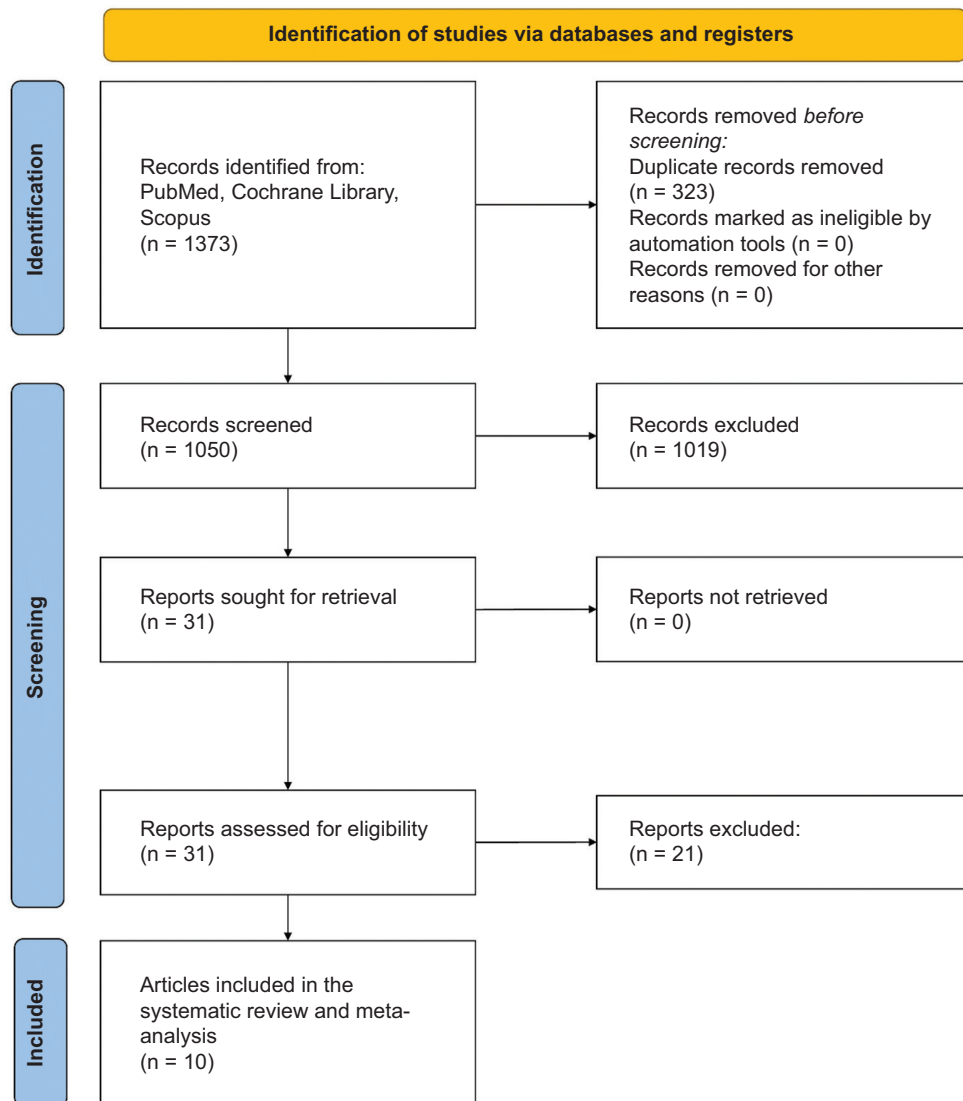


Figure 1 PRISMA flow diagram of the systematic review and meta-analysis

association between TL and GC risk. Studies from Asian countries demonstrated a stronger association, with a pooled OR of 3.09 (95%CI 1.60-5.98), compared to those from Western countries, where the pooled OR was 1.20 (95%CI 0.88-1.63). The test for subgroup differences was statistically significant ($P=0.0108$), suggesting that the association may significantly vary across geographic regions (Fig. 4).

To further investigate the association between GC risk and TL parameterization, we conducted an analysis of studies that used the median TL to parameterize TL and defined long and short TL, with the former as the reference. The pooled OR for GC being associated with TL across the studies of only dichotomous TL parameterization based on median TL was 2.72 (95%CI 1.24- 5.95), indicating a significant association ($P=0.0125$) (Supplementary Fig. 4). Additionally, we conducted an analysis using the second longest category of TL as the reference, compared with the longest, in order to examine the possibility of a U-shaped relationship. The synthesis found a

pooled OR of 1.52 (95%CI 0.84-2.75), suggesting that there was no significant U-shaped relationship between TL and GC risk ($P=0.1689$) (Fig. 5).

Publication bias and quality

A visual inspection of the funnel plot suggests some asymmetry, especially at the upper end, among the studies with smallest standard errors, which could be evidence of publication bias (Supplementary Fig. 5). Publication bias was assessed using both Egger's and Begg's tests for funnel plot asymmetry. Egger's test revealed a significant result, with a t-statistic of 3.08 ($df=8$) and a P-value of 0.0152. This suggests a potential for publication bias in the studies included in the meta-analysis. The bias estimate was 5.03 ($SE=1.63$), indicating that the observed effect may be influenced by a small degree of asymmetry in the funnel plot. Begg's test yielded a z-statistic

Table 1A General characteristics of studies included in the meta-analysis

Author & year [ref.]	Country	Type	Population	Ethnicity	%Male cases	%Male controls	Age cases	Age controls
Liu <i>et al.</i> 2009 [39]	China	Gastric cancer	Hospital-based (Xijing and Tangdu Hospitals, The Fourth Military Medical University)	Chinese Han	65%	63%	52.7	53.1
Hou <i>et al.</i> 2009 [43]	Poland	Gastric adenocarcinoma	Population-based (Warsaw, Poland)	European (Polish)	66.30%	64.70%	Not specified	Not specified
Sun <i>et al.</i> 2014 [44]	USA	Gastric cancer	Hospital-based (MD Anderson Cancer Center & Kelsey-Seybold Clinic)	Hispanic American	56.06%	52.00%	58.19±13.58	55.46±12.75
Du <i>et al.</i> 2015 [35]	China	Gastric cancer	Hospital-based (Jiangsu Province)	Chinese	74.30%	77.20%	Not specified	Not specified
Rode <i>et al.</i> 2016 [45]	Denmark	Stomach cancer	Population-based (Copenhagen City Heart Study & Copenhagen General Population Study)	Danish (European)	Not specified	Not specified	Not specified	Not specified
Pan <i>et al.</i> 2016 [40]	China	Gastric cancer	Hospital-based (Shandong Cancer Hospital, Jinan, Shandong Province)	Chinese Han	Matched Not specified	Matched Not specified	Matched Not specified	Matched Not specified
Liu <i>et al.</i> 2018 [46]	China	Gastric cardia adenocarcinoma	Hospital-based (Shandong Cancer Hospital, Shandong University)	Chinese Han	81.87%	85.29%	Not specified	Not specified
Wang <i>et al.</i> 2018 [36]	Singapore	Gastric adenocarcinoma	Population-based (Singapore Chinese Health Study)	Chinese (Hokkien, Cantonese)	Not specified	Not specified	Not specified	Not specified
Lili <i>et al.</i> 2020 [47]	China	Gastric carcinoma	Hospital-based (People's Hospital of Xinjiang Uygur Autonomous Region)	Chinese	53.20%	46.70%	62.51±7.76	63.69±9.26
Schneider <i>et al.</i> 2022 [48]	UK	Malignant neoplasm of the stomach	Population-based (UK Biobank)	Predominantly Caucasian	Not specified	Not specified	Not specified	Not specified

(Contd...)

Table 1A (Continued)

Study [ref.]	Study design	Cases/controls	Measurement method	DNA source	Effect estimate (95%CI)	TL categorization	Factors adjusted
Table 1B (Continuation)							
Liu <i>et al.</i> 2009 [39]	Case-control	396/378	RTL (T/S ratio) qPCR	PBL	3.12 (2.01–4.79)	Shortest RTL quartile vs longest RTL quartile	Age, sex, smoking, drinking, H. pylori
Hou <i>et al.</i> 2009 [43]	Case-control	300/416	RTL (T/S ratio) qPCR	PBL	2.04 (1.33–3.13)	Shortest RTL quartile vs longest RTL quartile	Age, sex, smoking, pack-years of smoking
Sun <i>et al.</i> 2014 [44]	Case-control	132/125	RTL (T/S ratio) qPCR	PBL	1.21 (0.65–2.27)	Median RTL	Age, sex, smoking, BMI
Du <i>et al.</i> 2015 [35]	Case-control	1136/1012	RTL (T/S ratio) qPCR	PBL	2.14 (1.58–2.88)*	Shortest RTL quintile vs longest RTL quintile*	Age, sex, smoking, drinking
Rode <i>et al.</i> 2016 [45]	Cohort study	81/65,145	RTL (T/S ratio) qPCR	PBL	1.02 (0.96–1.08)	RTL as a continuous variable, per 200 base-pairs decrease	Age, sex, body mass index, smoking status, tobacco consumption, alcohol intake
Pan <i>et al.</i> 2016 [40]	Case-control	574/774	RTL (T/S ratio) qPCR	PBL	4.10 (2.78–6.05)	Shortest RTL quartile vs longest RTL quartile	Age, sex, smoking, drinking
Liu <i>et al.</i> 2018 [46]	Case-control	524/510	RTL (T/S ratio) qPCR	PBL	2.18 (1.47–3.22)	Shortest RTL quartile vs longest RTL quartile	Age, sex, smoking, drinking
Wang <i>et al.</i> 2018 [36]	Prospective cohort study	220/26,540	RTL (T/S ratio) qPCR	PBL	1.05 (0.69–1.59)*	Shortest RTL quintile vs longest RTL quintile*	Age, sex, education, smoking, alcohol, dialect group, recruitment year
Lili <i>et al.</i> 2020 [47]	Case-control	1000/1100	RTL (T/S ratio) qPCR	PBL	12.67 (8.96–20.45)	Median RTL	Age, sex, smoking, drinking
Schneider <i>et al.</i> 2022 [48]	Cohort study	NR/425, 146	RTL (T/S ratio) qPCR	PBL	1.01 (0.91–1.11)	RTL as a continuous variable, decreased telomere length (per SD)	Age, sex, body mass index, ethnicity, current smoking, cumulative smoking, alcohol intake, Charlson Comorbidity Index

*Re-parameterization has been performed, as described in 2.4 Data Processing

CI, confidence interval; TL, telomere length; RTL, relative telomere length; T/S, telomere repeat copy number to single-copy gene copy number ratio; qPCR, quantitative polymerase chain reaction; PBL, peripheral blood leukocytes; BMI, body mass index; NR, not reported; SD, standard deviation

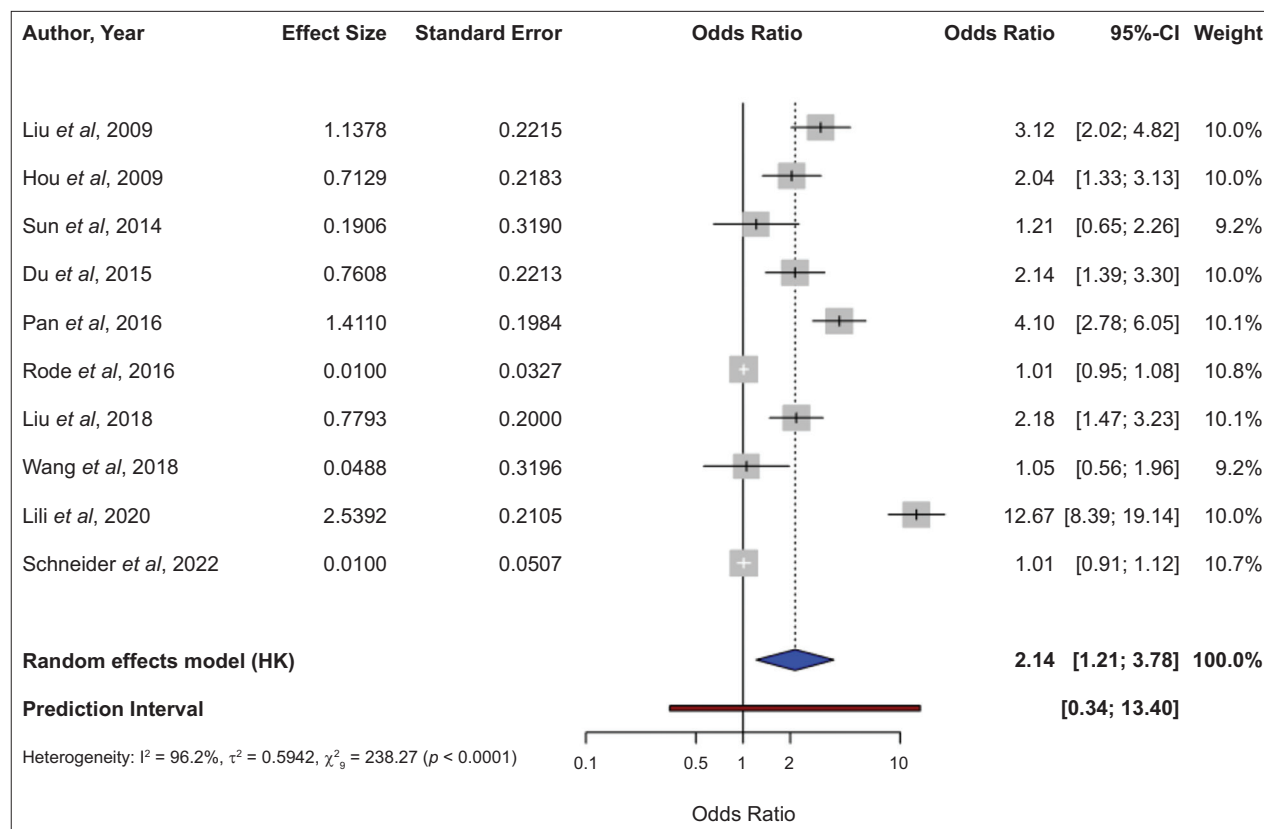


Figure 2 Forest plot of a meta-analysis depicting the association between telomere length and gastric cancer risk, using a random-effects model

of 0.09 and a P-value of 0.9287, which does not indicate significant publication bias. The bias estimate from this test was 1.00 (SE=11.18), further suggesting that there is no substantial evidence of bias in the dataset [41,42]. The quality assessment conducted using the NOS found that all studies scored at least 7, indicating that all studies included in the meta-analysis were of high quality.

Sensitivity analysis

A sensitivity analysis was conducted to assess the stability of the meta-analysis by systematically omitting each study and recalculating the pooled effect size and heterogeneity measures. The pooled OR ranged from 1.75 (95%CI 1.17-2.62) to 2.34 (95%CI 1.27-4.32), with no individual study exerting a disproportionate influence on the overall result. This supports the robustness of the findings and the persistence of the significant association between shorter TL and GC risk under all scenarios (Supplementary Fig. 6).

Discussion

Our present meta-analysis synthesizes evidence from 10 studies to quantify the relationship between TL and GC

risk. The main finding is that shorter telomeres significantly increase disease risk, with a pooled OR of 2.13 (95%CI 1.20-3.78, $P=0.0146$). These findings highlight the importance of telomere attrition as a contributor to gastric tumorigenesis.

From a clinical perspective, the relevance of leukocyte TL lies in providing a minimally invasive, systemic measure that could complement the clinical and pathological information currently used in gastric cancer assessment [20,21]. Leukocyte TL may also reflect host biological characteristics relevant to disease behavior, as GC cohorts have associated shorter telomeres with an immunosuppressive phenotype, advanced disease, recurrence and poorer survival [20,50,51]. In the pre-diagnostic setting, where early gastric cancer is frequently asymptomatic and population-wide endoscopy may be impractical, peripheral-blood TL could complement established demographic, familial, infectious and lifestyle factors in identifying individuals for more focused endoscopic assessment [21,52]. Following diagnosis, leukocyte TL may similarly be explored alongside tumor stage and other clinicopathological variables to refine prognostic stratification and identify patients who may require closer clinical surveillance. Thus, the principal translational interest is not the use of leukocyte TL in isolation, but its integration into multidimensional models of gastric cancer risk and clinical outcome.

At the mechanistic level, telomere shortening has long been recognized as an early, common genetic alteration leading

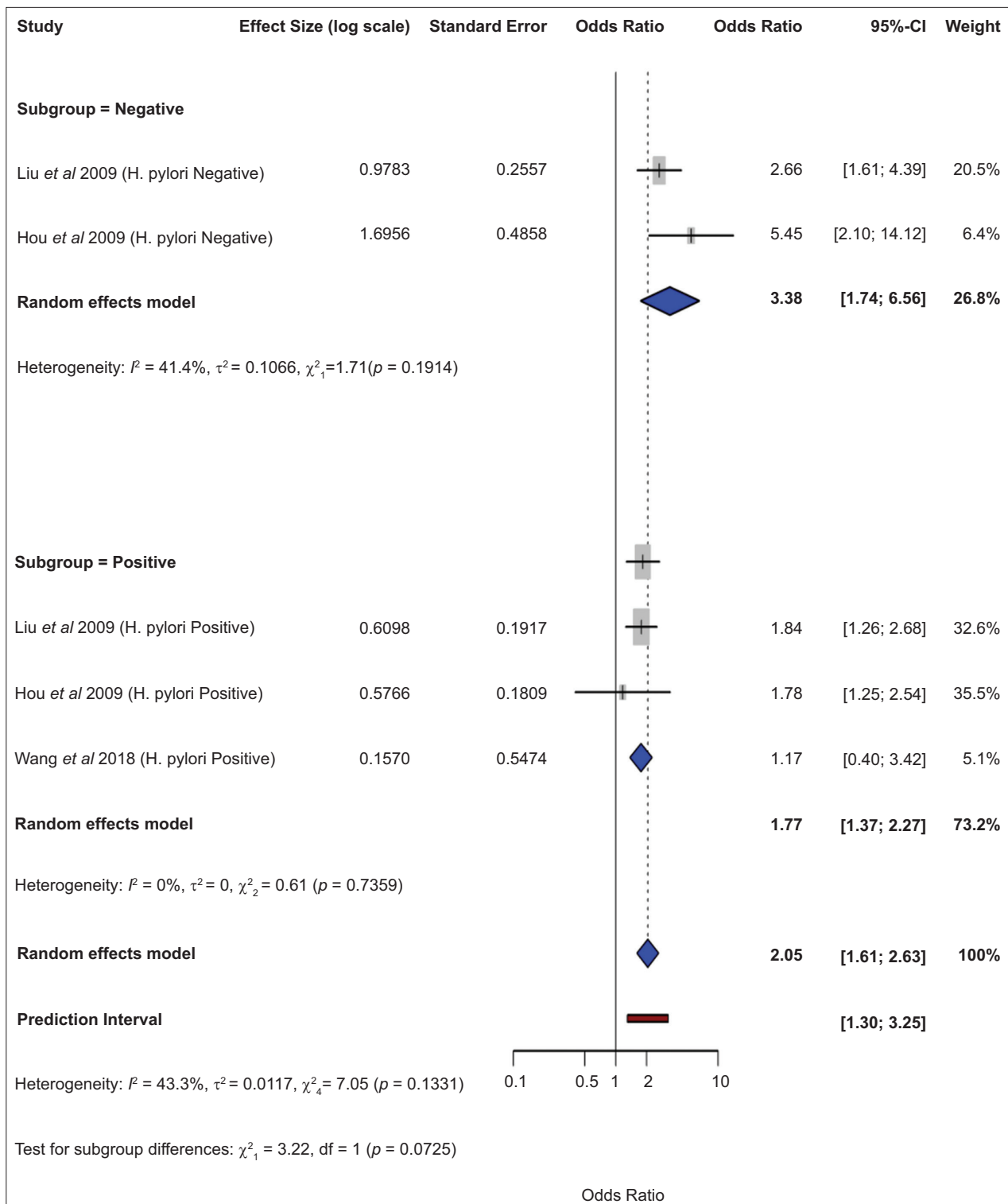


Figure 3 Forest plot of a subgroup analysis depicting the association between telomere length and gastric cancer risk stratified by *Helicobacter pylori* infection, using a random-effects model

to malignant transformation. Dysfunctional telomeres foster genomic instability, and an environment conducive to the accumulation of somatic mutations, promoting the formation of non-reciprocal chromosomal translocations,

which are hallmarks of epithelial tumors [15,53,54]. Animal models with critically short telomeres have a higher tumor burden and an enhanced predisposition to epithelial malignancies, partly due to the higher frequencies of

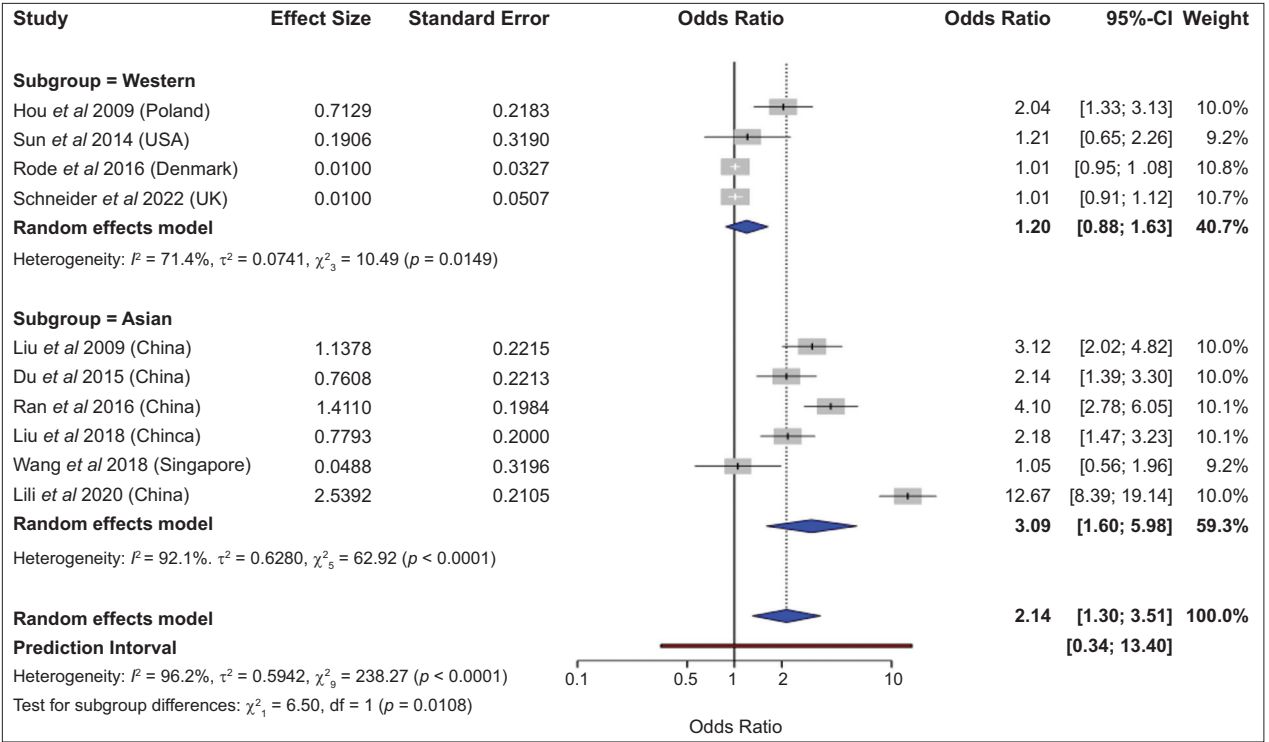


Figure 4 Forest plot of a subgroup analysis depicting the association between telomere length and gastric cancer risk stratified by geographic location (Asian vs. Western countries), using a random-effects model

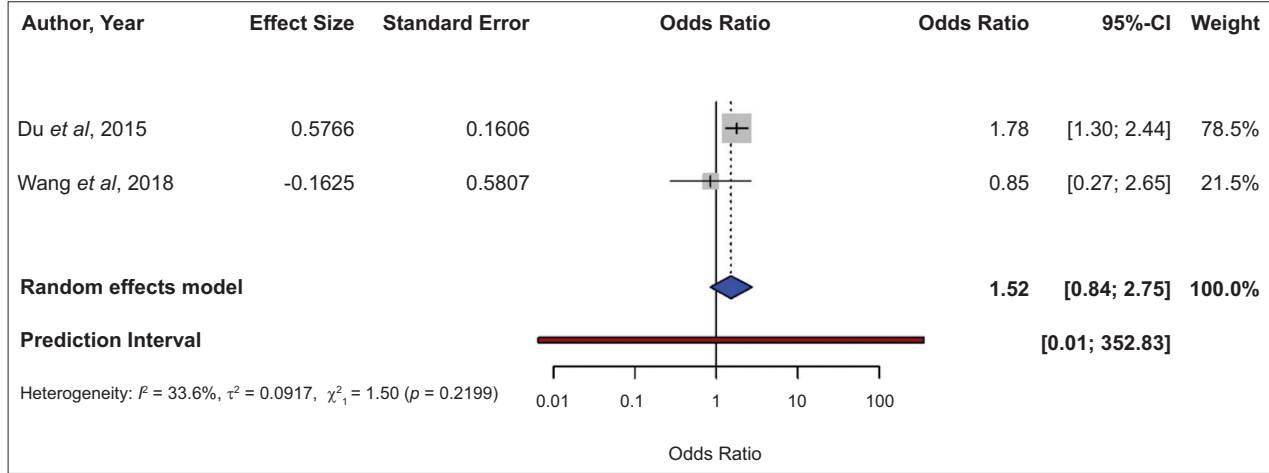


Figure 5 Forest plot of a meta-analysis depicting the association between telomere length (TL) and gastric cancer risk with the second longest category of TL as the reference, compared with the longest category

complex translocations, cytogenetic anomalies that mirror those found in human carcinomas [15,18]. Additionally, cells harboring telomere dysfunction exhibit reduced DNA repair capacity and complex chromosomal rearrangements [18,55]. In gastrointestinal malignancies, short telomeres have been associated with increased DNA methylation aberrations, chronic inflammation and intestinal metaplasia [36,50,56]. It has been suggested that these pathophysiological mechanisms may underlie the impact of telomere attrition on the malignant phenotype.

Notably, a subset of investigations in GC has also proposed a U-shaped relationship, where both extremely short and extremely long telomeres correlate with an elevated GC risk, suggesting that telomere biology exerts a dual influence on malignant transformation. Excessively long telomeres can support repeated cell cycles by conferring near-limitless replicative capacity. Because every round of genome duplication is an opportunity for replication errors, cells with unusually elongated telomeres might accumulate harmful mutations that promote transformation [18,53,57].

In an *in vitro* model of folic acid deficiency, early telomere elongation was linked to global DNA hypomethylation and markers of genomic instability, both regarded as hallmark events during carcinogenesis [58-60]. Genetic association studies demonstrated that alleles associated with both reduced and increased TL can predispose to various cancers [61,62]. Furthermore, clinically, a similar U-shaped pattern has been described for pancreatic cancer and breast cancer [63,64].

With regard to the possibility of a U-shaped relationship, we performed subgroup analyses. We conducted a subgroup of the studies reporting the relative risk measurements with parameterization based on median TL. The subgroups analysis identified a significant relationship between shorter TL and GC risk, concurring with our findings based on the highest compared to the lowest TL categories, and indicating that, overall, a shorter telomere confers a higher risk of GC. We also performed a subgroup analysis using the second longest category, compared with the longest, to ascertain the existence of a U-shape relationship; however, the results were non-significant. Most studies that reported parameterization based on quartiles or quantiles did not suggest a U-shaped relationship. However, the available data precluded the inclusion of most studies in the subgroup analysis, and the small number of available investigations makes it difficult to draw definitive quantitative conclusions. It is therefore critical that future studies include appropriate parameterization in order to ascertain the presence of a potential U-shape relationship in GC.

Risk factors associated with GC, including smoking, excessive alcohol consumption and *H. pylori* infection, may also interact with TL in modulating GC risk. Gastric *H. pylori* infection is a central etiologic factor in GC pathogenesis, and studies have found that mucosal cells harboring chronic *H. pylori* infection exhibit diminished TL [65,66]. This organism triggers chronic inflammation, which can induce heightened leukocyte turnover and greater oxidative stress, which have been found to contribute to accelerated telomere loss and telomere dysfunction [67,68].

Our subgroup meta-analysis showed a more pronounced association between short telomeres and GC risk in *H. pylori*-negative participants (OR 3.38, 95%CI 1.74-6.56) than in *H. pylori*-positive participants (OR 1.77, 95%CI 1.37-2.27), although the test for subgroup differences was not statistically significant ($P=0.0725$). One explanation is the phenomenon of competing risks, whereby individuals exposed to different carcinogenic pathways may develop tumors through distinct, and sometimes overlapping, mechanisms. Thus, when *H. pylori* is absent, telomere-driven carcinogenic processes might serve as a more dominant pathway leading to GC, while in *H. pylori*-positive individuals, multiple converging mechanisms of carcinogenesis, including direct mucosal damage and local immune dysregulation, may compete with, or partially overshadow, the role of telomere shortening. Adding further complexity, *H. pylori* detection in GC cases may be influenced by antibiotic exposures or disease-related changes. Thus, while *H. pylori* has been determined to contribute to GC risk, its interactions with telomere dynamics remain complex and merit further investigation.

Smoking is among the main risk factors for GC. Cigarette smoke contains a range of chemicals that generate reactive oxygen species, inducing oxidative damage and promoting telomere shortening [69,70]. Studies have reported a dose-response relationship between increasing pack-years of smoking and progressively shorter telomeres [71,72]. Some studies indicate that smokers with short telomeres carry a markedly greater risk of cancer than non-smokers with short telomeres, along with a synergy between short TL and tobacco [46,73]. However, our subgroup analysis suggests that both never-smokers and ever-smokers exhibit a similar significantly higher GC risk if telomeres are shortened; and we found no evidence of a statistical difference between these subgroups.

Studies suggest that habitual alcohol consumption might be linked to upregulation of telomerase, potentially leading to comparatively longer telomeres in some subgroups [74]. However, other investigations indicate that any protective or lengthening effect, if present, may be modest and overshadowed by the cumulative genotoxic effects of ethanol metabolism. Our subgroup analysis found that non-drinkers had a slightly higher pooled OR than ever drinkers, though this difference was not statistically significant.

Further, subgroup analysis based on geographic location revealed significant differences in the association between TL and GC risk, with studies conducted in Asia demonstrating a significant association, while among studies in western countries the association did not reach statistical significance. One potential explanation could be the differences in genetic, environmental and dietary factors between Eastern and Western populations, which may synergize with telomere attrition to heighten GC risk. Higher salt intake, common in Asian dietary patterns, has been associated with shorter TL, as the increased oxidative stress and inflammation caused by excessive salt intake potentially accelerate telomere shortening [75]. In Asia, chronic *H. pylori* infection is more prevalent, and has been linked with accelerated telomere attrition, thus potentially making short TL a more prominent risk factor for GC in these populations [76]. However, our study suggests that *H. pylori* infection decreases the association of short TL with GC. It is notable that, among Western studies, TL was parameterized in a continuous manner, rather than using a categorical approach, which could lead to the relationship being underpowered in the Western subgroup. Further studies are needed to elucidate these complex interactions and clarify the underlying mechanisms at play.

It has been proposed that telomere dynamics may exhibit sex-specific differences, with females generally possessing longer telomeres compared to males [77,78]. One potential explanation for this disparity involves the role of estrogen, which may exert a protective effect by promoting telomerase activity through the estrogen-responsive element located within the telomerase reverse transcriptase (hTERT) gene [79]. In a meta-analysis assessing the relationship between TL and colorectal cancer risk, a shift in the effect estimates was observed in female patients [78]. Our subanalysis found that the association between shorter telomeres and GC risk did not differ significantly between men and women.

Our meta-analysis revealed substantial heterogeneity, which may be attributed to a variety of factors, such as variations in study design, population demographics, and the extent to which confounding variables were accounted for. Publication bias was evaluated using both Egger's test and Begg's test, and the results were mixed. Egger's linear regression test for funnel plot asymmetry returned a statistically significant result ($t=3.08$, $df=8$, $P=0.0152$), suggesting the presence of asymmetry in the funnel plot and thus potential publication bias. The estimated bias was quantified as 5.03 (SE=1.63), indicative of an inflationary effect that could lead to an overestimation of the strength of the association between TL and GC risk.

However, the results of Egger's test must be interpreted with caution, since it is sensitive to variability in sample sizes across included studies, and significant heterogeneity in the study designs, populations and methodologies employed could artificially inflate the Type I error rate, especially given the number of studies in this analysis, which is at the lower limit for the utilization of Egger's test. In contrast, Begg's rank correlation test, which is generally considered less sensitive than Egger's test to small study effects, yielded a non-significant result ($z=0.09$, $P=0.9287$). The bias estimate from Begg's test was 1.00 (SE=11.18), a finding that further suggests that any bias present is relatively minimal. Additionally, all included studies were characterized by high methodological quality, based on the high NOS scores, indicating a relatively low risk of bias and good internal validity.

A potential limitation could be the variation in TL between peripheral blood and actual gastric tissue, which could introduce further complexity. Nonetheless, evidence shows a strong positive correlation between TL in blood and various somatic tissues, suggesting that leukocyte measurements can provide meaningful insights into systemic telomere biology [80]. Another potential limitation pertains to the variations in the categorization of TL. We performed re-parameterization of the risk estimates where possible to ensure homogeneity. Because covariance between TL categories was not reported, we assumed independence between estimates, which may potentially underestimate the variance if correlations exist. Additionally, re-parameterization was not always possible, as studies with the available data were insufficient to recalculate the relative risk measures to standardize TL categorization.

In summary, the current meta-analysis showed a possible association between short telomeres and a greater risk of GC. This result is consistent with mechanistic work pointing to telomere erosion as a prime instigator of chromosome instability. Although the majority of current data emphasizes the detrimental effect of telomere shortening, some findings raise the possibility that abnormally long telomeres can also facilitate gastric tumorigenesis, though our subgroup analysis did not confirm a statistically significant effect. Our analysis also elucidated the interactions between telomere biology and host factors, such as *H. pylori* infection, smoking and alcohol consumption, indicating that the association of telomere shortening with GC risk may be stronger in *H. pylori*-negative individuals, while finding no differences based on smoking and drinking habits. Furthermore, our study suggests that the association between TL and GC risk

may vary between Asian and Western regions. Future research should focus on replicating these findings within larger, multi-ethnic prospective cohort studies, aiming to minimize biases and enable comprehensive subgroup analyses that could help elucidate the complex interplay between telomere dynamics and gastric tumorigenesis. Furthermore, evaluating TL alongside measures of telomerase activity or telomere-maintenance gene polymorphisms might offer a more complete picture of telomeric alterations in tumorigenesis. Addressing these gaps is imperative for advancing our understanding of telomere dynamics in GC risk, and could potentially lead to novel therapeutic strategies aimed at modulating telomere biology in cancer prevention and treatment.

Summary Box

What is already known:

- Gastric cancer is commonly diagnosed at an advanced stage, and endoscopic screening is not readily applicable in low-incidence settings
- Telomere shortening promotes chromosomal instability and has been implicated in carcinogenesis, but its association with cancer risk differs across tumor types
- Published studies evaluating leukocyte telomere length and gastric cancer risk have yielded heterogeneous results

What the new findings are:

- Shorter leukocyte telomere length was associated with a greater risk of gastric cancer in the pooled analysis
- The association was stronger in Asian than in Western study populations, while the difference associated with *Helicobacter pylori* status was borderline
- No clear effect modification was observed by sex, smoking status or alcohol consumption, and the available data did not confirm a U-shaped association

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Supplementary material

Supplementary Table 1 PRISMA checklist

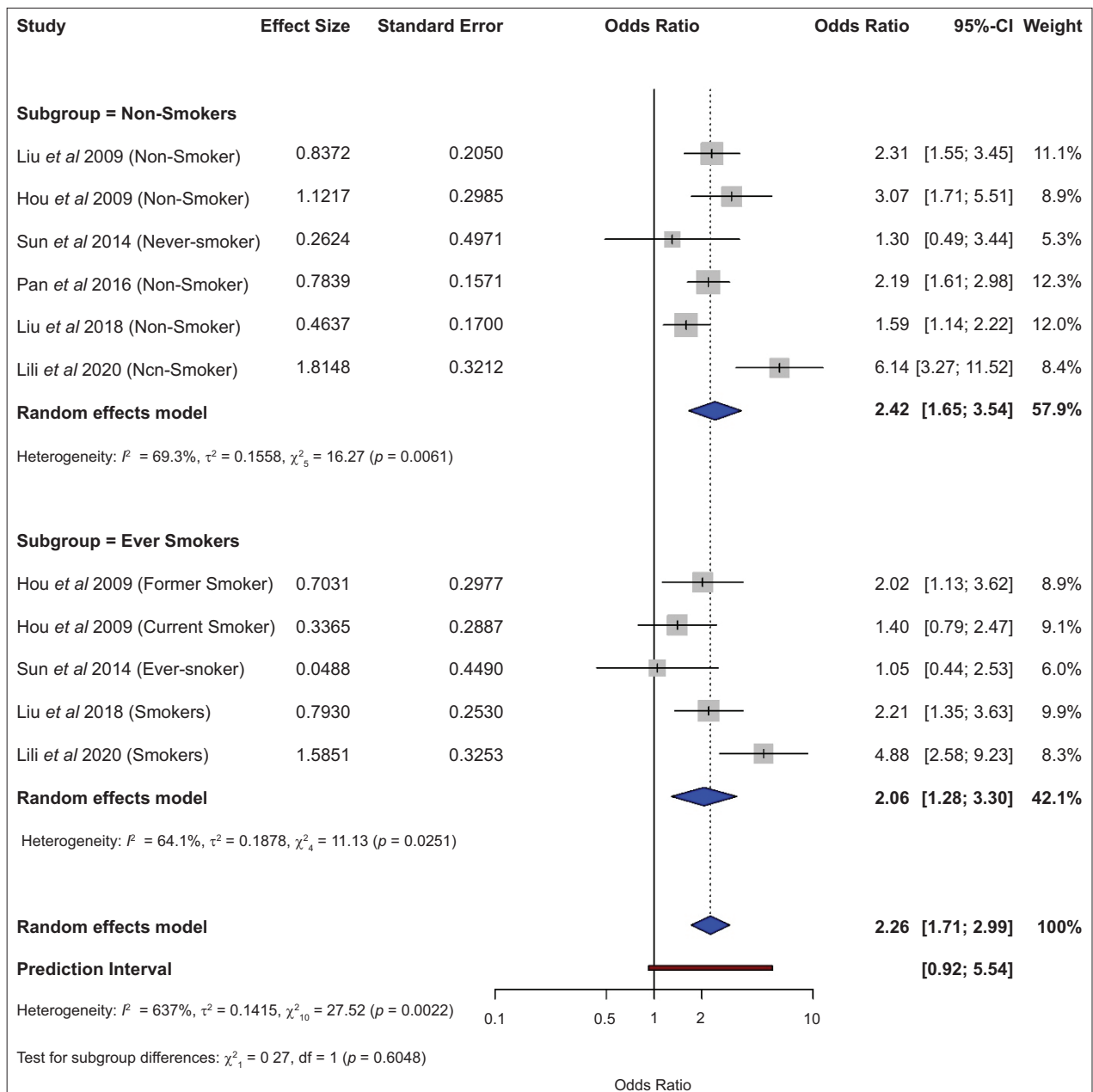
Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	NR
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	2
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	2, Figures, Supplementary Figures
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	2
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	2
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	2
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NR

(Contd...)

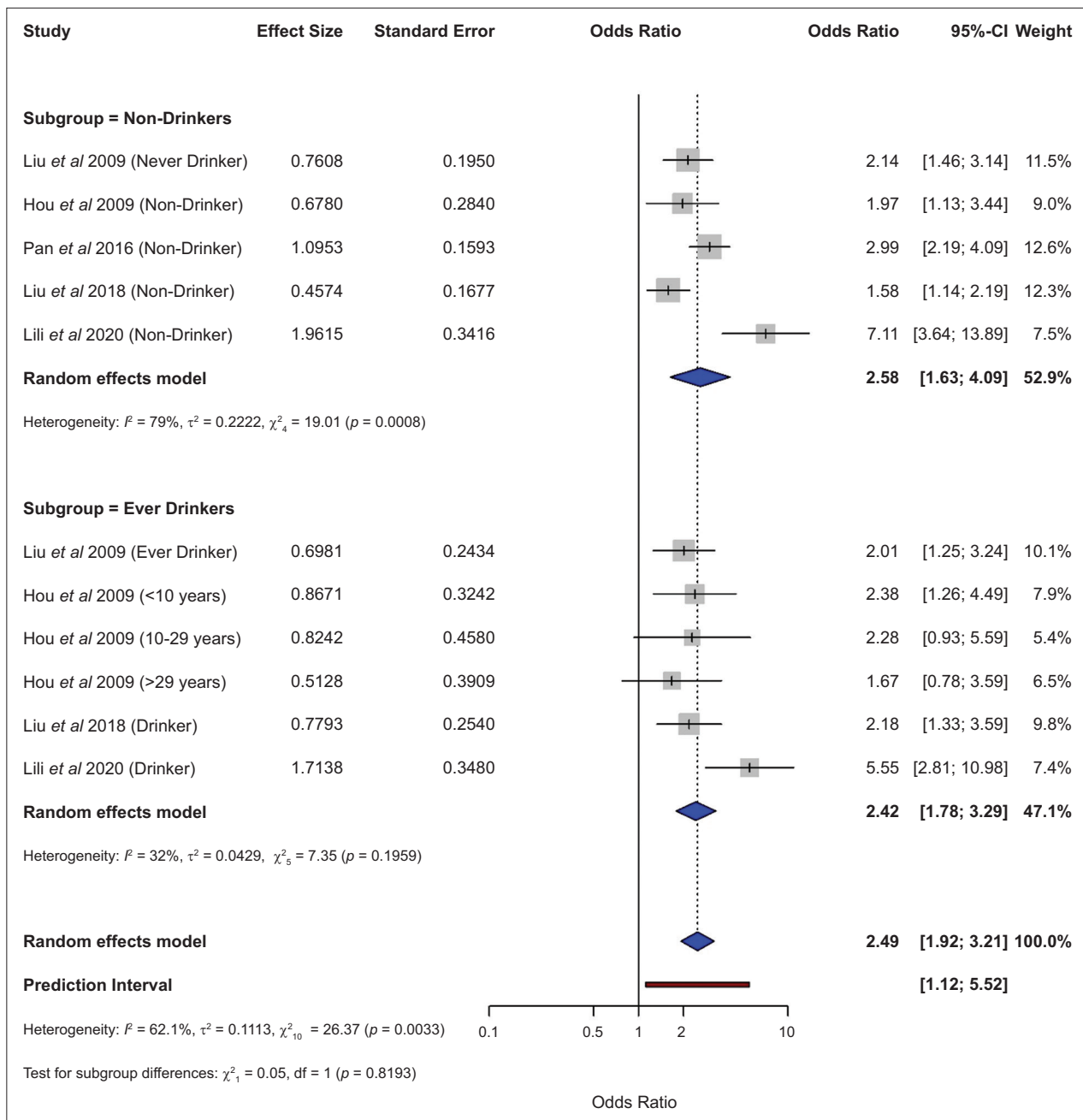
Supplementary Table 1 (Continued)

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3, Figures
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NR
Study characteristics	17	Cite each included study and present its characteristics.	3, Tables
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NR
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	3, Tables, Figures, Supplementary Figures
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3, Figures, Supplementary Figures
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3, Supplementary Figures
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3, Supplementary Figures
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NR
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	4
	23b	Discuss any limitations of the evidence included in the review.	4
	23c	Discuss any limitations of the review processes used.	4
	23d	Discuss implications of the results for practice, policy, and future research.	4, 5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Conflict of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NR

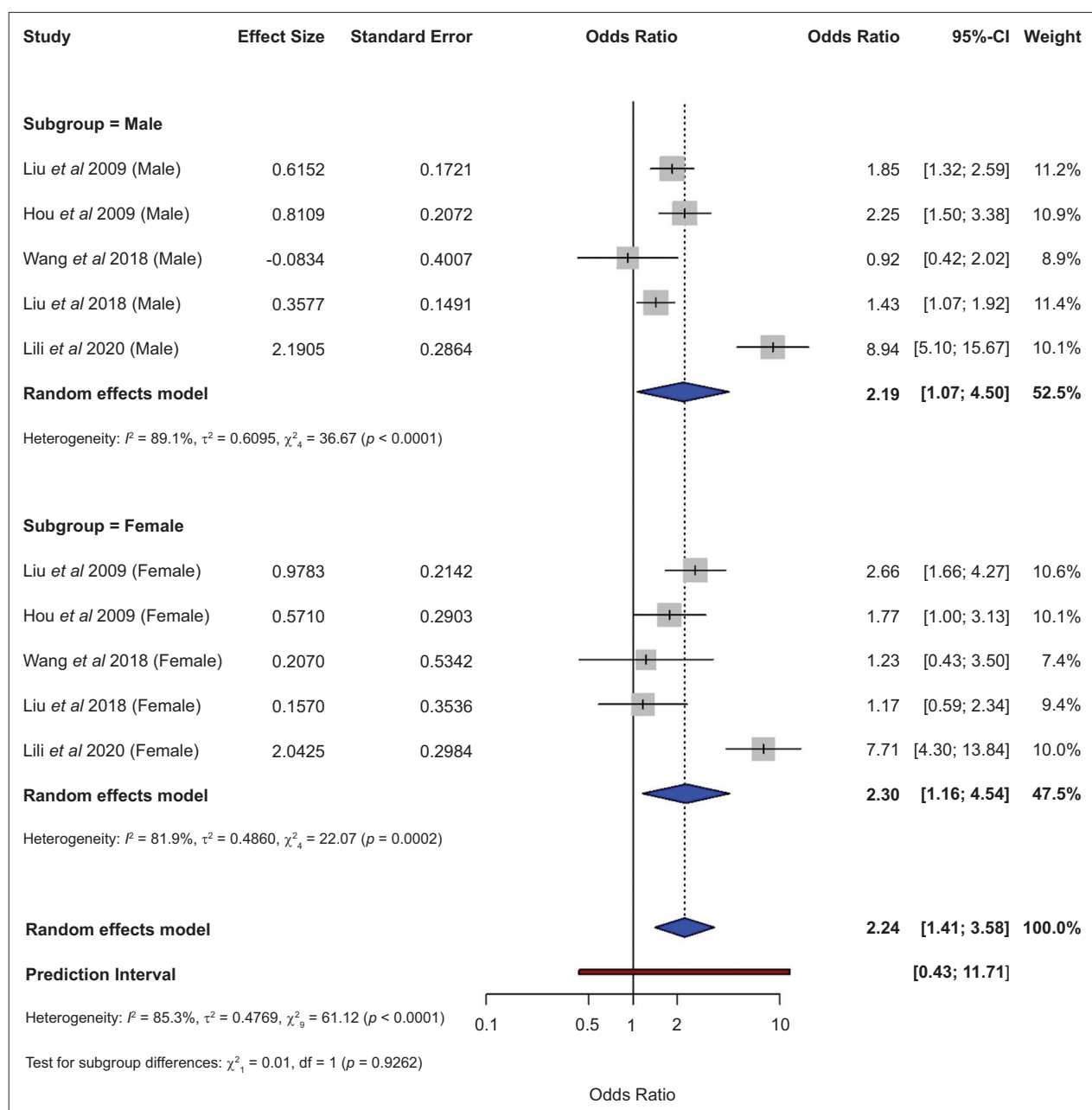
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>



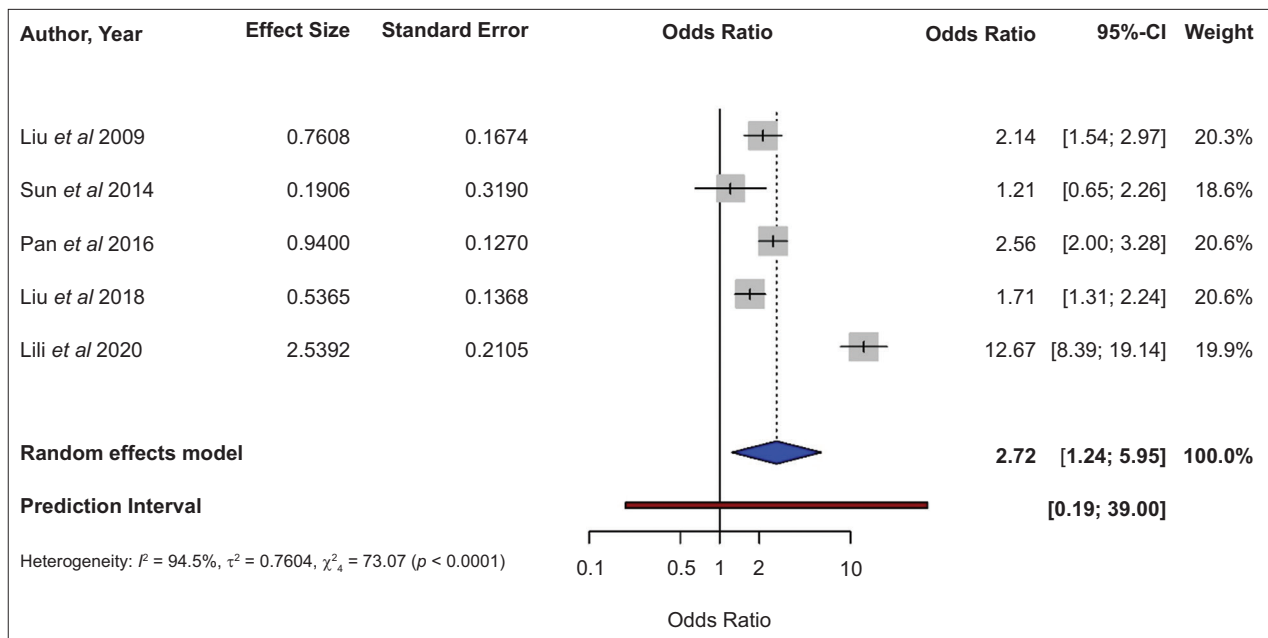
Supplementary Figure 1 Forest plot of a subgroup analysis depicting the association between telomere length and gastric cancer risk stratified by smoking status, using a random-effects model



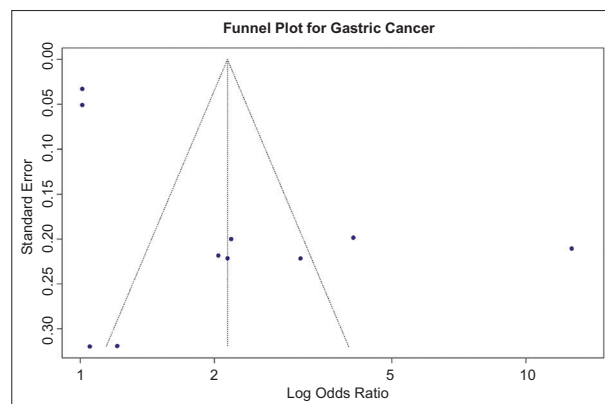
Supplementary Figure 2 Forest plot of a subgroup analysis depicting the association between telomere length and gastric cancer risk stratified by alcohol consumption, using a random-effects model



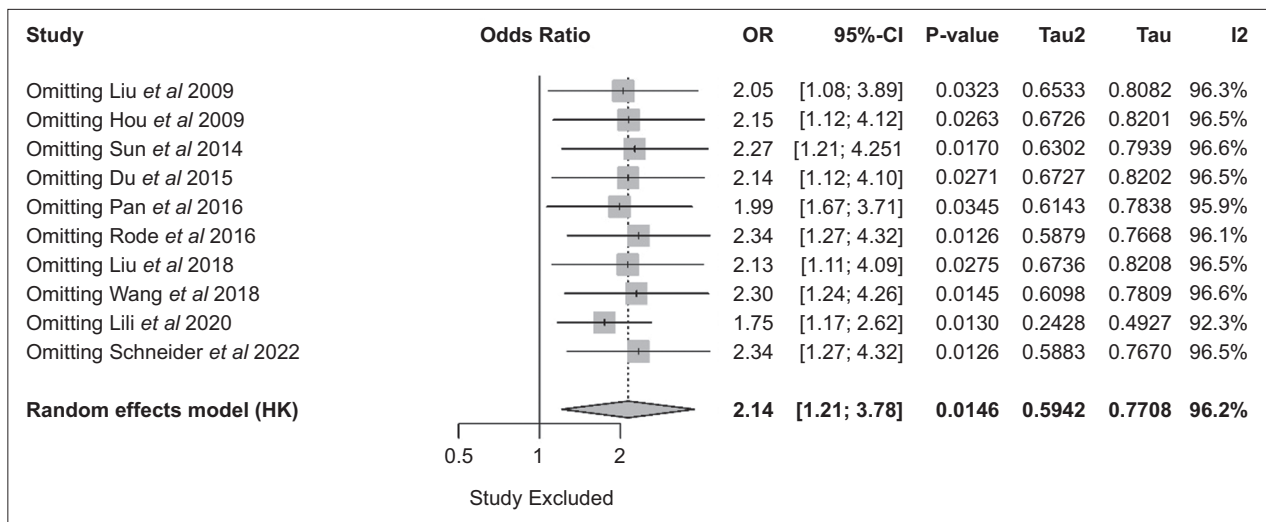
Supplementary Figure 3 Forest plot of a subgroup analysis depicting the association between telomere length and gastric cancer risk stratified by sex, using a random-effects model



Supplementary Figure 4 Forest plot of a meta-analysis depicting the association between telomere length (TL) and gastric cancer risk in studies reporting a dichotomous TL parameterization based on media TL, with long TL as the reference



Supplementary Figure 5 Funnel plot of studies included in the systematic review and meta-analysis



Supplementary Figure 6 Leave-1-out sensitivity analysis for the association between telomere length and gastric cancer risk