Meta-Analysis

Association between telomere length and diabetes mellitus: A meta-analysis

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Abstract
Objective: We investigated the relationship between diabetes and telomere length by meta-analysis.
Methods: We searched five popular databases for articles published between 1990 and 2015 using “diabetes” and “telomere” as search terms. Data were processed with RevMan5, and random- or fixed-effects meta-analysis was applied. The effects of geographical region, diabetes type, body mass index (BMI), age and sex were examined. Funnel plots were applied to evaluate publication bias.
Results: Seventeen articles were obtained from 571 references. We identified a significant association between telomere length and diabetes mellitus (standardized mean difference [SMD]: −3.41; 95% confidence interval [CI]: −4.01, −2.80; heterogeneity, I² = 99%) by comparing 5575 patients with diabetes and 6349 healthy individuals. The pooled SMD by geographic region indicated a significant association between shortened telomere length and diabetes mellitus (SMD: −3.41; 95% CI: −4.01, −2.80; heterogeneity, I² = 99%). In addition, telomere length was significantly associated with age (SMD: −3.41; 95% CI: −4.01, −2.80), diabetes type (SMD: −3.41; 95% CI: −4.01, −2.80), BMI (SMD: −1.61; 95% CI: −1.98, −1.23) and sex (SMD: −4.94; 95% CI: −9.47, −0.40).
Conclusions: The study demonstrated a close relationship between diabetes mellitus and telomere length, which was influenced by region, age, diabetes type, BMI and sex.

Keywords
Telomere length, diabetes mellitus, meta-analysis

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Introduction
Diabetes incidence continues to increase globally at alarming rates. In 2013, 382

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million people were diagnosed with diabetes, with more than 100 million of those in China alone.\textsuperscript{1} Diabetes mellitus is a metabolic disease characterized by hyperglycaemia and impaired biological functions leading to severe complications, such as cardiovascular, kidney and eye diseases. Treatment of diabetes and its co-morbidities imposes a high burden on the world economy, amounting to $548 billion USD in 2013 and an estimated $627 billion USD by 2035.\textsuperscript{1} Therefore, understanding the molecular mechanisms underlying diabetes as well as finding and developing efficient treatment strategies are more pressing than ever.

The concept of “telomeres” was first proposed by McClintock and Muller.\textsuperscript{2,3} They determined that the stability and integrity of the chromosome was retained within the ends of the chromosome, which Muller named the “telomere”.\textsuperscript{3} Thus, the telomere is located at the end of chromosomal DNA and is composed of thousands of tandem repeats of the TTAGGG nucleotide sequence and a number of associated proteins, which confer protection against chromosome degradation.\textsuperscript{4} The telomere is necessary for DNA replication. It undergoes shortening during each DNA replication cycle until it reaches a certain length, at which time cell apoptosis is signaled. Therefore, telomere length is often used as a biological marker for cell aging.\textsuperscript{5}

Accumulating evidence indicates that diabetes may affect changes in telomere length. Jeanclos\textsuperscript{6} was the first to demonstrate an association between type 2 diabetes mellitus (T2DM) and shortened telomere length. Similarly, Li\textsuperscript{7} determined that the leukocyte telomere length in patients with diabetes was shorter than that in healthy individuals. They suggested that with the development of diabetes, islet \( \beta \) cells undergo senescence or apoptosis, because the telomere length gradually becomes shorter, which in turn can lead to a cascade of damaging events characteristic of diabetes complications. Therefore, to further examine the association between diabetes mellitus and telomere length, this study employed a meta-analysis model to assess the contribution of geographical region, diabetes type, body mass index (BMI), age and sex on telomere length in patients with diabetes.

**Methods**

**Study eligibility and identification**

We performed systematic computerized searches of PubMed (MEDLINE), EMBASE, China National Knowledge Infrastructure, Wanfang data and the VIP database of China. We used “telomere” and “diabetes” as search terms to examine articles that were published between January 1\textsuperscript{st}, 1990 and December 31\textsuperscript{st}, 2015.

**Study selection and exclusion criteria**

We used the referenced QUADAS literature evaluation standard established by Whiting.\textsuperscript{8} Two authors (JW and LZ) reviewed studies for inclusion independently. Accordingly, the literature included in the meta-analysis was selected based on the following criteria: 1) it assessed the association between diabetes mellitus and telomere length; 2) it included case-control groups and a complete set of data; 3) the human subjects analyzed included adults only; and 4) it provided standardized mean differences (SMD) and 95% confidence intervals (CIs) or presented sufficient information to allow their computational calculations. The following exclusion criteria were used: 1) the studies contained incomplete data; 2) the studies were conducted using children or animal models; 3) the studies included patients with gestational diabetes; and 4) the subjects were diagnosed with other pathologies, such as heart or kidney diseases.
Quality assessment and data extraction

Study quality was independently assessed by two authors (XD and LC) using the Cochrane Risk of Bias Tool (Newcastle-Ottawa scale). Two authors (JW and XD) extracted data from selected articles independently. The following information was recorded from the selected literature: title, first author, year of publication, country, case-control basic information (subjects, age, sex and BMI), diabetes mellitus type, telomere length and the SMD and 95% CIs. The mean and SD (range, SE and CI for BMI) and other tests were tabulated along with the main findings reported in each study.

Meta-analysis

Meta-analyses were performed using RevMan5 software (The Cochrane Collaboration, Copenhagen, Denmark). Homogeneity was assessed using the $\chi^2$ test with Cochran Q and $I^2$ statistics. Heterogeneity was defined as low, medium and high when $I^2 < 25\%$, $25\% < I^2 < 50\%$ and $I^2 > 50\%$, respectively. The fixed-effect model was used when there was no significant heterogeneity among the included studies ($P > 0.05$ and $I^2 < 50\%$). In all other cases, the random-effects model was applied.

The SMD and 95% CIs were used to evaluate differences between groups. We used a funnel plot to evaluate publication bias. Subgroup analyses were performed to evaluate the effect of region (Asia, Europe and the USA), age (below and above 60 years old), diabetes type (T1DM and T2DM), BMI (normal, overweight and obese) and sex (male and female). $P$ values for all comparisons were obtained using a two-tailed model, and statistical significance was set at $\alpha < 0.05$.

Results

Literature search

Using the search terms “diabetes” and “telomere,” our initial search yielded 571 studies. After applying the inclusion/exclusion criteria, 522 papers were excluded. Of the 49 papers selected, only 17 were included in the meta-analysis, including 2 publications in Chinese and 15 in English. The article selection process is summarized in Figure 1, and the primary parameters of the study are presented in Table 1.

Association between telomere length and diabetes

From 17 studies, we extracted 5575 experimental cases and 6389 controls. The results using RevMan5 software are presented in Figure 2. There was a significant effect of heterogeneity ($\chi^2 = 2753.47$, $I^2 = 99\%$, $P < 0.00001$) among the studies included as well as a significant random-effect ($P < 0.05$). The pooled SMD ($-3.41$; 95% CI: $-4.01$, $-2.80$) and the diamond were located on the left side of the vertical line of the forest graph. These results indicated that telomere length in patients with diabetes was shorter than that in healthy individuals.

The shape of the funnel plots did not appear symmetrical, suggesting that there was a publication bias in the meta-analysis (Figure 3).

Subgroup analyses

The results of subgroup analyses and the respective sample sizes in each subgroup (region, age, type, BMI and sex) are summarized in Table 2.

The effect of geographical region on diabetes and telomere length

There were eight, five and four articles that included studies from Asia, Europe and the USA, respectively (Figure 4). The SMD in European studies ($-2.34$; 95% CI: $-4.65$, $-0.04$; $P = 0.05$) was significantly lower than that in Asian ($-4.73$; 95% CI: $-6.29$, $-3.17$; $P < 0.00001$) and US ($-2.94$; 95%
Additionally, we wanted to identify the difference in telomere length between patients with diabetes and healthy individuals from China (Figure 5). Analysis of the eight papers that included Chinese subjects revealed that the SMD was lower in Chinese populations (−2.00; 95% CI: −2.91, −1.08; \( P < 0.00001 \)) compared with that of other Asian countries (−14.88; 95% CI: −30.64, 0.87). This finding indicates that the telomere length SMD between patients with diabetes and healthy individuals in China was significantly lower than that in other Asian countries (\( P < 0.00001 \)); however, the difference was not significant in a non-Chinese population.

**The effect of age on diabetes and telomere length**

Telomere shortening is considered the molecular clock that triggers cell senescence.
| First Author         | Year | Country | Quantity | Type | Male | Mean Age | Mean BMI | Telomere Length | control | Quantity | Male | Mean Age | Mean BMI | Telomere Length |
|----------------------|------|---------|----------|------|------|----------|----------|----------------|---------|----------|------|----------|----------|----------------|
| Lu et al.\(^{12}\)  | 2007 | China   | 20       | 1    | 11   | 23.85    | —        | 8.29           |         | 20       | 11   | 28.1    | —        | 8.94          |
| Liu et al.\(^{13}\) | 2012 | China   | 21       | 2    | 11   | 44.9     | 23.73    | 1.34           |         | 47       | 24   | 42.5    | 22.48    | 3.83          |
| Ma D et al.\(^{14,6}\) | 2013 | China   | 34       | 1    | 21   | 26.32    | 20.38    | 1.77           |         | 40       | 21   | 32.25   | 21.82    | 2.39          |
| Ma D et al.\(^{14,6}\) | 2013 | China   | 62       | 2    | 35   | 50.15    | 23.39    | 1.67           |         |          |      |         |          |               |
| Dudinskaya et al.\(^{15}\) | 2014 | Russia  | 50       | 2    | —    | 56       | —        | 9.51           |         | 49       | —    | 53.47   | —        | 9.8           |
| Fyhrquist et al.\(^{16}\) | 2010 | Finland | 48       | 1    | 22   | 39       | 25       | 8.4            |         | 44       | 24   | 39.4    | 23.7     | 8.5           |
| Ma et al.\(^{17}\) | 2015 | China   | 38       | 2    | 17   | 45.68    | 24.4     | 1.58           |         | 31       | 15   | 41.63   | 24       | 3.98          |
| Adaikalakoteswari et al.\(^{18}\) | 2005 | India   | 40       | 2    | 20   | 49       | 25.2     | 6.01           |         | 40       | 20   | 49      | 23.5     | 9.11          |
| Murillo et al.\(^{19}\) | 2012 | Mexico  | 93       | 2    | 93   | 54.5     | 25.5     | 5.4            |         | 98       | 98   | 52.8    | 27.1     | 9.5           |
| Liu et al.\(^{20}\) | 2014 | China   | 71       | 2    | 40   | 54.55    | 25.21    | 2.01           |         | 52       | 30   | 51.27   | 23.86    | 2.28          |
| Sampson et al.\(^{21}\) | 2006 | USA     | 21       | 2    | 21   | 62       | 29.5     | 4              |         | 28       | 28   | 61.2    | 17.3     | 5.5           |
| Zee et al.\(^{22}\) | 2010 | USA     | 432      | 2    | 256  | 60       | 33.3     | 2.4            |         | 424      | 187  | 51      | 25.4     | 2.46          |
| Olivieri et al.\(^{23}\) | 2009 | Italy   | 103      | 2    | 61   | 70       | 29       | 0.44           |         | 104      | 52   | 69      | 27       | 0.53          |
| Testa et al.\(^{24}\) | 2011 | Italy   | 217      | 2    | 121  | 65.9     | 29.3     | 0.46           |         | 400      | 220  | 65.1    | 26.9     | 0.45          |
| Salpea et al.\(^{25}\) | 2010 | UK      | 569      | 2    | 338  | 68       | —        | 6.94           |         | 367      | 367  | 53      | —        | 7.85          |
| Monickaraj et al.\(^{26}\) | 2012 | India   | 145      | 2    | —    | 43.6     | 25.9     | 0.97           |         | 145      | —    | 41.4    | 24.5     | 1.2           |
| You et al.\(^{27}\) | 2012 | USA     | 1675     | 2    | 0    | 62.11    | 31       | 3.97           |         | 2380     | 0    | 62.12   | 27       | 4.12          |
| Shen et al.\(^{28}\) | 2012 | China   | 1936     | 2    | 1140 | 64       | 25.1     | 0.98           |         | 2080     | 1452 | 58      | 24.5     | 1.04          |

\(^{6}\) Ma Da included both type 1 and type 2 diabetes with one control group.

BMI, body mass index.
Figure 2. Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals. Results are presented using a random effects model. CI, confidence interval; IV, inverse variance method.

Figure 3. Funnel diagram analysis of telomere length comparison between patients with diabetes and healthy individuals.
and can be used as a biological marker of aging. We grouped the studies into two age categories: below and above 60 years of age. We determined that the pooled SMD for individuals older than 60 years of age (1.47; 95% CI: 2.19, 0.76; \( P < 0.00001 \)) was lower than that for younger individuals (5.45; 95% CI: 7.33, 3.57; \( P < 0.00001 \)). This indicates that the telomere length SMD between patients with diabetes and healthy individuals in older cohorts (>60 years of age) was significantly lower than that in younger cohorts (<60 years of age) (\( P < 0.00001 \)) (Figure 6).

*The effect of BMI on diabetes and telomere length*

We performed a subgroup analysis between patients with T1DM and patients with T2DM. The pooled SMD for patients with T1DM (0.74; 95% CI: 1.46, 0.03; \( P = 0.04 \)) was significantly lower than that for patients with T2DM (3.98; 95% CI: 4.65, 3.31; \( P < 0.00001 \)), demonstrating that the telomere length SMD between patients with T1DM and healthy individuals was significantly lower than that of patients with T2DM (Figure 7).

### Table 2. Results from the subgroup analysis of the meta-analysis.

| Characteristic | Studies | Case | Control | SMD (95% CI) | \( I^2 \) (%) | \( P \)-Value | \( P \)-Value |
|---------------|---------|------|---------|--------------|---------------|--------------|--------------|
| All Studies   | 17      | 5575 | 6389    | -3.41 (-4.01, -2.80) | 99            | <0.00001     | <0.00001     |
| Region        |         |      |         |              |               |              |              |
| Asia          | 8       | 2367 | 2495    | -4.73 (-6.29, -3.17) | 99            | <0.00001     | <0.00001     |
| Europe        | 5       | 987  | 964     | -2.34 (-4.65, -0.04) | 100           | <0.00001     | 0.05         |
| USA           | 4       | 2221 | 2930    | -2.94 (-3.97, -1.91) | 99            | <0.00001     | <0.00001     |
| Age           |         |      |         |              |               |              |              |
| > 60 years    | 7       | 4953 | 5783    | -1.47 (-2.19, -0.76) | 100           | <0.00001     | <0.0001      |
| < 60 years    | 10      | 622  | 606     | -5.45 (-7.33, -3.57) | 99            | <0.00001     | <0.00001     |
| Type          |         |      |         |              |               |              |              |
| T1DM          | 3       | 102  | 104     | -0.74 (-1.46, -0.03) | 83            | 0.003        | 0.04         |
| T2DM*         | 15      | 5473 | 6285    | -3.98 (-4.65, -3.31) | 99            | <0.00001     | <0.00001     |
| BMI           |         |      |         |              |               |              |              |
| Normal        | 3       | 155  | 158     | -3.28 (-5.06, -1.50) | 97            | <0.00001     | 0.0003       |
| Overweight    | 4       | 2095 | 2216    | -1.69 (-2.82, -0.56) | 98            | <0.00001     | 0.003        |
| Obese         | 5       | 2448 | 3336    | -1.12 (-1.75, -0.49) | 99            | <0.00001     | 0.0005       |
| Gender        |         |      |         |              |               |              |              |
| Male          | 2       | 114  | 126     | -7.46 (-19.49, 4.56) | 100           | <0.00001     | 0.22         |
| Female        | 1       | 1675 | 2380    | -0.11 (-0.17, -0.05) | –             | –            | 0.0007       |

*Data originate from the same paper (Ref. 14). The same control group was used for each comparison (n = 80). SMD, standardized mean difference; CI, confidence interval; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; BMI, body mass index.
**Figure 4.** Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals from different regions (Asia, Europe and the Americas). Results are presented using a random effects model. CI, confidence interval; IV, inverse variance method.

**Figure 5.** Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals from China and other countries in Asia. Results are presented using a random effects model. CI, confidence interval; IV, inverse variance method.
In obese individuals, the telomere length SMD between patients with diabetes and healthy individuals was lower than that in normal weight and overweight individuals (Figure 8).

**The effect of sex on diabetes and telomere length**

The pooled SMD for females (−0.11, 95% CI: −0.17, −0.05; P = 0.0007) was lower than that for males (−7.46; 95% CI: −19.49, 4.56). These results suggest that the telomere length SMD between patients with diabetes and healthy individuals in female cohorts was lower than that in male cohorts (P = 0.03); however, the difference was not significant in males (Figure 9).

**Discussion**

This meta-analysis study demonstrates that diabetes affects telomere length. Specifically, telomere length in patients with diabetes is reduced compared with that of healthy individuals. We reviewed 17 papers that met the inclusion criteria and conducted a five-subgroup meta-analysis that included geographical region, age, diabetes type, BMI and sex. We determined that telomere length in patients with diabetes varied based on geographical region. Specifically, European patients with diabetes displayed a reduced telomere length compared with that of Asian and US patients. Additionally, we demonstrated that telomere length was affected by diabetes type, BMI, age and sex. As such, patients with T1DM, obese patients, patients over 60 years of age and

![Figure 6. Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals of different ages (below and above 60 years of age). Results are presented using a random effects model.](image-url)
female patients all exhibited a shorter telomere length compared with that of patients with T2DM, lean patients, patients below 60 years of age and male patients, respectively.

Our results are in agreement with recent meta-analysis reports demonstrating a significant association between diabetes and telomere length that was influenced by geographical region and diabetes type. Our study builds upon previous work that indicated that there was a significant difference in telomere length SMD between Chinese patients with and without diabetes compared with that in patients from other Asian countries. However, it should be noted that our analyses included only two reports that studied Asian patients with diabetes and telomere length. Furthermore, we demonstrated that BMI and sex are stronger predictors of the association between diabetes and telomere length.

Telomere length is often used as a biological marker for cell aging, because with increased age, telomere length is shortened. However, how diabetes influences telomere length as a function of age is still unclear. Some studies have identified no age-related decline in telomere length between patients with T1DM and non-diabetic patients, while others have demonstrated an age effect. You compared Caucasian, African and Asian Americans and demonstrated that telomere length in Caucasian Americans was shorter than that of African and Asian Americans. Several contributing factors have been proposed that may account for these differences. For example, living at high altitudes could affect telomere length. Low oxygen levels at high altitudes could affect telomere length.

Figure 7. Forest plot depicting meta-analysis of telomere length comparison between patients with T1DM and T2DM and healthy individuals. Results are presented using a random effects model. CI, confidence interval; IV, inverse variance method.
Figure 8. Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals with different BMIs (normal, overweight and obese). Results are presented using a random effects model. BMI, body mass index; CI, confidence interval; IV, inverse variance method.

Figure 9. Forest plot depicting meta-analysis of telomere length comparison between patients with diabetes and healthy individuals based on sex (male and female). Results are presented using a random effects model. CI, confidence interval; IV, inverse variance method.
altitudes can induce hypoxia-inducible factor-1α, which can increase telomerase activity and preserve telomere length.\textsuperscript{36} However, low oxygen levels can increase oxidative stress, which may accelerate telomere shortening.\textsuperscript{37,38} Furthermore, poor socioeconomic status and adverse living environments have also been associated with shorter telomeres because of increased oxidative stress, poor nutrition, unhealthy behaviours and physical, emotional and psychological pressure.\textsuperscript{39–43}

T1DM and T2DM differ in their pathogenicity. Therefore, the mechanisms by which the two diseases might affect telomere length are also different. T1DM is a T-cell-mediated autoimmune disease, resulting from autoimmune destruction of pancreatic β-cells and typically leading to insulin deficiency.\textsuperscript{44,45} Markers of β-cell immune destruction include autoantibodies to insulin, islet cell autoantibodies, autoantibodies to glutamic acid decarboxylase and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β.\textsuperscript{46} T1DM is primarily first diagnosed in infants and children, and its diagnosis generally relies on autoantibody examination, with ketoacidosis often present as a first manifestation.\textsuperscript{47} Magalhães\textsuperscript{48} demonstrated a link between autoimmunity and telomere length. However, short telomeres may be secondary to T1DM autoimmune changes, although both may together contribute to T1DM aetiology. Two polymorphisms (BsmI, FokI) in the Vitamin D Receptor (\textit{VDR}) gene have been suggested as potential genetic factors underlying T1DM.\textsuperscript{45} However, the specific cause(s) of T1DM and/or how T1DM influences telomere length remain unclear. It is worth pointing out that in a recent cross-sectional study of patients with T1DM, relative telomere length did not correlate with HbA1c, oxidation or smoking but inversely correlated with age, T1DM duration, inflammation and vascular function.\textsuperscript{34} This speaks to the well-known complicated T1DM mechanisms that are affected by both genetic as well as environmental factors.\textsuperscript{49–51} Indeed, telomere length is determined early in life,\textsuperscript{52} with genetic factors\textsuperscript{53} and intrauterine environment playing an important role.\textsuperscript{54}

In contrast to T1DM, T2DM is characterized by insulin resistance and typically relative (rather than absolute) insulin deficiency.\textsuperscript{47} Almost 90\% of patients with T2DM are adults, although T2DM prevalence in children is on the rise because of increasing rates of childhood obesity.\textsuperscript{55,56} As such, a recent large study of 301 twin pairs demonstrated that individuals with short telomere lengths are more likely to develop insulin resistance later in life.\textsuperscript{57} Previous studies have demonstrated that oxidative stress is a major contributor to T2DM development.\textsuperscript{21} The telomere sequence is rich in guanine residues, and guanine is particularly prone to oxidative stress, which is markedly increased in uncontrolled diabetes.\textsuperscript{14,58,59} Therefore, it is likely that, at least in the case of T2DM, telomere length is influenced by oxidative stress. Once the telomere undergoes shortening, it increases the risk of β-cell injury and apoptosis, leading to a decline in islet cell functioning and diabetes development and progression.\textsuperscript{60,61} This is consistent with a recent report demonstrating that antioxidant defences are critical in maintaining telomere integrity, thereby reducing the progression of cardiovascular complications associated with T2DM.\textsuperscript{62} Several studies have identified a positive association between telomere length and T2DM time of onset and duration;\textsuperscript{19} however, this could be population-specific, as such a correlation was not identified in a study using Chinese patients.\textsuperscript{21,28}

Obesity is one of the most important contributors to diabetes development,\textsuperscript{63} with increasing obesity rates paralleling those of diabetes.\textsuperscript{64} It is well known that obesity causes and aggravates insulin
resistance and increases oxidative stress, leading to β-cell apoptosis. Thus, obesity development may shorten telomere length, although this relationship has been questioned. Indeed, our meta-analysis demonstrated that increased BMI resulted in reduced telomere length. Among the multitude of factors contributing to obesity and diabetes development, overconsumption of high-fat, high-energy foods plays a major role. Consumption of high-calorie, high-fat diets as well as the associated obesity have been shown to cause an increase in endoplasmic reticulum (ER) cellular stress. The ER is the organelle responsible for folding, maturation, quality control, trafficking and processing of secretory and membrane proteins. There is increasing evidence demonstrating that certain pathological stress conditions present in obese individuals disrupt ER homeostasis, leading to impaired control in the unfolded protein response, a complex process involved in the cellular stress response. Furthermore, obesity is characterized by a chronic low-grade inflammatory state, a condition characterized by enhanced adipocyte hypertrophy and hyperplasia, increased inflammatory cell infiltration, inflammatory cytokine activation and increased markers of fatty acid-induced oxidative and ER stress in various tissues. As such, mitochondrial oxidative stress injury has been linked with shortening telomere length in patients with T2DM, which may explain our results. In mice, short telomeres have been implicated in metabolic dysfunction via mitochondrial functional disruptions. Furthermore, disruption of Rap1, a telomere-binding protein, results in increased abdominal fat and insulin resistance. Finally, complications of diabetes, such as cardiovascular events, can also influence telomere shortening. However, such a correlation was not identified in patients with T1DM, but this effect might have been masked by survivor bias and vasoprotective drug treatment. Our study could not assess whether the effect of obesity on telomere length is more pronounced in individuals with both diabetes and obesity. Given the fact that both obesity and diabetes are associated with shorter telomere length, we speculate that the combination of obesity and diabetes may accentuate this effect; however, this remains to be elucidated.

In our meta-analysis study, we also determined that telomere length in females was shorter than that in males; however, the published results to date have been inconclusive. For example, Benetos et al. determined that telomere length in females was longer than that in males. Furthermore, the authors demonstrated that telomere length in leukocytes, which is heritable, was also longer in women than in men. Oestrogen can diminish oxidative stress and stimulate telomerase production, which protects telomere lengthening and attenuates telomere attrition, an effect that may be lost during menopause. Indeed, this is supported by studies investigating the effect of hormone therapy on telomerase activity that have demonstrated an upregulation of telomerase reverse transcriptase expression. This effect is mediated by the oestrogen-responsive element in the gene promoter, thus explaining longer telomeres in postmenopausal women undergoing hormone-replacement therapy. Oestrogen stimulates telomerase via the phosphoinositol 3-Kinase/Akt pathway or NO stimulation. Therefore, low oestrogen levels and/or diabetes-induced changes in telomere length might have accounted for the short telomeres observed in our analysis. Furthermore, women display increased diabetes-induced systemic inflammation compared with men and are at higher risk of cardiovascular events and developing diabetes complications, all of which can result in shorter telomeres.

In contrast, shorter telomeres have also been reported in male patients with diabetes, which has been attributed to poor control.
of diabetes in males compared with that in women, independent of smoking and drinking habits.\textsuperscript{28} Therefore, additional larger studies are required to conclusively determine whether sex plays a role in influencing telomere length in patients with diabetes.

A meta-analysis is a useful statistical technique that applies quantitative methods to systematically evaluate and summarize multiple research results.\textsuperscript{83} Based on heterogeneity, the pooled SMD and 95% CI resulting from the 17 referenced articles analysed, we demonstrated that diabetes accelerates the telomere shortening process. However, several limitations should be acknowledged when interpreting these results. These include a relatively low number of published studies, un-accounting variables in some studies (e.g., age of patients with diabetes differed from that of healthy individuals) as well as inconsistencies in calculating the telomere length (T/S ratio (T stands for telomere, S stands for single-copy gene) or KB (kilo base pairs)). Nevertheless, our findings are consistent with previous data indicating that diabetes shortens telomere length, aggravates cell apoptosis and ultimately impacts quality of life.\textsuperscript{84,85}

In summary, we have demonstrated that diabetes can significantly affect telomere length, an effect that is influenced by geographical region, diabetes type, obesity, age and sex. Understanding the mechanisms by which diabetes affects telomere length is important for diabetes mellitus prevention and treatment.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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