Current Molecular Medicine, **2026**, *26,* 209-221

META-ANALYSIS

The Association Between Telomere Length and Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

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Abstract: ***Introduction*:** Studies have stated that there has been a close association between the telomere length (TL) and the incidence of non-alcoholic fatty liver disease (NAFLD). The goal of this report is to explore the possible association between TL and NAFLD.

***Methods*:** This study adhered to the PRISMA guidelines for systematic reviews. An extensive literature search was conducted in the Cochrane Library, CINAHL, Scopus, PubMed, and Web of Science. The "meta" package in the R programming language, version 4.3.1, was used for statistical analysis.

***Results*:** The meta-analysis of the included studies showed a pooled standard mean difference (SMD) of -0.25 (95% CI: -0.39 to -0.10), indicating shorter TL in NAFLD patients. Subgroup analyses revealed significant TL shortening in NAFLD patients with body mass index (BMI) <28 (SMD = -0.68, 95% CI: -0.96 to -0.39) and in case-control (-0.35, 95% CI: -0.51 to -0.20) and cohort studies (-0.68, 95% CI: -1.19 to -0.17). An odds ratio (OR) meta-analysis of six studies found that individuals with short TL had 1.72 times higher odds of NAFLD, which was statistically significant (95% CI: 1.23-2.42, I^2 = 85%). Excluding one study reduced heterogeneity (I^2 = 37%) and increased the OR to 1.93 (95% CI: 1.45-2.56), confirming a strong association between short TL and NAFLD risk.

***Discussion*:** The findings suggest a potential link between shorter TL and NAFLD. The odds ratio analyses further emphasized the increased risk of NAFLD in individuals with short TL. Nevertheless, the residual heterogeneity highlights the need for further high-quality, standardized research.

***Conclusion*:** Our findings supported the connection between reduced TL and NAFLD. Regardless of significant between-study diversity, the results remained consistent even after repeated sensitivity evaluations. Despite these findings, the high heterogeneity highlights the need for further well-designed studies to confirm TL as a reliable biomarker for NAFLD risk and progression.

ARTICLE HISTORY

Received: October 24, 2024
Revised: April 07, 2025
Accepted: April 18, 2025

DOI:
10.2174/0115665240360593250805102356

Keywords: Nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), telomere length (TL), hepatocellular carcinoma.

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1875-5666/26 $65.00+.00

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a condition marked by excessive fat accumulation in the liver, occurring in individuals who consume little to no alcohol. Its prevalence is rapidly increasing, particularly in Western countries, and it is often associated with other metabolic conditions, including insulin resistance and obesity. NAFLD, a chronic metabolic disorder, appears to be more common in older adults, making it a significant public health concern [1]. NAFLD has important clinical implications, ranging from mild fat buildup in the liver to more severe liver damage, such as steatohepatitis, cirrhosis, liver failure, and a heightened risk of liver cancer and cardiovascular diseases [2, 3]. In Western nations, the rise in obesity and resistance to insulin has led to NAFLD becoming a prominent cause of hepatocellular carcinoma (HCC) [4]. NAFLD is a prevalent condition in these countries, ranging from 35.1% to 58.3% [5-7]. NAFLD involves a wide range of liver disorders, from mild steatosis to more severe types, including steatohepatitis. The risk of fibrosis and the likelihood of progressing to cirrhosis, as well as the potential development of HCC, can vary within this spectrum [8]. NAFLD-linked HCC is the fastest rising contributor to HCC on a worldwide scale, and death rates are expected to rise significantly in the next decade [9]. Research indicates that the annual incidence of HCC associated with NAFLD is 2.6% and 12.8% over three years in NAFLD-related cirrhosis [10]. Due to the increasing prevalence of NAFLD and its progression to more advanced diseases, understanding the underlying pathological factors and biomarkers with diagnostic and prognostic value is necessary [11].

Telomeres are protein-bound structures composed of 10-15 kilobase pairs of repeating DNA sequences (TTAGGG) located at the ends of chromosomes, protecting them from fusion and deterioration [12]. Damaged telomeres can fuse, leading to translocations, random chromosome breaks, and the formation of dicentric chromosomes. This process is correlated with increased chromosomal instability and a higher risk of cancer development [8]. Telomere shortening activates cellular senescence and promotes steatosis in hepatocytes through the p53-p21 and p16-Rb pathways. Senescent cells release IL-1b, IL-6, chemokines, and components of the SASP, leading to tissue degeneration and the continuation of senescence [13-15]. Telomere shortening is linked to chronic inflammation and oxidative stress [6]. Inflammation plays a key role in the development of various metabolic disorders and chronic diseases, including NAFLD [16, 17]. Short telomeres have been associated with specific pathologies such as aplastic anemia, pulmonary fibrosis, systemic sclerosis, atherosclerosis, and hepatic diseases such as chronic hepatitis, particularly hepatitis C, NAFLD, cirrhosis, and hepatocellular carcinoma [18-22]. Nevertheless, the relationship between telomere length and NAFLD remains a topic of controversy, with studies reporting conflicting results. Some studies, such as the one by Donati *et al*. [5], have reported reduced telomere length in NAFLD patients compared with healthy controls.

Additionally, Tang *et al*. [23] indicated that short telomeres can increase the incidence of NAFLD. However, Zhang *et al*. [24] reported a longer telomere length in NAFLD patients compared to controls. While Zhang *et al*. [24] conducted a study in China, evaluating telomere length in type 2 diabetes mellitus patients with NAFLD, Tang *et al*. [23] used data from NAFLD patients in the UK Biobank. The differences in population and underlying conditions may help explain these variations. Thus, this study aimed to clarify this relationship by conducting a comprehensive systematic review and meta-analysis, synthesizing available evidence to determine the potential role of TL in NAFLD. This investigation aims to reconcile the conflicting findings in the existing literature by examining whether telomere length is shorter in patients with NAFLD compared to those without the disease. Additionally, it aims to assess the likelihood of shorter telomere length in NAFLD patients by pooling the odds ratios and their corresponding 95% confidence intervals.

2. MATERIALS AND METHODS

This study was performed and reported in accordance with the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25]. The study protocol was also submitted and registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a submission ID of CRD42024615093.

2.1. Search Strategy

We conducted an extensive search across several electronic databases, including Cochrane Library, CINAHL, Scopus, PubMed, and Web of Science in February 2025. We utilized the following MeSH terms: ‘Telomere’ and ‘Non-alcoholic Fatty Liver Disease’. A detailed search strategy is provided in Table **S1**.

2.2. Study Selection

The data retrieved from database searches were consolidated, and duplicate entries were eliminated using EndNote X8. Two reviewers (N.M. and S.J.) independently evaluated the data based on title/abstract and full text to filter out any entries not relevant to the study's goals. To assess inter-rater reliability, Cohen’s kappa (κ) was calculated at 0.85, indicating strong agreement between reviewers. Disagreements were resolved through discussion, and when consensus could not be reached, a third reviewer (M.R.) was consulted. This study employed the PI/ECO (Population, Intervention/Exposure, Comparator, Outcome) framework to ensure a structured and transparent approach to study selection. (P) The population considered in this review consisted of individuals diagnosed with NAFLD or its subtypes, such as non-alcoholic steatohepatitis (NASH). (I/E) The

exposure of interest was telomere length, which was measured to assess its association with NAFLD. (C) The comparator group consisted of healthy controls or individuals without NAFLD, enabling a direct comparison of telomere length differences between affected and unaffected populations. (O) The primary outcome of interest was the association between telomere length and NAFLD status.

Studies were deemed eligible if they fulfilled the established criteria:

- • The study evaluated the relationship between TL and the heightened risk of NAFLD in NAFLD patients compared to those without the condition.
- • Included human subjects.
- • Studies involving human subjects of any age, gender, or ethnicity are eligible for inclusion.
- • Studies focusing on patients diagnosed with NAFLD or its subtypes, such as non-alcoholic steatohepatitis (NASH), are included.
- • Studies including healthy controls or participants without NAFLD are also eligible for comparison.
- Studies were excluded if they were:
- • Animal studies (Animal studies were excluded because the research question aims to investigate the relationship between telomere length and NAFLD specifically in human populations).
- • Reviews, conference abstracts, commentaries, minus original data (Reviews were excluded because they do not provide original data and are typically secondary sources that aggregate results from multiple studies).
- • Studies lacking sufficient data for analysis.

2.3. Data Extraction

Data extraction was conducted independently by two reviewers (N.M. and S.J.). In cases of disagreement, reviewers first discussed the discrepancies to reach a consensus, ensuring that both perspectives were considered and taken into account. To further clarify the resolution process, specific criteria were followed to guide the reviewers in assessing the data. These included ensuring that the study characteristics (*e.g.*, study design, sample size, outcomes) and measurements (*e.g.*, methods for measuring telomere length) were accurately represented. If discrepancies arose regarding the interpretation or reporting of data, the reviewers referred to the original study methodology and results section to clarify the correct data. If consensus could not be achieved, a third reviewer (M.R.) was consulted to make the final decision. The collected information consisted of the author(s), study design, publication year, sample size, participant characteristics, methods used for measuring TL, outcome measures, and effects.

2.4. Quality Assessment

A.H. examined the quality of the included studies, and Y.E. used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Tables **2** and **3**). In cases of discrepancies, a third reviewer's opinion (M.R.) was considered. Inter-rater agreement was evaluated using Cohen's kappa ($\kappa = 0.89$), suggesting almost perfect agreement, which supports the robustness of our quality assessment. This checklist reviews various aspects of study design, methodology, and reporting to determine the potential for bias and overall quality of evidence.

Criteria for evaluating studies included the measurement of exposure and outcome variables, sample representativeness, consideration of confounding factors, statistical analysis, and the authors' findings. They were categorized into three groups: low quality (studies scoring <60%), moderate quality (studies scoring 60%–79%), or high quality (studies scoring ≥ 80% of the total possible score), depending on how well they met the JBI checklist criteria [26].

2.5. Statistical Analysis

The analysis was performed using the "meta" package in the R programming language, version 4.3.1. In this study, two effect sizes, Standard Mean Difference (SMD) and Odds Ratio (OR) were used to perform meta-analysis in two different cases to explore the effect of TL on the status of NAFLD disease. The effect sizes reported in the selected studies fell into two categories: some compared TL (mean, median, or T/S ratio) between patient and control groups, while others reported the odds ratio (OR or HR) of NAFLD between individuals with short and normal TL. For the first case, we used SMD to facilitate comparison of the reported effects across different measurement units in the studies. To calculate SMD in the studies that reported the median and interquartile range, we estimated the mean and standard deviation utilizing the Quantile Estimation Method [27]. Furthermore, in terms of odds ratio effect sizes, some studies reported the odds ratio of long telomere length (TL) in NAFLD, which was converted using the reciprocal (1/OR) to reflect the odds ratio of short TL in NAFLD.

Analyses of overall effect size estimates were conducted using the random-effects model, and statistical heterogeneity was evaluated using the $\tau 2$ and I2 statistics, with values above 70% indicating high heterogeneity. A random-effects model was employed to account for the high heterogeneity ($I^2 > 70\%$) observed across studies. The random-effects model assumes that the actual effect size may vary between studies, which is appropriate given the diversity in study populations, designs, and methodologies. This model is preferred when significant variability exists between studies, as it provides more generalizable results than the fixed-effect model, which assumes a

single effect size across studies. The P-value of heterogeneity was calculated to determine whether statistical heterogeneity existed among the studies. To reduce heterogeneity, influence analysis [28] and leave-one-out sensitivity analysis were first performed to identify studies with outlier effect sizes and those that contributed significantly to heterogeneity, respectively. Next, using meta-regression, the potential impact of various confounders on the heterogeneity of studies was examined. Based on the results, subgroup analysis was then performed for the categories of confounders that showed a significant impact on the heterogeneity of studies. Subgroups were defined based on BMI categories (BMI < 28, BMI between 28 and 30, and BMI > 30) to examine whether BMI influences telomere length in NAFLD patients, with each category representing different levels of obesity-related metabolic conditions. Additionally, studies were stratified by study design (case-control, cohort, cross-sectional) to assess how the methodology impacts the observed effect of telomere length on NAFLD. BMI is relevant as it is associated with metabolic disorders that could impact telomere dynamics, while the study design may influence the consistency and reliability of the findings.

2.6. Ethical Consideration

Although this meta-analysis utilizes secondary data from previously published studies, ethical considerations remain important. Ethical approval and informed consent for the original studies have been obtained by them, as required by their respective institutional review boards or ethics committees.

3. RESULTS

3.1. Study Selection and Characteristics

As shown in Fig. (**1**), following a comprehensive search, we identified 358 possibly relevant publications. After removing duplicates, 265 remained. One hundred ninety-six of these publications were removed because they were deemed meaningless during the title and abstract screening. After evaluating the full texts of the remaining 58 records, 41 papers were excluded. Finally, 17 publications matching our criteria were included (Fig. **1**). A total of 5 cohort studies, 6 case-control studies, 1 RCT, and 5 cross-sectional studies were included. Four studies were conducted in China [6, 16, 24, 29], three in the United States [30-32], two in the United Kingdom [23, 33], and

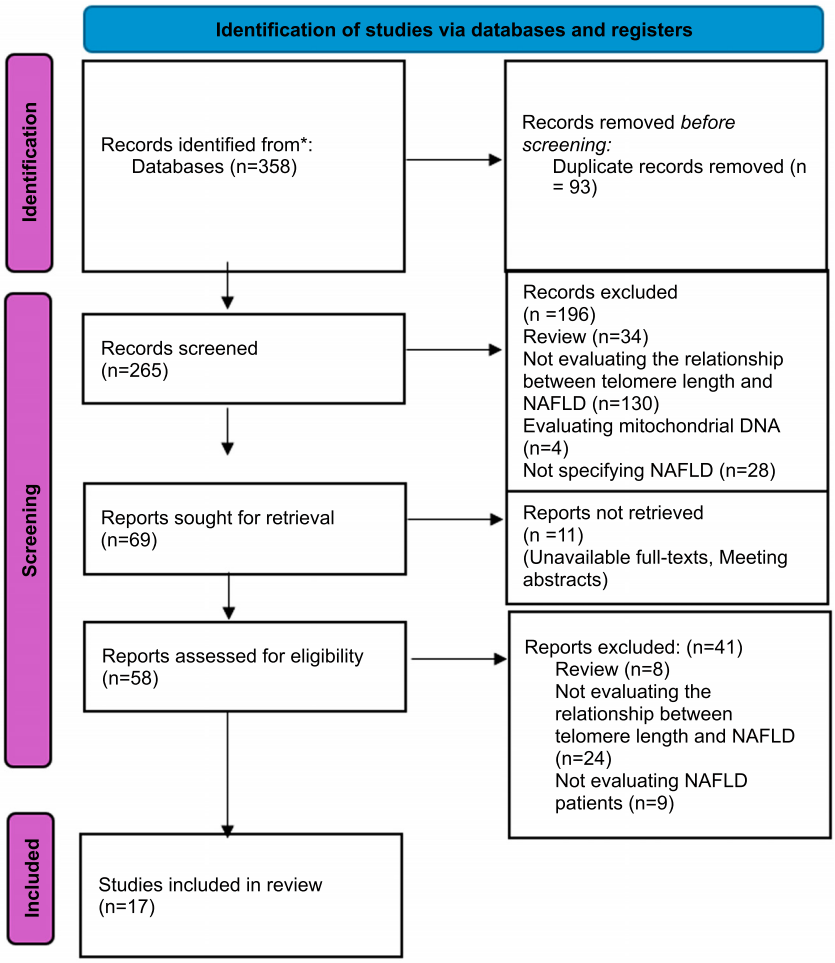

Fig. (1). PRISMA flow chart of the number of studies detected and included in this systematic review and Meta - analysis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

others originated in Italia [5], South Korea [34], Ukraine [35], Japan [36], Israel [8], Turkey [37], Spain [38], Finland [39]. Table **1** summarizes the study characteristics of the included studies.

3.2. Quality of the Included Studies

Based on JBI checklists, all included studies had an overall low risk of bias. The results of the quality assessment are presented in Tables **2**-**5**.

3.3. Meta-analyses

A total of 15 studies employed an appropriate effect size for the meta-analysis based on the standardized SMD. According to the preliminary analysis results, the pooled SMD was calculated as -0.25, indicating that telomere length in NAFLD patients is 0.25 units shorter compared to healthy individuals (95% CI: -0.39 to -0.10) (Fig. **S1**). However, due to the high degree of heterogeneity among the studies, we assessed the influence of individual studies. As illustrated in Fig. (**2**), three studies (Kim, Reja, and Tang) were identified as outliers and subsequently excluded from the analysis.

Following the exclusion of studies with outlier effect sizes relative to the remaining studies, the pooled SMD was calculated as -0.05 [95% CI: -1.48 to 1.38], which was not statistically significant. However, substantial heterogeneity persisted among the retained studies (I^2 = 99%). A sensitivity analysis was subsequently conducted, identifying four studies (Zhang *et al*. (2019), Emelyanov *et al*., Wojcicki *et al*., and Kandemir *et al*.) that contributed disproportionately to heterogeneity, which were subsequently excluded. This exclusion reduced heterogeneity to I^2 = 95%, and the recalculated pooled SMD yielded -0.47 [95% CI: -0.68; -0.26], indicating a statistically significant reduction in telomere length in the NAFLD group compared to the control group.

To further investigate potential sources of heterogeneity, univariable meta-regression analyses were performed for each predefined confounding factor. As summarized in the table below, the body mass index (BMI) of the NAFLD patients and the study design category (cohort studies) were identified as significant contributors to heterogeneity ($p < 0.05$) (Table **6**). BMI categories and study design type subsequently stratified subgroup meta-analyses to explore these associations further; the results are presented in Figs. (**3** and **4**), respectively.

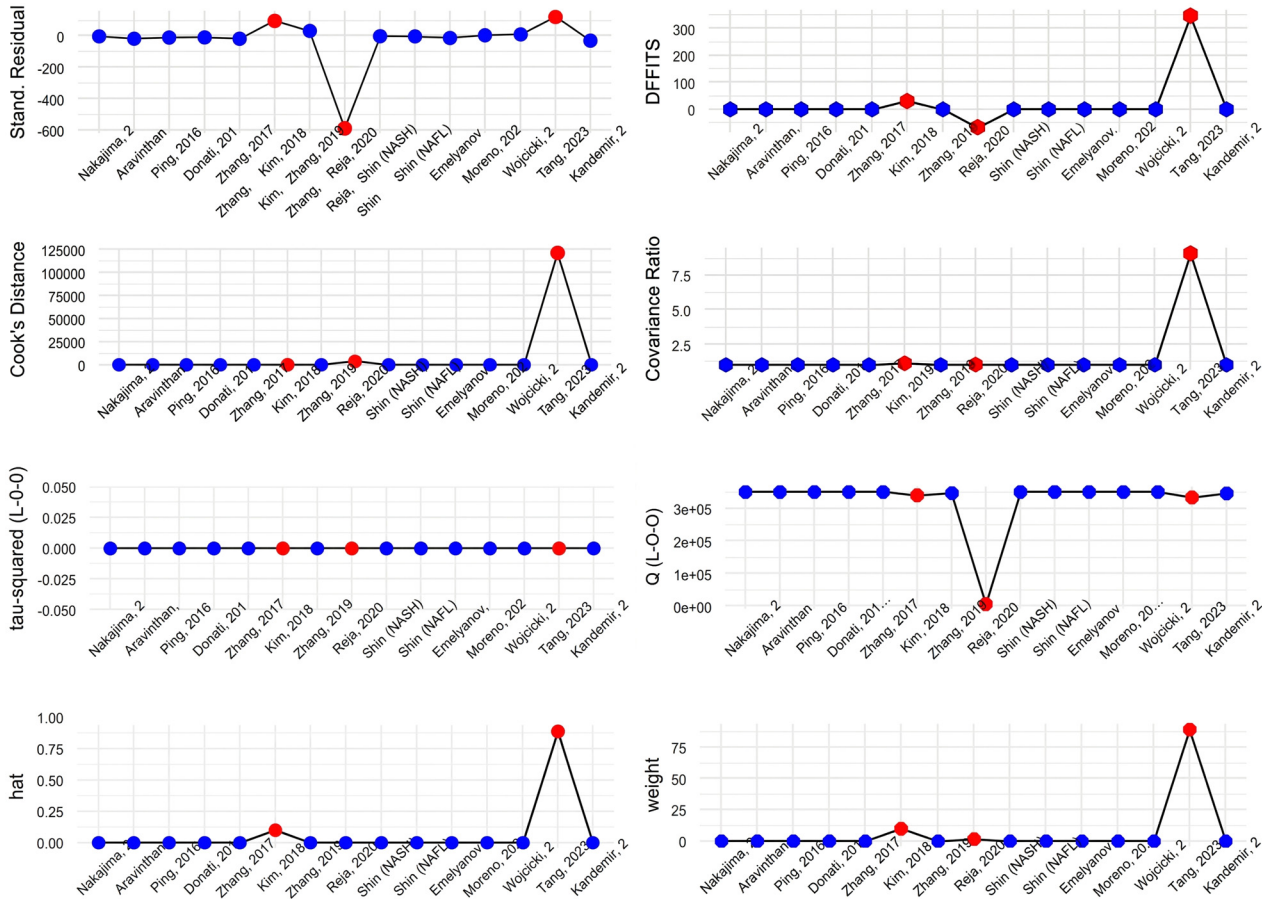

Fig. (2). Influence diagnostics for each of our studies. Influence diagnostics plot identifying studies with disproportionate effects on heterogeneity in the meta-analysis. Studies marked as outliers (Kim, Reja, and Tang) were removed to reduce heterogeneity and improve result stability. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Summary of the included studies. References*.

Year-Author (reference)	Country	Type of study	Follow-up duration	Population	Sex	Adjustments of confounding factors
2024-Kandemir [37]	Turkey	Case-control	No follow-up	83 (NAFLD: 63, Non-NAFLD: 20), 69 (Lean Controls)	38 Female, 45 Male (Obese); 34 Female, 35 Male (Controls)	Adjusted for BMI, Waist Circumference (WC), Blood Pressure (BP), HOMA-IR, ALT, AST, GGT, Total Cholesterol, Triglycerides, LDL, HDL, Creatinine, Albumin, and Genetic Variant (hTERT-MNS16A-VNTR)
2023-Linxi Tang *et al*. [23]	United Kingdom	Cohort	12.83 years	4809(NAFLD) 463039(NOT NAFLD)	2555 Female 2254 Male	Adjusted for Age, sex, income, education, alcohol intake frequency, history of cancer, and vascular/heart problems.
2023-Janet M. Wojcicki *et al*. [31]	United states	RCT	2 YEARS	123(NASH) 26(NOT NAFLD)	-	Stratified by ethnic and racial background and gender, multivariate analysis included age in years, age squared, educational attainment, place of birth, marital status, and poverty-to-income ratio, adjusted cell type composition
2023-Elena Moreno *et al*. [38]	Spain	Cohort	1 year	19(NAFLD) 8(HIV)	10 Female 9 Male	Age, sex, and metabolic syndrome
2023-D. V. Emelyanov *et al*. [35]	Ukraine	Case-control	No follow-up	76(NAFLD) 14(HEALTHY)	35 Female 41 Male	N/A
2022-Arto Korkiakoski *et al*. [39]	Finland	Cohort	21 YEARS	34.4%NAFLD (282) 20.9%NAFLD (282)	178 Female 104 Male 110 Female 172 Male	Age, Sex, and metabolic factors were matched in controls.
2021-Hee Kyung Shin *et al*. [34]	South Korea	Cross-sectional	No follow up	60(NAFLD) 23(NOT NAFLD)	34 Female 26 Male	Age, HDL, and cholesterol
2020-Kun Dong *et al*. [16]	China	Cross-sectional	No follow up	73(Advanced fibrosis) 136(No advanced fibrosis)	26 Female 47 Male	Age adjusted
2019-Min Zhang *et al*. [24]	China	Cross-sectional	No follow up	120(NAFLD) 120(NON NAFLD)	69 Female 51 Male	Age, BMI, and metabolic factors matched.
2018-Donghee Kim *et al*. [45]	United states	Cross-sectional	No follow up	2486(NAFLD) 4252(Non NAFLD)	N/A	Age, sex, ethnicity, metabolic factors, BMI, and Wist circumference
2017- Jing Zhang *et al*. [29].	China	Case-control	No follow up	100(NAFLD) 100(Healthy)	Female: 27 Male: 73	Age, Gender, Blood glucose and Blood pressure
2017-Janet M. Wojcicki *et al*. [32]	United states	Cross-sectional	No follow up	149(NAFLD)	29 Female 120 Male	Age, sex, ethnicity, waist circumference, smoking, diabetes
2017-Benedetta Donati *et al*. [5]	Italia	Case-control	No follow up	40(NAFLD-HCC) 45(NAFLD-cirrhosis) 50(NAFLD HCC) 89(NAFLD HCC) 64(Control)	Female: 13 Male: 27	Age and Sex Adjusted
2016-Fan Ping *et al*. [5]	China	Cohort	6 years	70(total) 39 NAFLD 21 non-NAFLD	N/A	BMI, insulin resistance, fasting insulin, systolic BP

(Table 1) Contd….

Year-Author (reference)	Country	Type of study	Follow-up duration	Population	Sex	Adjustments of confounding factors
2016-Ido Laish *et al*. [8]	Israel	Case-control	No follow up	22(NAFLD) 20(HEALTHY)	11 Female 11 Male	Age-matched controls.
2012-Aloysious Aravinthan *et al*. [33]	United Kingdom	Cohort	> 4 years	130(total) 70(case) 60(control)	Female: 17 Male: 53	Age and Sex matched
2006- Nakajima *et al*. [36]	Japan	Case-control	No follow up	55(total) 44(case) 11(control)	Female: 17 Male: 27	Age-matched

Table 2. Quality assessment of case-control studies.

Authors	1	2	3	4	5	6	7	8	9	10	score
Benedetta Donati *et al*. [5]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	10\10
Jing Zhang *et al*. [29].	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	9\10
D. V. Emelyanov *et al*. [35]	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	9\10
Tomoki Nakajima *et al*. [36]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	10\10
Kandemir [37]	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	9\10
Ido Laish *et al*. [8]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	10\10

Note: 1. Were the groups comparable other than the presence of disease in cases or absence of disease in controls? **2.** Were cases and controls matched appropriately? **3.** Were the same criteria used for the identification of cases and controls? **4.** Was exposure measured in a standard, valid, and reliable way? **5.** Was exposure measured in the same way for cases and controls? **6.** Were confounding factors identified? **7.** Were strategies to deal with confounding factors stated? **8.** Were outcomes assessed in a standard, valid, and reliable way for cases and controls? **9.** Was the exposure period of interest long enough to be meaningful? **10.** Was appropriate statistical analysis used?

Table 3. Quality assessment for cross-sectional studies.

Authors	1	2	3	4	5	6	7	8	score
Janet M. Wojcicki *et al.* [31]	yes	yes	yes	yes	yes	yes	yes	yes	8\8
Donghee Kim *et al.* [45]	yes	no	yes	yes	yes	yes	yes	yes	7\8
Hee Kyung Shin *et al.* [34]	yes	yes	yes	yes	yes	yes	yes	yes	8\8
Kun Dong *et al.* [16]	yes	yes	yes	yes	yes	no	yes	yes	7\8
2019-Min Zhang *et al.* [24]	yes	no	yes	yes	yes	yes	yes	yes	7\8

Note: 1. Were the criteria for inclusion in the sample clearly defined? **2.** Were the study subjects and the setting described in detail? **3.** Was the exposure measured validly and reliably? **4.** Were objective, standard criteria used for measurement of the condition? **5.** Were confounding factors identified? **6.** Were strategies to deal with confounding factors stated? **7.** Were the outcomes measured validly and reliably? **8.** Was appropriate statistical analysis used?

Table 4. Quality assessment for cohort studies.

Authors	1	2	3	4	5	6	7	8	9	10	11	score
Arto Korkiakoski *et al.* [39]	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes	9/11
Aloysious Aravinthan *et al.* [33]	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes	9\11
Moreno *et al.* [38]	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	10/11
Ping *et al.* [6]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	10/11
Tang *et al.* [23]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11/11

Note: 1. Were the two groups similar and recruited from the same population? **2.** Were the exposures measured similarly to assign people to both exposed and unexposed groups? **3.** Was the exposure measured validly and reliably? **4.** Were confounding factors identified? **5.** Were strategies to deal with confounding factors stated? **6.** Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? **7.** Were the outcomes measured validly and reliably? **8.** Was the follow-up time reported and sufficient to be long enough for outcomes to occur? **9.** Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored? **10.** Were strategies to address incomplete follow-up utilized? **11.** Was appropriate statistical analysis used?

Table 5. Quality assessment for randomized clinical trials.

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	score
Janet M. Wojcicki *et al*. [32]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	13\13

Note: Was proper randomization used for the assignment of participants to treatment groups? **2.** Was allocation to treatment groups concealed? **3.** Were the treatment groups similar at the baseline? **4.** Were participants blind to treatment assignment? **5.** Were those delivering treatment blind to treatment assignment? **6.** Were outcome assessors blind to treatment assignment? **7.** Were the treatment groups treated identically, other than the intervention of interest? **8.** Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored? **9.** Were participants analyzed in the groups to which they were randomized? **10.** Were outcomes measured in the same way for treatment groups? **11.** Were outcomes measured in a reliable way? **12.** Was appropriate statistical analysis used? **13.** Was the trial design appropriate, and were any deviations from the protocol explained?

Table 6. Meta regression results for various confounders.

Covariates	Estimate	se	pval	ci.lb	ci.ub	r2
Years	0.0077	0.023	0.7364	-0.0373	0.0528	0%
Age.tr	-0.0057	0.0153	0.7087	-0.0357	0.0243	0%
BMI.tr	0.1168	0.0484	0.0157	0.022	0.2117	52.11%
NAFLD.subtypes Cat: NASH/NAFL	0.3196	0.3281	0.3301	-0.3235	0.9627	0%
NAFLD.subtypes Cat: Unstated	0.2721	0.2849	0.3394	-0.2862	0.8304	0%
study.type Cat: Case-Control	0.051	0.161	0.750	-0.263	0.3645	0%
Study.type Cat: cohort	-0.504	0.179	0.005	-0.858	-0.152	69%
Diabetic.type2 Cat: yes	0.0681	0.2372	0.774	-0.3968	0.5329	0%

Note: B: regression coefficient, Se: Standard error, Pval: P-value, Ci.lb & Ci.ub: Lower and upper bounds of the Confidence interval, r2: R-squared

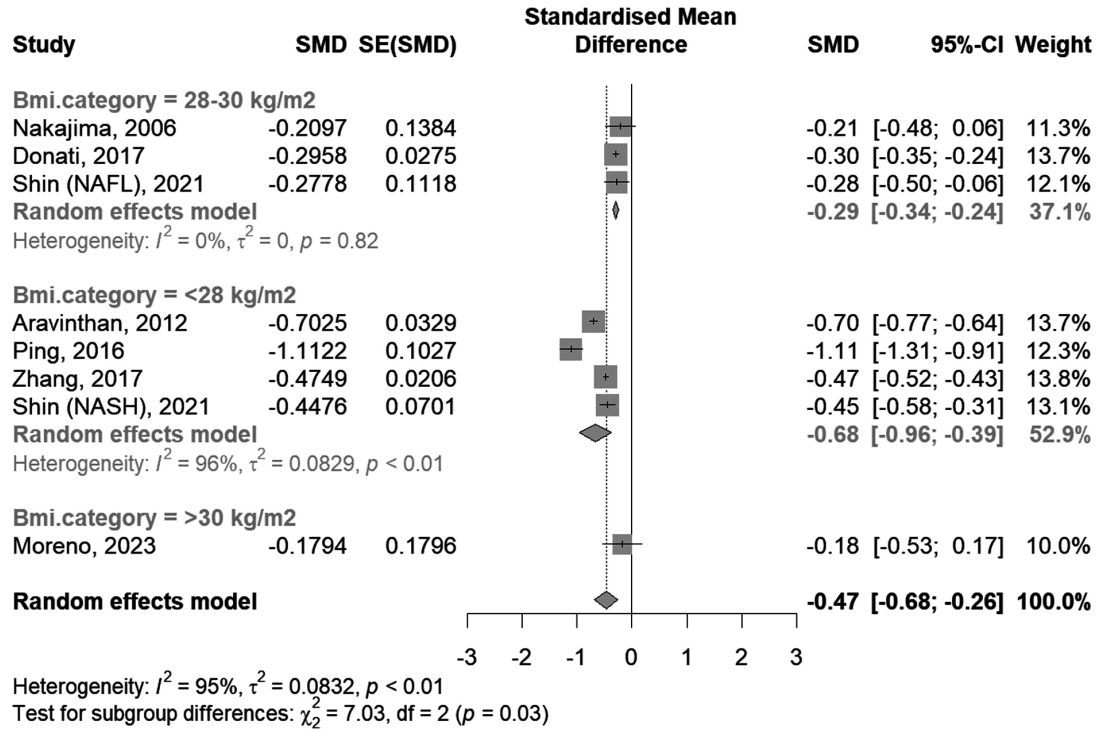

Fig. (3). Forest plot displaying the association between telomere length (TL) and NAFLD in different BMI subgroups. Individuals with BMI <28 showed a significant TL reduction in NAFLD patients (SMD = -0.68, 95% CI: -0.96 to -0.39, I^2 = 96%), whereas those with BMI 28–30 had a more homogeneous effect (SMD = -0.29, 95% CI: -0.34 to -0.24, I^2 = 0%), indicating that BMI may influence TL-NAFLD associations. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.4. Subgroup Meta-analysis by BMI Categories

Based on reports from multiple studies, three BMI categories were defined to assess differences in telomere length among individuals with NAFLD compared to control groups. The analysis outcomes for each category are detailed below.

For individuals with a BMI of less than 28, the findings indicated that telomere length in NAFLD patients was significantly shorter by 0.68 units compared to the control group, with a 95% confidence interval ranging from -0.96 to -0.39. However, substantial heterogeneity was observed among the studies included in this subgroup, as reflected by an I^2 value of 96%.

In the subgroup of individuals with a BMI between 28 and 30, the analysis revealed that telomere length in NAFLD patients was statistically shorter by 0.29 units relative to the control group. The 95% confidence interval for this difference ranged from -0.34 to -0.24. Notably, no significant heterogeneity was detected among the studies included in this subgroup.

For individuals with a BMI greater than 30, the analysis was limited to a single study. This study reported a reduction in telomere length of 0.18 units in the NAFLD group compared to the control group. However, the observed difference was not statistically significant (Fig. **3**).

3.5. Subgroup Meta-analysis by Study Types

Subgroup analysis by study design revealed that in case-control studies, patients with NAFLD had significantly shorter telomeres compared to controls (SMD = -0.35, 95% CI: -0.51 to -0.20, I^2 = 93%). Similarly, cohort studies demonstrated a more pronounced reduction in telomere length among NAFLD patients (SMD = -0.68, 95% CI: -1.19 to -0.17, I^2 = 92%). The cross-sectional study subgroup, which analyzed non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver (NAFL) separately, also reported a significant decrease in telomere length in NAFLD patients compared to controls (SMD = -0.39, 95% CI: -0.55 to -0.22, I^2 = 40%). The NAFLD patients were, on average, 0.39 units shorter than the healthy controls, with a 95% confidence interval ranging from -0.55 to -0.22 (Fig. **4**).

3.6. Other Subgroup Analyses

A subgroup analysis was conducted based on diabetes status. Among non-diabetic participants, the standardized mean difference was -0.50 (95% CI: -0.82 to -0.17), with a heterogeneity of I2 = 91% and p < 0.01. For diabetic participants, the effect size was slightly smaller, with an SMD of -0.43 (95% CI: -0.71 to -0.15) and a heterogeneity of I^2 = 98%, p < 0.01. The test for subgroup differences was not statistically significant (p = 0.77), indicating that the effect did not

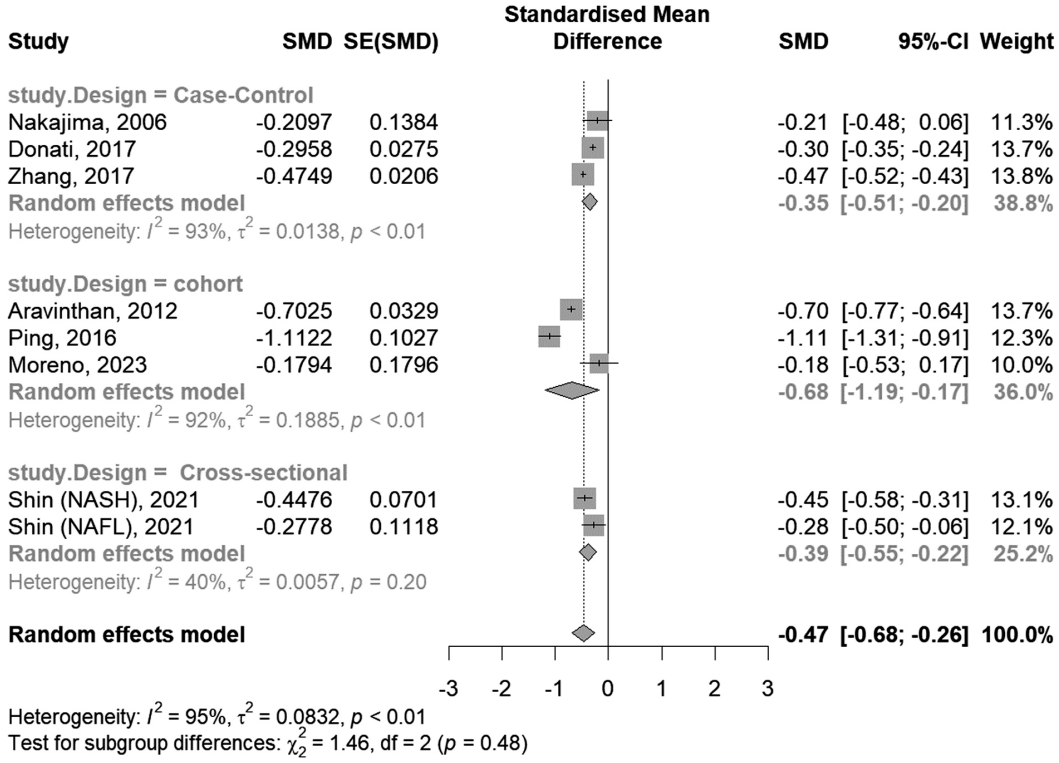

Fig. (4). Forest plot comparing telomere length differences in NAFLD patients across study designs. Case-control studies demonstrated a significant reduction in TL (SMD = -0.35, 95% CI: -0.51 to -0.20, I^2 = 93%), while cohort studies showed a more pronounced effect (SMD = -0.68, 95% CI: -1.19 to -0.17, I^2 = 92%). Cross-sectional studies exhibited lower heterogeneity (I^2 = 40%), suggesting potential methodological influences on results. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

significantly differ between diabetic and non-diabetic individuals (Fig. **S2**).

Further stratification by age groups revealed that among individuals aged 50 to 60 years, the standardized mean difference was -0.43 (95% CI: -0.66 to -0.21) with I^2 = 90%, p < 0.01. For participants aged 60 years and older, the effect size was slightly larger, with an SMD of -0.54 (95% CI: -1.11 to 0.04) and a heterogeneity of I^2 = 97%, p < 0.01. In the 40- to 50-year-old category, the SMD was -0.47 (95% CI: -0.52 to -0.43), based on a single study. The test for subgroup differences showed no significant variation between age groups (p = 0.92), suggesting a consistent effect across different age categories (Fig. **S3**).

3.7. Results Based on OR

Among the included studies, 6 articles reported the OR to investigate the chance of short TL in NAFLD patients. Based on the meta-analysis, the pooled OR estimate for these 6 studies was 1.72 (1.23-2.42), indicating that the odds ratio of having NAFLD is 1.7 for people with short TL compared to the Control Group. However, the heterogeneity rate in this study was 85%, which was significant. Thus, by conducting a sensitivity analysis, we evaluated the impact of each study, and the results indicated that excluding the study conducted by Linxi Tang *et al*. reduced the heterogeneity ratio to 37%. The pooled odds ratio obtained after excluding this study was 1.93, indicating that the odds of having NAFLD in individuals with short TL were 93% higher than in the control group, which was also statistically significant (95% CI: 1.45–2.56) (Fig. **5**).

4. DISCUSSION

We performed a thorough examination and meta-analysis of 17 documents to explore the correlation between TL and NAFLD. The overall OR for NAFLD and short telomeres was 1.93 (95% CI: 1.45-2.56, I2 = 37%), and the pooled SMD across all included studies was -0.25 (95% CI: -0.39 to -0.10). However, the findings on the relationship between TL and NAFLD have been inconsistent across different studies. For instance, a case-control study involving 70 NAFLD individuals under extended observation and 60 controls, using donor livers matched for age and sex, found that the mean fluorescent intensity (MFI) of hepatocyte telomeres, a validated indicator of telomere length [31], was significantly reduced in individuals with NAFLD compared to the control group (553 vs. 1053, P < 0.0001). They demonstrated that the accumulation of fat in liver cells leads to DNA damage and telomere degradation, possibly due to oxidative stress. This could explain the accelerated shortening of telomeres in hepatocytes of NAFLD patients [33]. In contrast, another case-control investigation involving 240 diabetics found that individuals suffering from NAFLD had substantially longer hepatocyte leukocyte telomere length in the early stages of type 2 diabetes. In this study, the weighted mean telomere length was reported. TL of patients varied from 4502 base pairs (bp) to 8993 bp. After accounting for age, the TL in type 2 diabetes mellitus (T2DM) patients with NAFLD (6400.2 ± 71.8 bp) was significantly greater compared to T2DM patients without NAFLD (6023.7 ± 49.5 bp) (P < 0.001). Furthermore, T2DM patients with NAFLD exhibited longer TL than those without NAFLD across all age groups (20–39 years, 40–59 years, and ≥60 years). They also discovered that the rate of TL shortening in individuals with T2DM and NAFLD was greater than that in those without a longer duration of diabetes, suggesting that individuals with T2DM and NAFLD may eventually have a shorter TL [24]. These results might be due to the complex pathogenesis of T2DM. Furthermore, some case-control studies have revealed an opposite association. For example, Korkiakoski *et al*. demonstrated in a 21-year follow-up that TL in seniors had an independent relationship with both the frequency of NAFLD and the anticipated mortality in NAFLD patients [39]. Others, however, found the link to be statistically insignificant, as Ping *et al*. indicated that NALFD patients had shorter telomeres compared to the controls after a 6-year follow-up [5].

Despite significant between-study diversity, the results remained consistent even after repeated sensitivity evaluations. The observed heterogeneity may stem from several factors, including differences in study populations (*e.g*., variations in age, gender

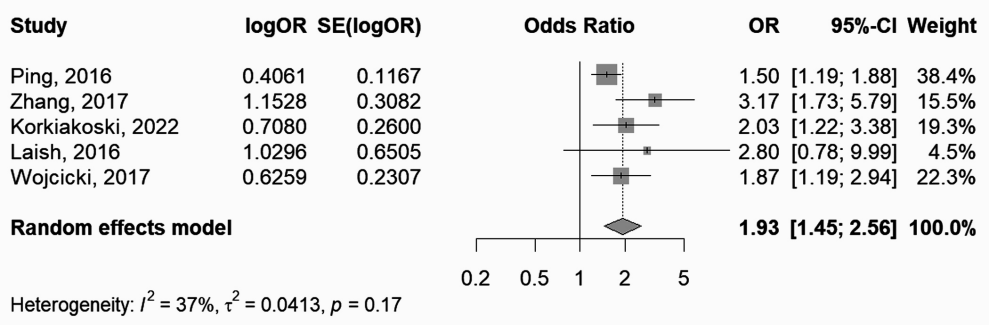

Fig. (5). Forest plot displaying the pooled odds ratio (OR) for the association between short TL and NAFLD. The initial OR analysis (I^2 = 85%) suggested high heterogeneity, which was reduced to I^2 = 37% after excluding one study (Tang *et al*.), confirming a stronger and more reliable association (OR = 1.93, 95% CI: 1.45–2.56). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

distribution, and BMI), discrepancies in study design (case-control vs. cohort studies), diverse sample sizes, and variations in follow-up durations. Additionally, variations in adjustment for confounding factors, such as metabolic conditions, lifestyle variables, and genetic predispositions, could further contribute to the inconsistencies.

For the first time, Tang *et al*. conducted prospective research to investigate the connection between TL and NAFLD, where TL was evaluated using the quantitative PCR method. They were also the first to use a population-based approach to establish telomere length as a mediator between NAFLD and age [23]. Aging is a key risk factor for several age-related illnesses, including NAFLD [40]. Telomere shortening occurs as part of the aging process, causing cell senescence and steatosis through the p53–p21 and p16–Rb pathways [41]. Several studies have indicated that patients with NAFLD exhibit shorter telomeres, elevated p21 expression, increased γ -H2AX expression, and nuclear expansion in their hepatocytes [23, 42, 43]. Aravinthan *et al.* were the first to use cell cycle phase markers to demonstrate G1/S phase arrest of the cell cycle in NAFLD, where p21 typically acts [33]. The correlation between elevated p21 expression in hepatocytes and the severity of fibrosis stage, as well as unfavorable liver outcomes in NAFLD, is well-established, owing to its pivotal involvement in cellular senescence [42, 44]. Much research has also established the association between the shortening of the TL in liver tissue and cirrhosis; it was discovered that a shorter hepatocellular TL is linked to the level of fibrosis. For example, Zhang *et al.* showed that Short TL has been associated with increased risk of NAFLD and worsening fibrosis [29].

STUDY LIMITATIONS

This study faced some limitations. A limited sample size can limit the generalizability of our findings. Additionally, while all included studies were assessed using the JBI checklist and classified as having a low risk of bias, some studies did not achieve the highest score. In addition, variations in the reporting and adjustment of confounders, such as BMI and metabolic status, may have influenced the overall findings. Despite conducting meta-regression and subgroup analyses to address this, residual confounding cannot be entirely ruled out. Furthermore, a key limitation of this meta-analysis is the high heterogeneity observed across the included studies, likely due to differences in study design, population characteristics, and the adjustments made for confounders. While we conducted sensitivity analyses, meta-regression, and subgroup analyses to explore sources of heterogeneity, some degree of variability remained, which may influence the interpretation of pooled effect estimates.

In terms of future research, further longitudinal studies are needed to establish a causal relationship between TL shortening and NAFLD progression. Investigating the effectiveness of interventions such as antioxidants, lifestyle modifications, or pharmacological agents in maintaining telomere length could provide valuable insights into novel therapeutic approaches. Additionally, exploring the molecular mechanisms underlying TL dynamics in NAFLD may uncover new biomarkers or therapeutic targets, offering a more comprehensive understanding of disease pathology.

In terms of prevention, the study's findings may encourage lifestyle modifications, such as weight management, regular physical activity, and improved dietary habits, to preserve telomere length and mitigate the development of NAFLD.

CONCLUSION

In conclusion, our findings demonstrate a possible association between shorter TL and an increased likelihood of NAFLD. The interpretation of these results must consider the high heterogeneity observed in the included studies, which was only partially mitigated through sensitivity analyses, subgroup analyses, and meta-regression. Further research is essential to establish the causal mechanisms and identify the clinical applications.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: MR; data collection: SK; supervision: MV; methodology: SK; investigation: YE; draft manuscript: NMS, AMH, SZG, MSJ; validation: SJ. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

NAFLD	=	Non-Alcoholic Fatty Liver Disease
TL	=	Telomere Length
SMD	=	Standard Mean Difference
OR	=	Odds Ratio
BMI	=	Body Mass Index
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CI	=	Confidence Interval
SASP	=	Senescence-Associated Secretory Phenotype
T2DM	=	Type 2 Diabetes Mellitus
NASH	=	Non-Alcoholic Steatohepatitis
HCC	=	Hepatocellular Carcinoma
RCT	=	Randomized Controlled Trial
JBI	=	Joanna Briggs Institute

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

The data of current study are available from the corresponding author, on a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article. The PRISMA checklist is also provided as supplementary material on the publisher's website.

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