Ageing Research Reviews 81 (2022) 101707

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Association between leucocyte telomere length and the risk of atrial fibrillation: An updated systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Leucocyte telomere shortening
Biological aging
Atrial fibrillation
Predictor
Meta-analysis

ABSTRACT

Background and aims: Advancing age is the most important risk factor of atrial fibrillation (AF). The shortening of telomere length is a biomarker of biologic aging. There is an increasing body of evidence that leucocyte telomere length (LTL) is associated with the risk of AF development. However, the results in these studies were controversial. The current systematic review and meta-analysis was conducted to examine the role of LTL in predicting the incidence of AF.

Methods and results: Observational studies reporting the association between LTL and the risk of AF were retrieved through 25th June, 2022 from PubMed and Embase. A total of twelve studies including 18,293 patients were included in the present analysis. Leucocyte telomere shortening was found to be an independent predictor of AF as a continuous variable in both univariate [OR:2.14; 95%CI(1.48,3.10); $P < 0.0001$] and multivariate analyses [OR:1.41;95%CI(1.11,1.79); $P = 0.005$], as well as categorical variable in multivariate analysis [OR:1.53; 95%CI(1.04,2.27); $P = 0.03$]. Furthermore, leucocyte telomere shortening was significantly associated with recurrent AF [OR:4.32;95%CI(2.42,7.69); $P < 0.00001$] but not new-onset AF [OR:1.14; 95%CI(0.90,1.45); $P = 0.29$]. Leucocyte telomere shortening was also associated with an increased risk of persistent AF [OR:14.73;95%CI (3.16,68.67); $P = 0.0006$] and paroxysmal AF [OR:2.74;95%CI(1.45,5.18); $P = 0.002$]. Besides, LTL was an independent predictor for progression from paroxysmal AF to persistent AF [OR:3.2;95%CI (1.66,6.18); $P = 0.0005$]. Differences between males [OR:1.99; 95%CI(1.29,3.06); $P = 0.002$] and females [OR:0.86; 95%CI (0.29,2.56);$P = 0.79$] were observed.

Conclusions: Leucocyte telomere shortening predicts the risk of AF, especially recurrent AF. The predictive value is more prominent in males than in females. Shortening in LTL can predict the progression from paroxysmal to persistent AF.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in the general population (Krijthe et al., 2013), and is associated increased risks of cardiovascular diseases and overall mortality (Miyasaka et al., 2007). Advancing age, which prolongs exposure to diabetes, smoking, hypertension, hypercholesterolaemia and other cardiovascular risk factors, has been demonstrated to be a significant risk factor for AF (Dai et al., 2012; Lee et al., 2021). Epidemiological evidence suggests that 80% of AF patients are 65 years and older (Shah et al., 2021). Telomeres are specialised nucleoprotein structures tandem TTAGGG repeats at the chromosome end (Allende et al., 2016). Cell division, environmental factors, oxidative stress and inflammation contribute to telomere shortening (Allende et al., 2016; Nilsson et al., 2013). Cells will rapidly enter the senescent or apoptotic state when telomeres shorten beyond a certain threshold (Nilsson et al., 2013). Peripheral blood leucocytes telomere length (LTL) adequately reflects telomere length of other cells, thus, LTL can be regarded as a marker of

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https://doi.org/10.1016/j.arr.2022.101707
Received 8 January 2022; Received in revised form 18 July 2022; Accepted 2 August 2022
Available online 3 August 2022

biologic aging (Allende et al., 2016; Nilsson et al., 2013). Chronological aging independent of LTL shortening has been demonstrated to be responsible for the risk of AF, but the impact of LTL as a marker of biologic aging on AF has not been studied adequately.

Recently, some observational studies have reported that leucocytes telomere shortening is at increased risks of AF (Hu et al., 2019; Liu et al., 2021; Margaritis et al., 2014; Pan et al., 2019; Sinner et al., 2020; Wang et al., 2021). Pan et al. (2019) enroled 25 recurrent AF patients and 80 no recurrent AF patients who received catheter ablation therapy. Peripheral blood mononuclear cells were collected to measure LTL and LTL was found to be shorter in patients with recurrent AF than in those without. Receiver operating characteristic curve analysis showed that LTL cut-off $<$ 6.14 kbp had a sensitivity of 0.79 and specificity of 0.68 to predict recurrent AF. However, some reported inconsistent results (Kalstad et al., 2021; Roberts et al., 2014; Siland et al., 2017; Staerk et al., 2017; Zhang et al., 2018). The Framingham Heart Study (Staerk et al., 2017) comprised 1143 AF-free participants and used multivariable Cox models to examine the association between LTL and AF. After 15 years mean follow-up, no significant association was found. Our previous study (Zhang et al., 2018) of 50 paroxysmal AF patients and 100 AF-free patients showed there was no significant difference in LTL between two groups, but the LTL of paroxysmal AF patients tended to be shorter than that of AF-free patients. Our previous meta-analysis (Zhang et al., 2018) found that LTL was not associated with higher risk of AF. However, we just performed univariate and multivariate analyses for continuous and categorical variables with only six studies included, the lack of comparable subgroups made it difficult to conduct further subgroup analyses. In addition, the role of LTL in the progression of AF has not been studied. In light of these contradictory findings, there is a necessary to update the association between LTL and AF across these studies and examine the underlying factors that may have accounted for the seemingly disparate results.

Therefore, we conducted a comprehensive, updated systematic review and meta-analysis to examine the association between LTL and the risk of AF. Further analyses were subsequently conducted to examine the predictive value of LTL between different fibrillation types, AF definitions and genders.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis of observational studies was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Two reviewers, in duplication, systematically and independently searched PubMed and Embase database according to the prespecified selection criteria until 25 June,2022. The following search terms were used:(telomere) AND (atrial fibrillation OR AF). Searches were not restricted by language, data of publication, country, or sample size. To ensure saturation, references listed in the retrieved articles were scrutinised manually for further studies.

2.2. Selection criteria

All observational studies reported an association between LTL and AF with available risk estimate were included in this meta-analysis. With the aim of investigating whether leucocyte telomere shortening is at an risk of developing AF, the following inclusion criteria was applied to identity eligible studies: (1)the study design was observational studies included prospective cohort studies, retrospective cohort studies, case-control studies or cross-sectional studies; (2)the studies were conducted in general population; (3)patients had a define diagnosis of AF based on history, electrocardiography(ECG) or Holter monitoring; (4)appropriate measurements of LTL were reported; (5)the hazard ratio(HR), odds ratio(OR) or risk ratio(RR) along with their corresponding 95% confidence intervals (CI) for the association between LTL and AF were provided, or with available data to calculate. In addition to the published articles, conference abstracts that provided the required data were also included. For multiple studies from the same cohort or focusing on the same event, only those studies with the largest sample size and the longest follow-up duration were considered for inclusion. When uncertainties or discrepancies occurred, two investigators reviewed the papers through intensive reading together to reach joint conclusions, the final disagreement was resolved by a senior reviewer.

2.3. Data extraction

Two blinded reviewers separately extracted the required data from each qualified study using the standard data correlation extraction table and subsequently cross-checked the extracted results. The following data were extracted: (1)publication details: first author's last name, publication year, location; (2)baseline characteristics of included patients: sample size, male ratio, mean age, the origin of the studied population, duration of follow-up, diagnoses of AF types; (3)study design; (4)definition of AF; (5)methods of AF detection; (6)risk estimate. In case divergent views occurred between the two investigators, a third reviewer would make suggestions.

2.4. Quality assessment

To limit heterogeneity derived from the differences among included studies, two blinded reviewers independently performed methodological quality assessment of included cohort studies and case control studies using the Newcastle-Ottawa quality assessment scale according to the following three aspects: (1) selection of patients (four items, one star each); (2) comparability of cohorts or groups (one item, up to two stars); (3)the outcome evaluation for cohort studies and the exposure evaluation for case-control studies (three items, one star each). Varying from zero to nine stars, the studies were graded as good if they met $\geq$ 7 stars, fair if they met 4–6 stars, and poor if they met$<$ 4 stars. Quality of the cross-sectional study was assessed by American Agency for Healthcare Research and Quality cross-sectional study evaluation criterion with eleven items. Varying from zero to eleven stars, the studies were graded as good if they met $\geq$ 8 stars, fair if they met 5–7 stars, and poor if they met$<$ 5 stars.

2.5. Statistical analysis

We analyzed all the adjusted and unadjusted HR/OR/RR along with the corresponding 95%CI to evaluate the magnitude of association between LTL and AF. Our aim is to examine whether shortened LTL is a risk factor of AF, thus, for those studies that reported their conclusions from another perspective that whether longer LTL was a protective factor of AF, we calculated the required data by taking the reciprocal. To assess the overall statistical heterogeneity among studies which includes clinical decisions, diagnosis methods and statistical components, the I^2 statistic derived from the standard chi-square test was evaluated and used to select an appropriate effect model for pooled estimation. I^2 value between 0% and 25% indicates insignificant heterogeneity,26–50% indicates moderate heterogeneity, and 76–100% indicates significant heterogeneity. If I^2 value $>$ 50%, the random effects model was used for it is better to explain the significant heterogeneity among studies; otherwise, the fixed-effects model was used. To evaluate the influence of individual studies on the estimated relative risk, a sensitivity analysis by leaving out specific studies at a time were performed. Prespecified subgroup analysis regarding study location (China, USA and Europe), follow-up duration ($>$10 years and $<$10 years), methods of AF diagnosis (ECG and Holter monitoring) and study population type(hospital-based and community-based) were performed to investigate potential sources of heterogeneity. Publication bias was evaluated by inspecting the funnel plots. A two-tailed P-value of 0.05 for pooled estimates and a two-

tailed P-value of 0.1 for heterogeneity test were considered statistically significant. All statistical analyses were performed with the Review Manger, version 5.3 (RevMan; The Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study selection

A flow diagram of the data search and study selection is shown in Fig. 1. Initially, a total of 209 studies were identified from PubMed and Embase. After excluding 49 duplicates, 160 records were further excluded for the following reasons: 73 were irrelevant to the current analysis; 25 were laboratory studies; 22 were review articles; 6 were letters or editorials and 2 were case reports. A total of 22 studies remained after screening and subsequently,10 studies were excluded for the absence of helpful HR/OR/RR. Finally, a total of 12 articles were included in our meta-analysis (Kalstad et al., 2021; Liu et al., 2021; Margaritis et al., 2014; Pan et al., 2019; Roberts et al., 2014; Siland et al., 2017; Sinner et al., 2020; Staerk et al., 2017; Su et al., 2019; Wang et al., 2021, 2022; Zhang et al., 2018).

3.2. Baseline characteristics

The baseline characteristics of the included studies are summarised in Table 1. Twelve studies involving 18,293 patients were included (Kalstad et al., 2021; Liu et al., 2021; Margaritis et al., 2014; Pan et al., 2019; Roberts et al., 2014; Siland et al., 2017; Sinner et al., 2020; Staerk et al., 2017; Su et al., 2019; Wang et al., 2021., 2022; Zhang et al., 2018) and two entries were conference abstracts with available data (Margaritis et al., 2014; Sinner et al., 2020). In all twelve studies, seven were cohort studies (Kalstad et al., 2021; Margaritis et al., 2014; Pan et al., 2019; Roberts et al., 2014; Siland et al., 2017; Staerk et al., 2017; Su et al., 2019), four were case-control studies (Liu et al., 2021; Sinner et al., 2020; Wang et al., 2021; Zhang et al., 2018) and one were cross-sectional study (Wang et al., 2022). The proportion of male participants ranged from 29% (Roberts et al., 2014) to 100% (Liu et al., 2021), and mean age from 49 (Siland et al., 2017) to 75 (Kalstad et al., 2021) years old. The mean follow-up period varied from 1 year(Pan et al., 2019) to a maximum of 15.1 years (Staerk et al., 2017). Among the included studies, endpoint of six studies was reported in the form of HR (Pan et al., 2019; Roberts et al., 2014; Siland et al., 2017; Staerk et al., 2017; Su et al., 2019; Wang et al., 2022), one study was reported in the form of RR (Margaritis et al., 2014), and the remaining studies were in the form of OR(Kalstad et al., 2021; Liu et al., 2021; Sinner et al., 2020; Wang et al., 2021; Zhang et al., 2018). The diagnosis of AF was varied among individual studies, six were based on ECG findings (Kalstad et al., 2021; Roberts et al., 2014; Siland et al., 2017; Sinner et al., 2020; Staerk et al., 2017; Wang et al., 2021), four were obtained from Holter monitoring (Liu et al., 2021; Pan et al., 2019; Su et al., 2019; Zhang et al., 2018), one study reported on AF detected by ECG or Holter monitoring (Wang et al., 2022) and one study did not report on the modality used (Margaritis et al., 2014). Most common type of atrial fibrillation was paroxysmal AF (Margaritis et al., 2014; Pan et al., 2019; Wang et al., 2021, 2022; Zhang et al., 2018), and only two study reported findings on persistent AF (Wang et al., 2021, 2022). The quality assessment of the twelve studies is also presented in Table 1.

3.3. Relationship between LTL and AF

When analyzed as continuous variable, leucocyte telomere shortening was found to be significantly associated with the risk of AF in univariate analysis [OR:2.14;95%CI(1.48,3.10); $P < 0.0001$](Fig. 2A) as well as multivariate analysis [OR:1.41;95%CI(1.11,1.79);$P = 0.005$] (Fig. 2B). A significant relationship was also observed when leucocyte telomere shortening was analyzed as categorical variable in multivariate

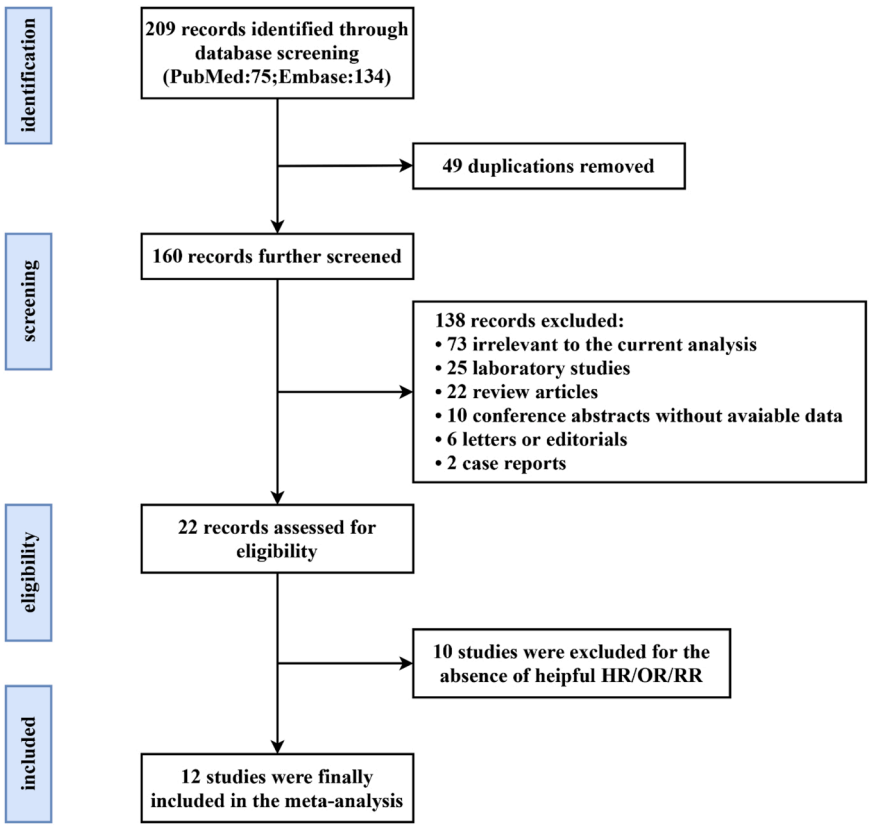

Fig. 1. A PRISMA flow chart of study selection process in the meta-analysis.

Table 1
General characteristics of studies included in this meta-analysis.

First author and year	Location	Study design	Study population	Total patients	Male	Mean age	Definition of AF	Method of AF detection	Type of AF	Follow-up	Risk estimate	Quality score
Kalstad 2021	Norway	Cohort	Hospital-based	299	70.2%	75 years	NA	ECG	NA	2 years	OR	9
Liu 2021	China	Case control	Hospital-based	192	100%	60 ± 8 years	NA	Holter	NA	NA	OR	8
Margaritis 2014	UK	Cohort	Hospital-based	475	NA	NA	New-onset AF	NA	Paroxysmal AF	NA	RR	9
Pan 2019	China	Cohort	Hospital-based	131	65.6%	51.96 ± 11.47 years	Recurrent AF	Holter	Paroxysmal AF	1 year	HR	8
Roberts 2014	America	Cohort	Community-based	1675	29%	72.16 ± 0.13 years	New-onset AF	ECG	NA	11.6 years	HR	9
Siland 2017	Netherlands	Cohort	Community-based	7775	50%	49 ± 13 years	New-onset AF	ECG	NA	11.4 ± 2.9 years	HR	9
Sinner 2020	Germany	Case control	Community-based	5552	60.9%	56.89 years	NA	ECG	NA	NA	OR	8
Staerk 2017	America	Cohort	Community-based	1143	47.2%	60.0 ± 8.6 years	New-onset AF	ECG	NA	15.1 ± 4.2 years	HR	9
Su 2019	China	Cohort	Hospital-based	282	53.9%	65.39 ± 10.45 years	Recurrent AF	Holter	NA	14.20 ± 5.04 months	HR	9
Wang 2021	China	Case control	Hospital-based	350	59.1%	61.25 years	NA	ECG	Paroxysmal AF and persistent AF	NA	OR	8
Wang 2022	China	Cross-sectional	Hospital-based	269	58.4%	67.2 ± 10 years	NA	ECG or Holter	Paroxysmal AF and persistent AF	854.9 ± 18.7 days	HR	9
Zhang 2018	China	Case control	Hospital-based	150	54.7%	62.03 ± 0.81 years	NA	Holter	Paroxysmal AF	NA	OR	8

AF: atrial fibrillation; ECG: electrocardiogram; HR: hazard ratio; OR: odds ratio; RR: risk ratio.

analysis [OR:1.53;95%CI(1.04,2.27); P = 0.03] (Fig. 2C). Variables considered in the multivariate analyses are listed in Table S1 in the supplementary appendix. Significant heterogeneity was present in all above analysis: leucocyte telomere shortening as continuous variable in univariate analysis (I^2 =82%; P < 0.00001; Fig. 2A); multivariate analysis (I^2 =85%; P < 0.00001; Fig. 2B); and as categorical variable in multivariate analysis (I^2 =62%;P = 0.03; Fig. 2C).

Of the twelve studies, four investigated that whether leucocyte telomere shortening increases the risk of new-onset AF (Margaritis et al., 2014; Roberts et al., 2014; Siland et al., 2017; Staerk et al., 2017) and two focused on recurrent AF (Pan et al., 2019; Su et al., 2019). Our meta-analysis found no significant association between leucocyte telomere shortening and the risk of new-onset AF [OR:1.14;95%CI(0.90, 1.45); P = 0.29;I^2 = 71%] with significant heterogeneity among individual studies. However, a close correlation was observed between leucocyte telomere shortening and the risk of recurrent AF [OR:4.32;95%CI(2.42,7.69); P < 0.00001;I^2 = 0%]without heterogeneity (Fig. 3A), indicating that leucocyte telomere shortening may be a predictor of recurrent AF.

Four of the included studies investigated the potential association between leucocyte telomere shortening and the risk of paroxysmal AF (Margaritis et al., 2014; Pan et al., 2019; Wang et al., 2021; Zhang et al., 2018), one study examined persistent AF (Wang et al., 2021) and two studies investigated the progression from paroxysmal to persistent AF (Wang et al., 2021, 2022). Our meta-analysis found that leucocyte telomere shortening was a predictor of paroxysmal AF [OR:2.74;95%CI (1.45,5.18); P < 0.0001;I^2 = 43%]with moderate heterogeneity. And the magnitude of association was evaluated to be much more significant for persistent AF [OR:14.73;95%CI(3.16,68.67); P = 0.0006] (Fig. 3B). More surprisingly, we found that LTL was an independent predictor for progression from paroxysmal AF to persistent AF [OR:3.2;95%CI (1.66, 6.18); P = 0.0005] (Fig. 3B).

To identify the influence of gender on the risk of AF, subgroup analyses were performed. The result showed that shortened leucocyte telomere was associated with the risk of AF in males [OR:1.99;95%CI (1.29,3.06);P = 0.002;I^2 = 0%]without any heterogeneity, but not in females [OR:0.86;95%CI(0.29,2.56);P = 0.79] (Fig. 3C). Visual inspection of the funnel plots suggested little publication bias (Fig. S1A-C).

3.4. Sensitivity and subgroup analyses

Sensitivity analysis was conducted to explore the potential origin of heterogeneity. Among the twelve studies, Pan et al. (2019), Roberts et al. (2014) and Staerk et al. (2017) measured LTL by Southern blot analysis of terminal restriction fragment lengths, while others used a quantitative real time PCR method (Kalstad et al., 2021; Liu et al., 2021; Margaritis et al., 2014; Siland et al., 2017; Sinner et al., 2020; Su et al., 2019; Wang et al., 2021, 2021; Zhang et al., 2018). Excluding the Pan et al. (2019) and Roberts et al. (2014) from the univariate analysis did not have an impact on the main results[OR:2.08;95%CI (1.60,2.72); P < 0.00001], while reducing heterogeneity from 82% to 37% (Fig. S2A). In categorical variable analysis, only Roberts et al. (2014) used Southern blotting and after its removal,I^2 reduced from 62% to 34% without influence on the main results [OR:1.80;95%CI(1.18,2.72); P = 0.006] (Fig. S2B). Hence, the methods of LTL measurement seems to be an important origin of heterogeneity.

Subgroup analyses were subsequently performed to further identify potential sources of heterogeneity. The results of subgroup analysis were listed in Table 2. Leucocyte telomere shortening was associated with an increased risk of AF in both studies from China with no heterogeneity

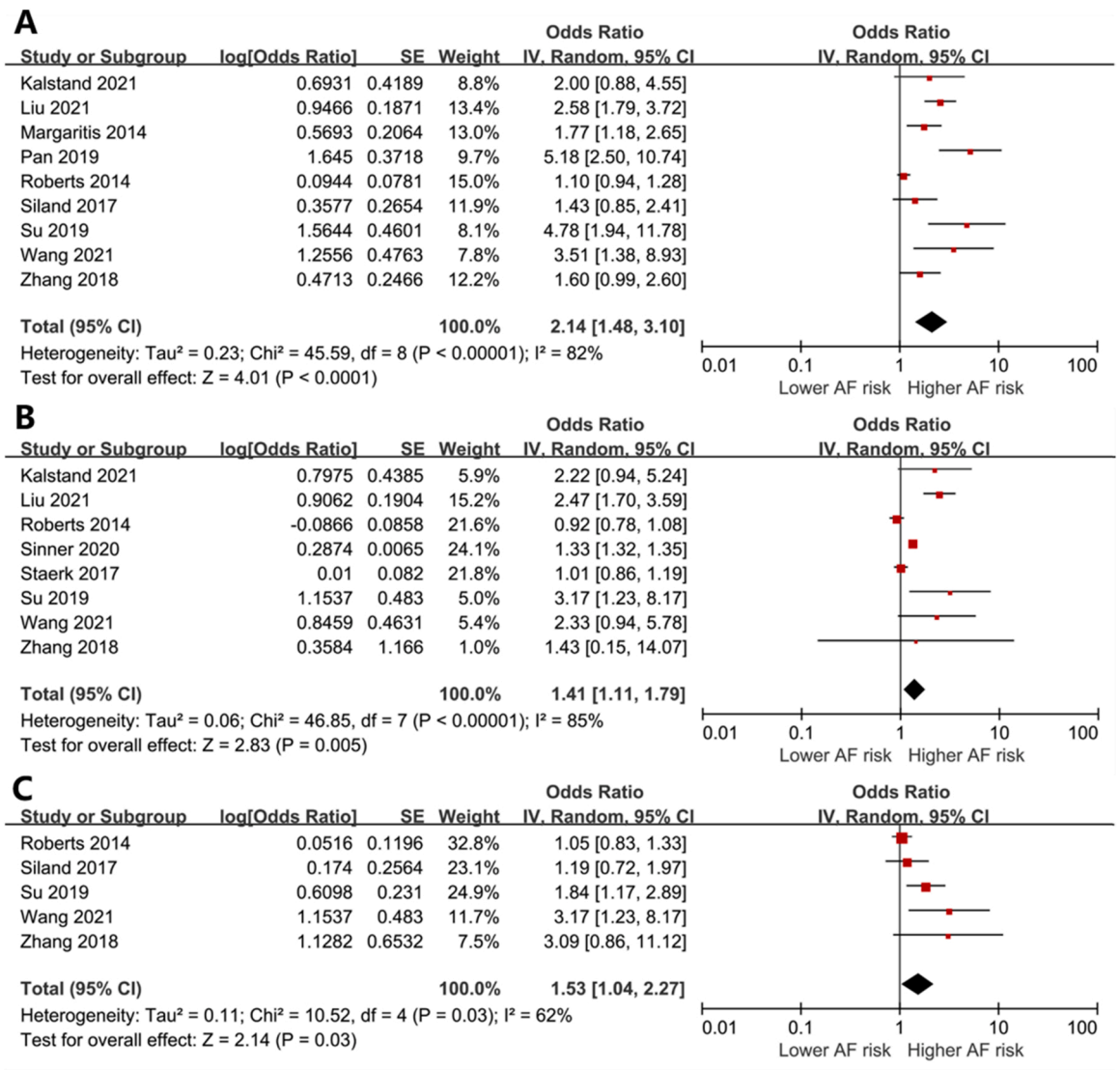

Fig. 2. Forest plots of leucocyte telomere length and the risk of AF. (A)The shortening of LTL as a continuous variable and the risk of AF in univariate analysis. (B) The shortening of LTL as a continuous variable and the risk of AF in multivariate analysis. (C) The shortening of LTL as a categorical variable and the risk of AF in multivariate analysis. LTL: leucocyte telomere length; AF: atrial fibrillation; CI: confidence interval.

(Liu et al., 2021; Pan et al., 2019; Su et al., 2019; Wang et al., 2021; Zhang et al., 2018) [OR:2.81;95%CI(2.10,3.18);P < 0.00001; $I^2 = 0\%$] and studies from Europe with mild heterogeneity (Kalstad et al., 2021; Margaritis et al., 2014; Siland et al., 2017; Sinner et al., 2020) [OR:1.37; 95%CI(1.23,1.53); P < 0.00001;$I^2 = 9\%$]. No significant association between leucocyte telomere shortening and the risk of AF was observed in studies originating from the United States (Roberts et al., 2014; Staerk et al., 2017) [OR:0.96;95%CI(0.86,1.08); P = 0.54; $I^2 = 0\%$] and there was no heterogeneity (Fig. 4A). Therefore, difference between the location of studies originated from possibly account for the observed heterogeneity.

Subgroup analysis was also performed for the study follow-up duration. Meta-analysis of three studies with a follow-up period shorter than 10 years (Kalstad et al., 2021; Pan et al., 2019; Su et al., 2019) showed that LTL was much shorter in participants who developed AF compared with those without [OR:3.49;95%CI (2.10,5.79); P < 0.00001; $I^2 = 10\%$] with mild heterogeneity. However, meta-analysis of three studies with a follow-up period longer than 10 years (Roberts et al., 2014; Siland et al., 2017; Staerk et al., 2017) found that LTL was similar between AF and non- AF patients [OR:0.99; 95%CI (0.86,1.15); P = 0.91; $I^2 = 28\%$] with insignificant heterogeneity (Fig. 4B), indicating that the follow-up period may be another source of heterogeneity.

To examine the influence of methods of AF diagnosis on the results, we conducted further subgroup analyses. Compared with ECG [OR:1.21; 95%CI (0.97,1.51); P = 0.10; $I^2 = 85\%$], Holter monitoring revealed a more significant relationship between leucocyte telomere shortening and the risk of AF [OR:3.00; 95%CI (2.04,4.39); P < 0.00001; $I^2 = 15\%$] (Fig. 4C). Moreover, subgroup analysis was also performed for the study population. A meta-analysis of seven studies included hospital-based patients (Kalstad et al., 2021; Liu et al., 2021; Margaritis et al., 2014; Pan et al., 2019; Su et al., 2019; Wang et al., 2021; Zhang et al., 2018) showed that leucocyte telomere shortening was a persuasive predictor of AF [OR:2.44; 95%CI(1.89,3.15); P < 0.00001;$I^2 = 10\%$] with mild heterogeneity. However, meta-analysis of four studies included community-based patients (Roberts et al., 2014; Siland et al., 2017; Sinner et al., 2020; Staerk et al., 2017) did not reach statistical significance [OR:1.12; 95%CI(0.89,1.42); P = 0.34; $I^2 = 90\%$] with significant heterogeneity (Fig. 4D).

Therefore, we propose the methods of LTL measurement, publication location, follow-up duration, methods of AF diagnosis and the study population could be the potential reasons for the heterogeneity.

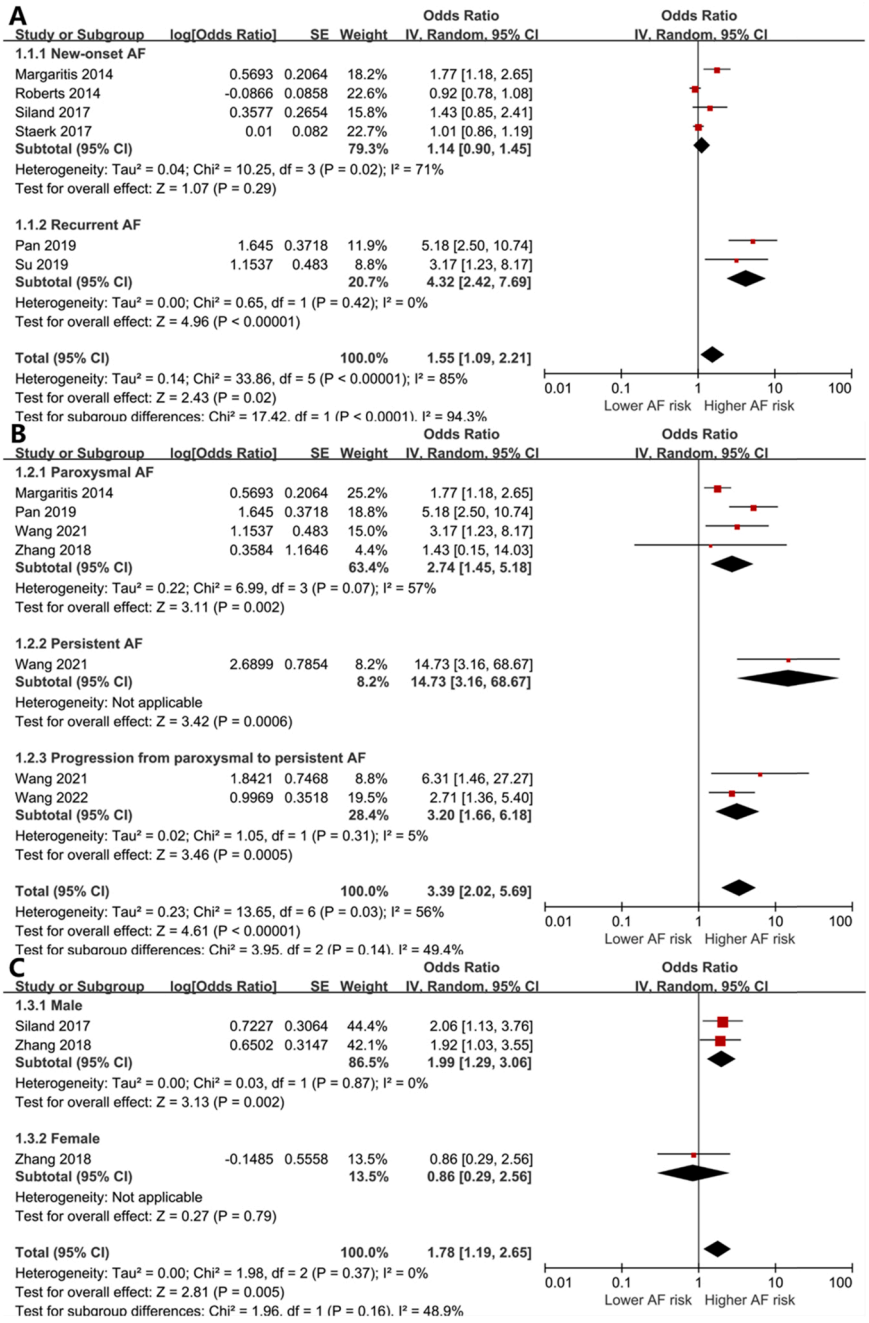

Fig. 3. Further analysis of leucocyte telomere length and the risk of AF for (A) definitions of AF, (B) different types of AF and (C) gender differences.

Table 2
Subgroup analysis of the association between leucocyte telomere shortening and the risk of atrial fibrillation.

			Meta-analysis			Heterogeneity	
	Subgroup	Number of studies	OR	95%CI	P-value	I^2 (%)	P value
Study location	China	5	2.81	2.10–3.78	< 0.00001	0	0.45
	USA	2	0.96	0.86–1.08	0.54	0	0.42
	Europe	4	1.37	1.23–1.53	< 0.00001	9	0.35
Follow-up duration	> 10 years	3	0.99	0.86–1.15	0.91	28	0.25
	< 10 years	3	3.49	2.10–5.79	< 0.00001	10	0.33
Methods of AF diagnosis	ECG	6	1.21	0.97–1.51	0.1	85	< 0.00001
	Holter	4	3.00	2.04–4.39	< 0.00001	15	0.32
Study population	Hospital-based	7	2.44	1.89–3.15	< 0.00001	10	0.35
	Community-based	4	1.12	0.89–1.42	0.34	90	< 0.00001

AF: atrial fibrillation; CI: confidence interval; ECG: electrocardiogram; OR: odds ratio.

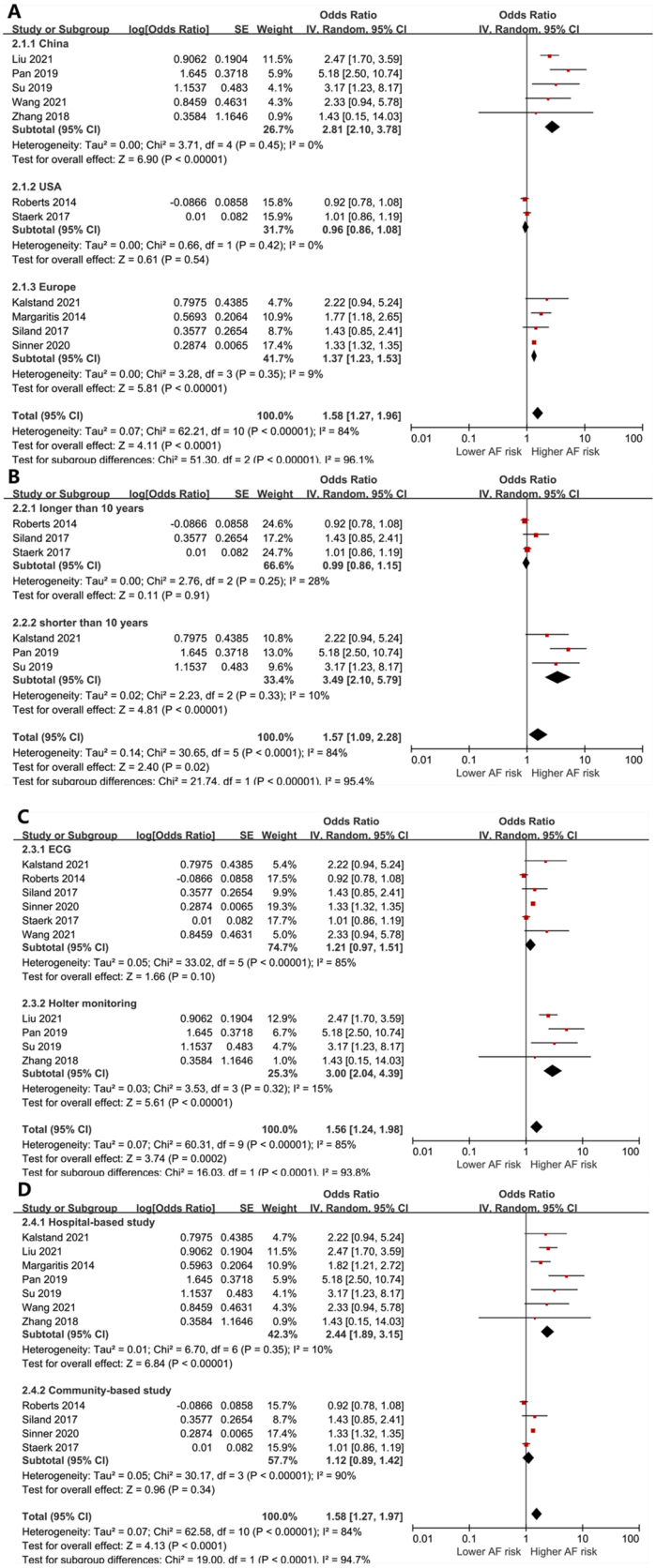

Fig. 4. Over-all subgroup analyses. The results of subgroup analysis based on (A)study location; (B)follow-up duration; (C)diagnostic methods of AF and (D)the source of participants. ECG: electrocardiogram.

4. Discussion

4.1. Main findings

The current updated meta-analysis evaluated the associations between LTL and the risk of AF, the main findings are that: (1) patients who have shortening in LTL are more likely to develop AF; (2) LTL shortening can predict AF recurrence; (3) the relationship between leucocyte telomere shortening and the risk of AF was particularly prominent for males; (4) the shortening of LTL can predict AF progression.

4.2. LTL predicts the risk of AF

AF is a prevalent cardiovascular disease in the world with age as one of the most important risk factors. Accompanying the aging of populations worldwide, the incidence and prevalence of AF are on the rise, rising sharply after age 65 (Kornej et al., 2020). Various risk factors contributes to the development of AF (Tse et al., 2016). For example, the mutated Granulocyte colony stimulating factor located at upstream of the Bruton's Tyrosine kinase mediated signalling could cause severe congenital neutropenia (Dwivedi and Greis, 2017; Dwivedi et al., 2019). Neutropenia can lead to the decline of human resistance, prone to inflammatory infiltrative heart disease, and then induce AF.

An increasing number of studies support an association between LTL and AF. However, the results remain controversial. The Framingham Heart Study (Staerk et al., 2017) with a mean follow-up time of 15.1 ± 4.2 years found that chronological age, rather than biologic age, predicted the risk of AF. The age of study participants increased with the duration of follow-up, and the value of LTL in predicting AF in older patients may mitigate due to other increased risk factors (Andrade et al., 2014). A study enroled 299 myocardial infarction patients (Kalstad et al., 2021) showed no significance associations with AF for LTL [OR:2.22;95%CI(0.94,5.29);P = 0.071], myocardial infarction may be a residual confounding and make it unable to establish causal pathways.

Recently studies have shown that leucocyte telomere shortening is a powerful predictor of AF. A case-control study enroled 2475 patients with AF from the prospective AFLMU cohort and 3077 control individuals free of AF from the community-based KORA Study found that compared with those without AF, AF patients have significantly shorter telomere length. After adjustment for sex, hypertension, diabetes and body mass index, this relation remained. The following propensity-score matched model of subjects with and without AF confirmed the main results (Sinner et al., 2020). A study conducted by Liu et al. found that the LTL of patients with AF was significantly shorter than the control group. Multivariable logistic regression confirmed that LTL was inversely associated with the risk of AF. Besides, receiver operating characteristic curves indicated the specificity and sensitivity of predicting AF using LTL (Liu et al., 2021).

In our meta-analysis, leucocyte telomere shortening was found to be significantly associated with AF as a continuous variable in univariate analysis and multivariate analysis, as well as categorical variable in multivariate analysis. We could conclude that biological aging is an independent predictor of AF. It's worth noting that compared with univariate analysis, correlation between LTL and the risk of AF reduced in multivariate analysis because variables such as age, systolic blood pressure, body mass index, myocardial infarction and heart failure had a significant interaction with telomere LTL for the relationship with incident AF (Siland et al., 2017).

4.3. LTL is a predictor of recurrent AF

In recent years, percutaneous radiofrequency catheter ablation (RFCA) has become an effective and standard therapy for AF and is recommended for symptomatic patients who are refractory to antiarrhythmic drug therapy (Efremidis et al., 2021; Kirchhof et al., 2016; Morillo et al., 2014; Reynolds et al., 2010). Risk factors including cardiovascular diseases, high $CHADS_2$ score and poor left atrial substrate could lead to a high incidence of recurrent AF after RFCA (Chao et al., 2011; Li et al., 2018; Liu et al., 2020; Tuan et al., 2010). Pro-inflammatory markers have also been shown to predict AF recurrence (Bazoukis et al., 2019; Bin Waleed et al., 2019), as confirmed by systematic reviews and meta-analyses (Issac et al., 2007; Weymann et al., 2018, 2017). Sometimes it is difficult to detect and diagnose AF on ECG, especially paroxysmal AF which can be asymptomatic and only diagnosed incidentally or by screening. In our subgroups analyses, we observed a significant association between LTL and the risk of AF in studies reporting on AF diagnosed by Holter monitoring [OR:3.00; 95% CI (2.04,4.39); P < 0.00001] but not ECG [OR:1.21; 95%CI (0.97,1.51); P = 0.10]. However, Holter needs dynamic continuous monitoring and may be overlooked in the clinic. Thus, a biomarker which predicts recurrent AF after RFCA remains to be identified. Leucocyte telomere shortening was found to be significantly associated with recurrent AF in our meta-analysis[OR:4.32;95%CI(2.42,7.69); P < 0.00001], while no significant association in new-onset AF was demonstrated[OR:1.14;95% CI(0.90,1.45);P = 0.29], indicating that LTL could be a more objective predictor of recurrent AF. In support of this notion, recent studies have reported that LTL was shorter in the patients with recurrent AF than in those without after catheter ablation by measuring the LTL of Peripheral blood mononuclear cells, and receiver operating characteristic curve analysis for LTL indicated better power to predict recurrent AF after RFCA (Pan et al., 2019; Su et al., 2019).

4.4. Gender differences

Male gender is one of the risk factors of AF. The Framingham Heart Study which followed 3999 men and 4726 women from 1968 to 1999 found that at age 40 years, lifetime risks for AF were 26.0% for men and 23.0% for women. And at age 80 years, lifetime risks for AF were 22.7% in men and 21.6% in women (Lloyd-Jones et al., 2004), indicating that the incidence rate of AF displays a slight dominance toward males. A recent study evaluated the association between LTL and AF showed that in the analysis stratified for sex, telomere length in men was associated with AF, but no association was found for women (Siland et al., 2017). To identify the gender differences between LTL and AF, we performed corresponding subgroup analyses. Significant association was found between shortening in LTL and the risk of AF for men [OR:1.99;95%CI (1.29,3.06);P = 0.002], but not for women [OR:0.86; 95%CI (0.29, 2.56);P = 0.79]. However, only two studies reported the results of males with AF and only one study reported females. More research is required in the future to further examine the differences in the relationship between shortening in LTL and AF risk for men and women.

4.5. Shortened LTL is an independent predictor of progression from paroxysmal AF to persistent AF

AF can be classified as three different types, including paroxysmal AF: recurrent episodes< 7 days and can spontaneously convert to normal sinus rhythm; persistent AF: duration of episodes> 7 days and permanent AF when sinus rhythm can no longer be reached (Heijman et al., 2014). There are significant differences between paroxysmal AF and persistent AF in clinical characteristics, reactivity to antiarrhythmic drugs and ablation therapy (Schotten et al., 2016). The progression of AF from paroxysmal to persistent significantly increases the risk of associated complications and decreases the success rate of rhythm control therapy (Carlquist et al., 2016; Heijman et al., 2014). The underlying molecular mechanisms for the development of AF and the factors that regulate the progression of paroxysmal AF to persistent AF are still unknown, previous studies have shown that miRNAs modulate atrial electrical or structural remodelling (McManus et al., 2014; Wang et al., 2018). Prevention of AF was related to activation of AMP-activated protein kinase which could improve mitochondrial function, gap

junction proteins, and cellular ultrastructure in atrial myocardium (Ozcan et al., 2021). Prognostic benefits and helpful guide therapeutic decisions could be provided with the ability of predicting which patients will progress to persistent AF. What's more, it insights into the mechanisms of AF progression (Carlquist et al., 2016).

Our previous study including 100 non-AF patients and 50 paroxysmal AF patients found that there was no significant difference in LTL between patients with paroxysmal AF and those without it. After adjusting for age, BMI, fibrinogen, D- dimer, and left atrial diameter, no significant association was observed (Zhang et al., 2018). The Intermountain Heart Collaborative Study, a cross-sectional analysis, found that mean LTL did not differ between persistent AF and participants without AF. While significant shortening of LTL was observed in paroxysmal AF groups (Carlquist et al., 2016). Our meta-analysis including four studies reported on paroxysmal AF (Margaritis et al., 2014; Pan et al., 2019; Wang et al., 2021; Zhang et al., 2018) and one study reported on persistent AF (Wang et al., 2021) found that shortened LTL was a significant risk factor for both paroxysmal AF with an OR of 2.74(95%CI:1.45–5.18) and persistent AF with an OR of 14.73(95% CI:3.16–68.67). What's more, a definitive conclusion could be reached from presented two studies (Wang et al., 2021, 2022) that shortened LTL is an independent predictor of progression from paroxysmal AF to persistent AF[OR:3.2;95%CI (1.66,6.18); P = 0.0005].

In our opinion, the disparity in results between these studies may come from the different selection of the study population. Our previous study was inclusion of only 50 paroxysmal AF subjects, which may lead to the difference in results. Participants enroled into the Intermountain Heart Collaborative Study were all individuals underwent angiography and most of whom had coronary heart disease, which could lead to potential selection bias.

4.6. Limitations

Some potential limitations should be noted in this systematic review and meta-analysis. Firstly, only articles published on PubMed and Embase were included, which may result in inadequate resource retrieval. Secondly, in view of the characteristics of the including studies, LTL was analyzed as a continuous and categorical variable in individual studies, so it was unattainable to pool all the studies together. Thirdly, our meta-analysis focused on whether shortened LTL is a risk factor of AF, while five studies reported their conclusions from another perspective that longer LTL is a protective factor of AF. Thus, we calculated the required data by taking the reciprocal, which might influence the combined results. Finally, given that the available data limited, the present meta-analysis is short of a comparable subgroup of permanent AF.

4.7. Future directions

As a marker of biological aging, LTL shortening is an independent predictor of AF occurrence and recurrence after catheter ablation. In addition, the predictive value of LTL shortening in AF progression can help clinicians identify potential high-risk groups of persistent AF and initiate rhythm control therapy as soon as possible. However, the predictive value of LTL in female AF patients and the interaction of other AF risk factors such as advanced age and myocardial infarction history are still unclear, and prospective studies are needed to resolve the controversies of current studies. Besides, the interaction mechanism between LTL shortening and AF is still unknown. Restoring LTL can effectively improve the aging phenotype and pathological changes of tissue cells, which may provide a new target for the prevention and treatment of AF. This assumption might be addressed in future studies.

5. Conclusions

Our meta-analysis supports that leucocyte telomere shortening, as a marker of biologic aging, is a predictor of AF occurrence, recurrence and progression, especially for men.

Data Availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by National Natural Science Foundation of China, China (81970270, 82170327 to TL), Tianjin Natural Science Foundation, China (20JCZDJC00340, 20JCZXJC00130 to TL).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101707.

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