

Air pollution and telomere length: a systematic review of 12,058 subjects

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Background: Over recent decades, adverse effects of ambient air pollution on the cardiovascular system have been clearly demonstrated. However, the underlying mechanisms are not fully elucidated. Air pollution may accelerate biological aging and thereby the susceptibility to cardiovascular diseases (CVDs). Telomeres are tandem repetitive DNA complexes that play a critical role in maintaining chromosome stability. There are, however, heterogeneities among the reported effects of air pollution on telomere. This study sought to evaluate the existing literature on the association between air pollution and telomere length (TL).

Methods: Two reviewers independently searched on electronic databases including PUBMED, EMBASE, SCOPUS, WEB OF SCIENCE and Ovid. The key terms were “air pollution” and “telomere” without language restriction. Articles relating to tobacco smoke were excluded.

Results: A total of 12,058 subjects from 25 articles remained for final review. All were observational studies: 14 cross-sectional, 6 cohort and 5 case-control studies. Nineteen (76%) assessed leukocyte telomere length (LTL) of which 15 found associations between air pollution and shorter TL, 2 with longer TL, 1 had mixed results, and a study of patients with type 2 diabetes found non-significant associations with TL. One found longer TL from saliva. The remaining studies were of placental cells, buccal cells or sperm and all reported shorter TL associated with air pollution. Particulate matter (PM) was investigated in 8 articles, and the remainder assessed black carbon (BC), benzene, lead, cadmium and polycyclic aromatic hydrocarbon (PAH). Geographically, 11 studies were conducted in Europe, with 10 in Asia and 4 in North America. While all followed Cawthon’s protocol for TL assessment, discordance in the reporting formats did not allow us to perform a quantitative meta-analysis.

Conclusions: Most of the studies support the association of shorter TL with air pollution. Uniform reporting format would be warranted for future studies to estimate true effect size of air pollution on TL.

Keywords: Air pollution; telomere length (TL); systematic review

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Introduction

Air pollution is a ubiquitous public health issue. Indoor and outdoor air pollution are the 3rd and 9th risk factors for worldwide mortality and morbidity (1). It is estimated that 4.3 million urban people will die prematurely due

to outdoor air pollution in 2050, which accounts for 65% of the total death all over the world (2). Although air pollutants has long been understood to affect the respiratory system, the adverse effects on the cardiovascular system cause mortality impacts that exceed those from lung diseases and cancers (3,4). The impact of both short and

long term exposure to air pollution on the cardiovascular system has been confirmed by epidemiological studies (4). Long term exposure to air pollutants contributes to the risk of both ischemic and non-ischemic cardiovascular disease (CVD) (5). Acute effects of elevated ambient particulate matter (PM) levels are more likely to occur on people who are elderly or already have CVD, even if this has not been recognized (4). The length of the chromosomal telomere is a biological clock, reflecting the biological aging process of cells. CVD is known clearly as age-related disease and researchers have been working on identifying a biomarker to reflect aging, as people with same chronological age may have different health status (6). Studies have demonstrated that individuals with shorter leukocyte telomere length (LTL) have an increased risk of myocardial infarction (7,8), coronary heart disease (9), heart failure (10), hypertension (11) and stroke (8). One study using Mendelian randomization approach proved causal effect of shorter genetically determined telomere length (TL) on CVD and cancer (12). TL can be a cardiovascular biomarker for biological aging. Until now, inflammatory reactions and oxidative stress are understood as critical mechanisms linking air pollution with related morbidity and mortality (13). These processes also accelerate telomere shortening (6). However, the reported relationships between air pollution and telomeres are inconsistent. Therefore, the aims of this study were to summarize the effects of air pollution on TL through a systematic review of literature, and to identify possible issues, including the factors hampering the quantification of the pooled estimates.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline when performing our systematic review and meta-analysis (14). Electronic databases including PubMed, Embase, Scopus, Web of Science as well as Ovid (with all resources) were searched for articles that had examined the association between air pollution and TL. There was no restriction to language and study type. “Telomere”, “air pollution”, “air pollutant”, “particulate matter” and related free text terms were used for the search. Search hedges created are listed in the online supplementary material (Supplementary file). The first search was performed on 18 January 2016, and the last search was performed on 16 August 2017.

We followed the US Environmental Protection Agency

criteria for ambient air pollutants, such as PM, nitrogen oxides (NO_x), carbon monoxide (CO), sulfur dioxide (SO₂), and ozone (O₃). There was no restriction to language and no time limit on publication date. We excluded studies of tobacco smoke, animal, cell-line, and genetic studies. Published conference abstracts, reviews, editorials and duplicates were also excluded. The most extensive article was chosen when more than one publication included the same content. When information was insufficient to make a judgment on the eligibility of a study, efforts were made to contact its corresponding author to obtain further information.

Two reviewers (Bing Zhao and Kazuaki Negishi), independently searched for studies and reviewed full-text through screening title and abstract using inclusion and exclusion criteria. A standard protocol was used to extract data from appropriate articles. The information collected included location, publication year, study design, samples size, tissue source, age, sex, participant characteristics, air pollutants and levels, monitoring methods, mean and standard deviation of TL, the outcome of association, and the characteristics of control group.

The Newcastle-Ottawa Quality Assessment Scale for cohort studies (15) was used as a unified standard to assess the quality of included studies. This tool contains eight items with three main components: selection, comparability, and outcome. The number of stars the study obtained represents the assessment results. A maximum of nine stars can be given for each study.

Results

The systematic search identified 2,151 titles (*Figure 1*). After removing 425 duplicates, 1,726 records were screened. After title and abstract review, a further 1,665 records were excluded. After full text screening of the 61 remaining articles, 25 articles that examined the relationship between air pollution and TL were finally included in this systematic review.

Table 1 summarizes the characteristics from the 25 articles (n=12,058 subjects) included in qualitative analysis (16-40). The sample sizes ranged from 14 (24) to 6,796 (40). All were observational studies: 14 cross-sectional (16-18,22-24,26,27,32-35,38,40), 6 cohort (20,29,30,36,37,39) and 5 case-control studies (19,21,25,28,31). All applied Cawthon's protocol based on polymerase chain reaction (PCR) analysis method to measure TL: 19 studies (n=10,568 subjects) assessed LTL (16,18-20,22-27,30-33,36-40), 2 studies with placenta TL (17,28), 2 for buccal cell telomere

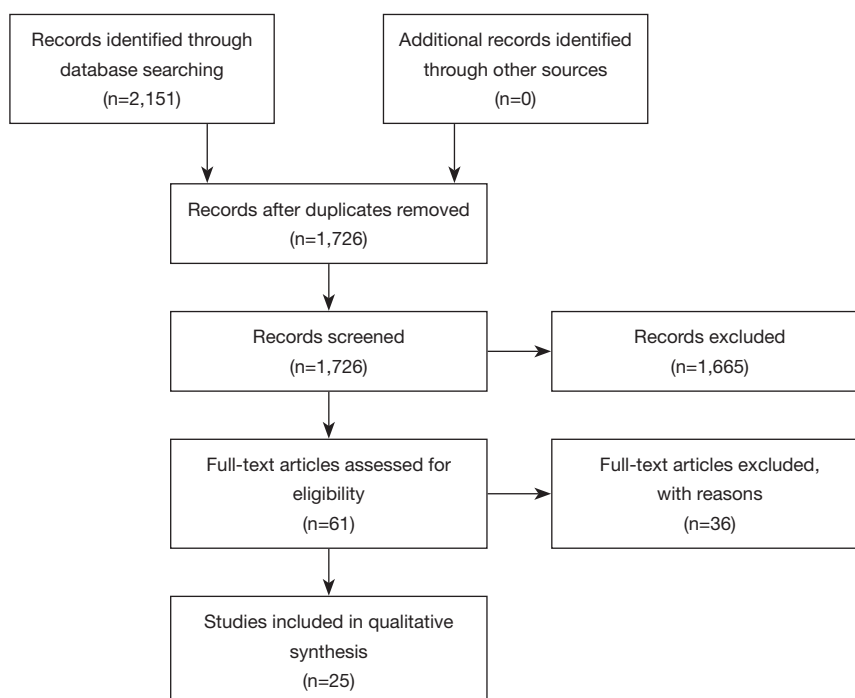


Figure 1 PRISMA flow chart. This flow chart illustrates the selection process for identified articles.

(21,34) and 2 from sperm (29) and saliva (35) respectively (Figure 2). Among two versions of Cawthon's protocols, 6 studies (16,17,27,33,35,38) followed Cawthon's newer version published in 2009 (41), while remaining articles applied the original Cawthon's method (42). Geographically, 11 studies were conducted in Europe (17,19,20,23,25,26,31-33,35,36), with 10 in Asia (16,18,21,22,27-29,34,38,39) and 4 in North America (24,30,37,40). Multiple ethnicities were included: 7,023 Americans, 3,254 Europeans and 1,781 Asians. The comparative groups were those who exposed to filtered air or clean air; and those not exposed to air pollution.

The concentration of airborne PM was investigated in 8 articles (20,22,33-37,39). Seven (22,33-37,39) of these examined the association between PM <2.5 μm in aerodynamic diameter (PM_{2.5}) and TL, and PM <10 μm in aerodynamic diameter (PM₁₀) were reported in 5 articles (20,22,35,36,39). Dioni *et al.* (20) and Wong *et al.* (37) used PM data from multiple sites in factories to calculate the personal exposures. One study included both personal and ambient air pollutants. Small-sized gravimetric samplers were carried by study subjects to measure personal PM_{2.5} exposure and ambient PM₁₀ data were obtained from the local environmental agency (22). Personal exposure

monitors (PEMs) were used in a pilot study (34). Pieters *et al.* (33), Walton *et al.* (35) and Ward-Caviness *et al.* (36) estimated PM level from fixed monitoring sites. Xia *et al.* (39) measured real-time ambient PM level using an Environmental Dust Monitor, and data for other gaseous pollutants were obtained from governmental monitoring stations.

Urinary metabolite for polycyclic aromatic hydrocarbons (PAHs) of workers were measured as a marker of personal exposure in 4 studies (18,26,29,31), while Lee *et al.* (24) calculated individual exposure to PAHs via monitoring site and outdoor residential samples. Occupational air pollutants studied included benzene (16,23), toluene (23,26) and welding fumes (25). A study focused on traffic pollutants used the distance from major road and traffic density to estimate the exposure data. Exposure to lead and cadmium was assessed through blood (32,38,40) and placental measurements (28). McCracken *et al.* (30) estimated the annual ambient black carbon (BC) exposure on elderly veterans based on a spatiotemporal model. One study examined long term effect of indoor air pollution from household fuel combustion on LTL via related questions to assess the pollution level (27).

Of 19 articles examined the association between LTL

Table 1 Summary of included studies

Author	Year	Study design	Location	Air pollutants	Sample	Population (sample size)	TL assay
Bassig <i>et al.</i> (16)	2014	Cross-sectional	China	Benzene	Leukocyte	Worker (n=43); unexposed workers (n=43)	MMqPCR with T/S ratio; Cawthon 2009
Bijnens <i>et al.</i> (17)	2015	Cross-sectional	Belgium	Traffic	Placenta	Twins' mother (n=130)	MMqPCR with T/S ratio; Cawthon 2009
Bin <i>et al.</i> (18)	2010	Cross-sectional	China	PAHs	Leukocyte	Coke oven worker (n=145); medical staff (n=68)	qPCR with T/S ratio; Cawthon 2002
De Felice <i>et al.</i> (19)	2012	Case-control	Italy	Atmospheric pollution	Leukocyte	Pregnant women (n=50); controls (n=50)	qPCR with T/S ratio; Cawthon 2002
Dioni <i>et al.</i> (20)	2011	Panel	Italy	PM ₁₀ ; PM ₁	Leukocyte	Male steel workers (n=57)	qPCR with T/S ratio; Cawthon 2002
Eshkoor <i>et al.</i> (21)	2011	Case-control	Malaysia	Occupational	Buccal cell	Car repair workers (n=120); controls (n=120)	qPCR with T/S ratio; Cawthon 2002
Hou <i>et al.</i> (22)	2012	Cross-sectional	China	PM _{2.5} ; EC; PM ₁₀	Leukocyte	Truck driver (n=60); indoor office worker (n=60)	qPCR with T/S ratio; Cawthon 2002
Hoxha <i>et al.</i> (23)	2009	Cross-sectional	Italy	Benzene; toluene	Leukocyte	Traffic officer (n=77); office worker (n=57)	qPCR with T/S ratio; Cawthon 2002
Lee <i>et al.</i> (24)	2017	Cross-sectional	US	PAHs	Leukocyte	11–18 years children (n=14)	qPCR with T/S ratio; Cawthon 2002
Li <i>et al.</i> (25)	2015	Case-control	Sweden	Welding fumes	Leukocyte	Welders (n=101); controls (n=127)	qPCR with T/S ratio; Cawthon 2002
Li <i>et al.</i> (26)	2011	Cross-Sectional	Sweden	N-nitrosamine; PAH; CS ₂ ; toluidines	Leukocyte	Workers in the rubber industry (n=157)	qPCR with T/S ratio; Cawthon 2002
Lin <i>et al.</i> (27)	2017	Cross-sectional	China	Household fuel combustion	Leukocyte	Cancer-free non-smoking participants (n=137)	MMqPCR with T/S ratio; Cawthon 2009
Lin <i>et al.</i> (28)	2013	Case-control	China	Cadmium; Lead	Placenta	Puerpera (n=227); control (n=93)	qPCR with T/S ratio; Cawthon 2002
Ling <i>et al.</i> (29)	2016	Cohort	China	PAHs	Sperm	Male college students (n=444)	qPCR with T/S ratio; Cawthon 2002
McCracken <i>et al.</i> (30)	2010	Panel	US	BC	Leukocyte	Never-smoking veteran (n=165)	qPCR with T/S ratio; Cawthon 2002
Pavanello <i>et al.</i> (31)	2010	Case-control	Poland	PAHs	Leukocyte	Coke oven worker (n=48); controls (n=44)	qPCR with T/S ratio; Cawthon 2002
Pawlas <i>et al.</i> (32)	2015	Cross-sectional	Poland	Lead	Leukocyte	Children (n=99)	qPCR with T/S ratio; Cawthon 2002
Pieters <i>et al.</i> (33)	2015	Cross-sectional	Belgium	PM _{2.5}	Leukocyte	Elderly (n=166)	MMqPCR with T/S ratio; Cawthon 2009
Shan <i>et al.</i> (34)	2014	Cross-sectional	China	PM _{2.5} ; BC	Buccal cell	Women (n=23)	qPCR with T/S ratio; Cawthon 2002
Walton <i>et al.</i> (35)	2016	Cross-sectional	UK	NO _x ; NO ₂ ; PM ₁₀ ; PM _{2.5}	Saliva	8–9 years children (n=333)	MMqPCR with T/S ratio; Cawthon 2009

Table 1 (continued)

Table 1 (continued)

Author	Year	Study design	Location	Air pollutants	Sample	Population (sample size)	TL assay
Ward-Caviness <i>et al.</i> (36)	2016	Cohort	Germany	PM ₁₀ ; PM _{2.5} ; BC; NO _x	Leukocyte	Participants from KORA F4 (n=1,777)	qPCR with T/S ratio; Cawthon 2002
Wong <i>et al.</i> (37)	2014	Cohort	US	PM _{2.5}	Leukocyte	Male boilermaker (n=48)	qPCR with T/S ratio; Cawthon 2002
Wu <i>et al.</i> (38)	2012	Cross-sectional	China	Lead	Leukocyte	Battery plant workers (n=144)	MMqPCR with T/S ratio; Cawthon 2009
Xia <i>et al.</i> (39)	2015	Panel	China	PM (0.25 to 10), other	Leukocyte	Type 2 diabetes (n=35)	qPCR with T/S ratio; Cawthon 2002
Zota <i>et al.</i> (40)	2015	Cross-sectional	US	Lead; cadmium	Leukocyte	Participants from NHANES by CDC (n=6,796)	qPCR with T/S ratio; Cawthon 2002

BC, black carbon; CDC, centers for disease control; CS₂, carbon disulphide; EC, elemental carbon; KORA F4, 4th follow-up of the Cooperation for Health Research in the Region of Augsburg; MMqPCR, Monochrome Multiplex Quantitative Polymerase Chain Reaction; NHANES, National Health and Nutrition Examination Survey; NO_x, nitrogen oxides; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; qPCR, quantitative real-time polymerase chain reaction; T/S ratio, the ratio of telomere repeat copy number to single copy gene copy number.

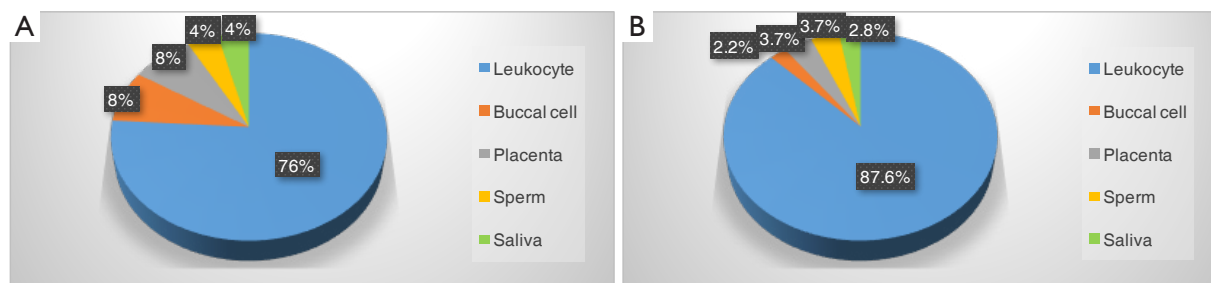


Figure 2 Sources of telomere length assessment. (A) Based on the number of articles. 76% of studies evaluated leukocyte TL, while buccal cell, placenta, sperm and saliva are the other resources. (B) Based on the number of participants. Among these studies, leukocyte was used for 87.6% of population, placenta for 3.7%, sperm for 3.7%, saliva for 2.8% and buccal cell for 2.2%. TL, telomere length.

and air pollution, 15 found shorter LTL with air pollution (18,19,23-27,30-33,36-38,40), 2 longer (16,20) and 1 mixed result (22) (Table 2). The one remaining study showed non-significant association between LTL and short-term exposure to PM or other gaseous pollutants in type 2 diabetes patients (39). TL from saliva was found to be longer after pollution in children (35). The remaining five studies of placenta (17,28), buccal cells (21,34) or sperm (29) reported shorter TL with air pollution (Figure 3).

Traffic pollutants appear to be associated with shorter LTL (23,24) and placental TL (17). The length of telomeres was reduced with the increase in traffic exposure in these three cross-sectional studies. One used airborne benzene and toluene to indicate the degree of pollution, one study selected ambient PAHs for vehicle exhaust, and the other

used the distance to main road and residential surrounding greenness to estimate exposure. However, inconsistent result was demonstrated in a study where workers were used products containing benzene (16). Similarly, Hou *et al.* (22) found that truck drivers had increasing TL with personal exposure to PM_{2.5}, elemental carbon and ambient PM₁₀ on the inspection day, while their TL became shorter after 14 days. Interestingly, children from London exposed to traffic pollution had longer TL in salivary cells (35).

Coke oven workers showed shorter TL in both China (18) and Poland (31), where people are widely exposed to PAHs. People who worked in rubber (26), battery (38), boiler (37), welding (25) and car repair (21) environments all showed shorter TL. However, a group of male steel worker had longer TL after three consecutive working days (20).

Table 2 Main findings of included studies

Author	Year	Findings	Changes
Bassig <i>et al.</i> (16)	2014	Longer TL in workers exposed >31 ppm of benzene (1.37±0.23 vs. 1.26±0.17, P=0.03)	Longer
Bijnens <i>et al.</i> (17)	2015	Doubling the distance to the nearest major road was associated with a 5.32% (95% CI: 1.90 to 8.86%, P=0.003) longer placental TL at birth An interquartile increase (22%) in maternal residential surrounding greenness (5 km buffer) was associated with an increase of 3.62% (95% CI: 0.20 to 7.15%, P=0.04) in placental TL	Shorter
Bin <i>et al.</i> (18)	2010	Coke-oven workers had shorter LTL [1.10±0.75 vs. 1.43±1.06, P=0.026, P (adjust) =0.020] Stratification analysis found shorter LTL in male (1.08±0.73 vs. 1.51±1.10, F=9.212, P=0.003) and non-drinking groups (0.96±0.38 vs. 1.26±0.46, F=6.484, P=0.012)	Shorter
De Felice <i>et al.</i> (19)	2012	TL was shorter in exposed pregnant women (1.27 vs. 3.11, P<0.001) hTERT mRNA 28% lower in exposed group (1.123 vs. 1.401, P<0.001) TL decreased with increasing the proximity from polluted area (P=0.004)	Shorter
Dioni <i>et al.</i> (20)	2011	LTL was longer after exposure (1.43±0.51) compared with baseline (1.23±0.28, P<0.001) Post exposure LTL was positively associated with PM ₁₀ (β=0.30, P=0.002) and PM ₁ (β=0.29, P=0.042) hTERT expression was lower (1.31±0.75 vs. 1.68±0.86, P<0.001), but the decrease in hTERT expression did not show a dose-response relationship with PM	Longer
Eshkooor <i>et al.</i> (21)	2011	Workers with the mutated genotype (Ile-Val, Val-Val) had shorter TL (0.23±0.35 vs. 1.93±4.53, P=0.008), as well as the workers with wild genotype Ile-Ile (0.30±0.67 vs. 2.65±7.94, P=0.019)	Shorter
Hou <i>et al.</i> (22)	2012	TL was longer in drivers (0.87, 95% CI: 0.74 to 1.03) than office workers (0.79, 95% CI: 0.67 to 0.93, P=0.001) TL increased in association with personal PM _{2.5} (5.2%, 95% CI: 1.5 to 9.1; P=0.007), personal EC (4.9%, 95% CI: 1.2 to 8.8, P=0.01), and ambient PM ₁₀ (7.7%, 95% CI: 3.7 to 11.9; P<0.001) on examination days PM ₁₀ over the 14 days was associated with shorter TL (-9.9%, 95% CI: -17.6 to -1.5, P=0.02)	Mixed
Hoxha <i>et al.</i> (23)	2009	Adjusted mean LTL was 1.10 (95% CI: 1.04 to 1.16) in traffic officers and 1.27 in referents (95%CI: 1.20 to 1.35) (P<0.001) Traffic officers had shorter LTL within each age category. Among traffic officers, adjusted mean relative LTL was shorter in individuals working in high (n=45, LTL = 1.02, 95% CI: 0.96 to 1.09) compared to low traffic intensity (n=32, LTL =1.22, 95% CI: 1.13 to 1.31) (P<0.001) LTL decreased with increasing levels of personal exposure to benzene (P=0.004) and toluene (P=0.008)	Shorter
Lee <i>et al.</i> (24)	2017	Inverse linear relationship was found between ambient PAHs exposure and TL. Each 1 ng/m ³ increase in PAH456 with a decrease of -0.14 units (95% CI: -0.25 to -0.11, P=0.01) in TL	Shorter
Li <i>et al.</i> (25)	2015	Welders and controls did not differ in RTL (P=0.090) Every working year as a welder was associated with 0.0066 units shorter TL (95% CI: -0.013 to -0.00053, P=0.033)	Shorter
Li <i>et al.</i> (26)	2011	N-nitrosamines exposure lead to telomere shortening [measured (n=60) N-nitrosamines β-coefficient =-10 (95% CI: -17 to -1.9) P=0.016; estimated (n=157) N-nitrosamines β-coefficient =-5.3, (95% CI: -9.5 to -0.97) P=0.016]	Shorter

Table 2 (continued)

Table 2 (continued)

Author	Year	Findings	Changes
Lin <i>et al.</i> (27)	2017	Shortest LTL (0.70±0.17) was found in participants who were exposed to combusted solid fuel for three decades. Accumulative effect of cooking fuel usage was inversely correlated with LTL ($\beta=-0.07$ 95% CI: -0.13 to -0.02, $P=0.01$)	Shorter
Lin <i>et al.</i> (28)	2013	Placental cadmium concentration was negatively correlated with placental TL ($r=20.138$, $P=0.013$) No significant correlation between placental lead concentration and placental TL ($r=0.027$, $P=0.639$)	Shorter
Ling <i>et al.</i> (29)	2016	Urinary 1-OHPyr ($\beta=-0.385$, 95% CI: -0.749 to -0.021, $P=0.038$) and 1-OHNap ($\beta=-0.079$, 95% CI: -0.146 to -0.011, $P=0.023$) were inversely associated with STL which remained after adjusting for confounders	Shorter
McCracken <i>et al.</i> (30)	2010	IQR increase in annual BC (0.25 $\mu\text{g}/\text{m}^3$) was associated with 7.6% decrease (95% CI: -12.8 to -2.1) in LTL	Shorter
Pavanello <i>et al.</i> (31)	2010	Coke-oven workers had shorter TL ($P=0.038$) Years of work in cokery ($P=0.008$) and p53 hypomethylation ($P=0.001$) were the principal determinants of shorter TL	Shorter
Pawlas <i>et al.</i> (32)	2015	Relative TL shorter in higher Pb group [0.99 (0.63–2.09) vs. 1.18 (0.49–2.06), $P=0.008$] B-Pb was significantly inversely associated with rTL in the children	Shorter
Pieters <i>et al.</i> (33)	2015	5 $\mu\text{g}/\text{m}^3$ increasing in annual PM _{2.5} was associated with a decrease of 16.8% (95% CI: -26.0% to -7.4%, $P=0.0005$) in TL	Shorter
Shan <i>et al.</i> (34)	2014	High exposed women had 43% shorter TL (95% CI: -113, 28); high 3.3±2.3 vs. low 5.4±4.5, $P=0.19$	Shorter
Walton <i>et al.</i> (35)	2016	Increase in annual NO _x [model coefficient 0.003, (95% CI: 0.001 to 0.005), $P<0.001$], NO ₂ [0.009 (0.004, 0.015), $P<0.001$], PM _{2.5} [0.041, (0.020, 0.063), $P<0.001$] and PM ₁₀ [0.096 (0.044, 0.149), $P<0.001$] were associated with increased TL	Longer
Ward-Caviness <i>et al.</i> (36)	2016	BC was inversely associated with TL in men ($\beta=-0.28$, 95% CI: -0.47, -0.08, $P=0.005$)	Shorter
Wong <i>et al.</i> (37)	2014	Each 1 mg/m ³ /h increase in cumulative PM _{2.5} with a decrease in relative TL of -0.04 units	Shorter
Wu <i>et al.</i> (38)	2012	Shorter LTL in workers with abnormal BLL and/or ULL (1.66±0.63 vs. 1.91±0.46, $P=0.010$) LTL was in negative correlation with BLL, ULL, working length and body mass index LTL has strong inverse correlation with BLB ($r=-0.70$, $P<0.0001$) in those with abnormal BLL and ULL	Shorter
Xia <i>et al.</i> (39)	2015	Non-significant association between short-term PM exposure with TL in type 2 diabetes patients	No change
Zota <i>et al.</i> (40)	2015	The highest and lowest quartiles of blood and urine cadmium were associated with -5.54% (95% CI: -8.70, -2.37) and -4.50% (95% CI: -8.79, -0.20) shorter LTLs, with dose-response relationship (P for trend <0.05). There was no association between blood lead and LTL	Shorter

1-OHNap, 1-hydroxynaphthalene; 1-OHPyr, 1-hydroxypyrene; 95% CI, 95% confidence intervals; BC, black carbon; BLB, body lead burden; BLL, lead levels in blood; EC, elemental carbon; hTERT, Human Telomerase Reverse Transcriptase; IQR, interquartile range; LTL, leukocyte telomere length; mtDNA, mitochondrial DNA; PAHs, polycyclic aromatic hydrocarbons; Pb, Lead; PM, particulate matter; STL, sperm telomere length; TL, telomere length; ULL, lead levels in urine.

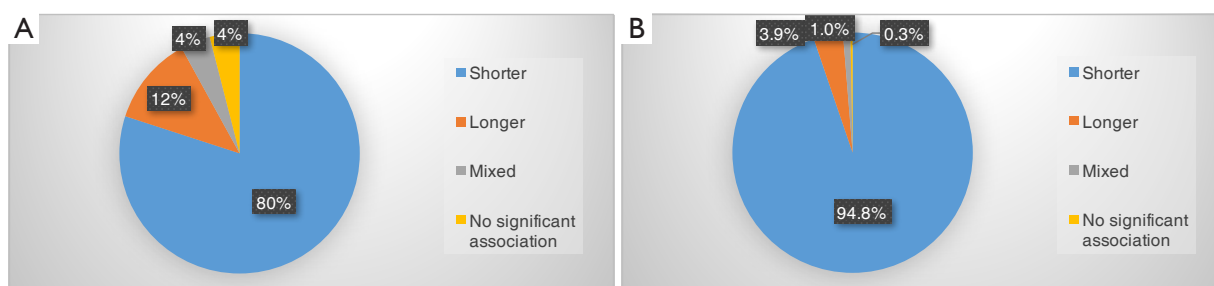


Figure 3 Outcome of telomere length. (A) Based on the number of articles. 20 of 25 studies found association between shorter telomere with air pollution, with 3 longer and 1 mixed result. Remaining one study did not demonstrate significant association between LTL and short-term exposure to PM or other gaseous pollutants in type 2 diabetes patients. (B) Based on the number of participants. 94.8% of population in these studies demonstrated the association between air pollution with shorter telomere length. LTL, leukocyte telomere length; PM, particulate matter.

In contrast to short-term exposure, the dynamic change of TL tends to be different when focusing on annual exposure to air pollutants. Pieters *et al.* (33) demonstrated that annual $5 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ enhancement was related to 16.8% decreasing in TL of elderly people. Similarly, the TL of elderly men was decreased by 7.6% with increasing in the interquartile range of annual BC ($0.25 \mu\text{g}/\text{m}^3$) (30), and this association was stronger among men more than 75 years old. This inverse association between annual BC and TL in male was replicated by another study (36). Pawlas *et al.* (32) found that children with higher blood lead levels had shorter telomeres. In another study lead was not associated with placenta TL, while placental cadmium concentration was correlated with shorter placental TL (28). Similarly, participants in a US national survey also displayed associations between cadmium and shorter TL while the result was not significant for lead (40). Another study showed that pregnant women who lived near waste landfill sites highly exposed to atmospheric pollution from garbage burning had shorter TL (19). The rubbish in this region has mismanaged involving illegal industrial waste as well as household waste. Women exposed to biomass smoke from cooking which contain $\text{PM}_{2.5}$ and BC had TL measured from buccal cells. More heavily exposed women had 43% shorter TL compared with the low exposure group (34). This was corresponding to another finding between exposure to cooking solid fuel and shorter LTL (27). A study of people with type 2 diabetes did not find significant relationship between TL and short term ambient PM or other gaseous pollutants (39).

Ten studies (19,29,30,32,34-37,39,40) were awarded more than seven stars and remaining 15 studies (16-18,20-

28,31,33,38) were graded stars with the number from four to six (Table 3).

Discussion

This is the first systematic review of studies assessing the association between air pollution and TL. The dominant findings (80% of articles and 94.8% of subjects) were that that air pollution was associated with shorter TL. While results of studies of leukocyte TL and salivary TL had diverse outcomes, telomeres from buccal cells, placental tissue and sperm all became shorter after exposure. Although all reports used Cawthon's protocol for TL measurements and most evaluated chromosomes from leukocytes, discordant reporting formats did not allow a quantitative meta-analysis.

The telomere is a region of tandem repetitive DNA and protein complexes that cap the ends of chromosome, playing a critical role in maintaining chromosome stability (43). Due to the requirement of 5' to 3' replication and RNA primer, DNA polymerase cannot fully duplicate the end of the chromosome in somatic cells, which leads the telomere shortened after each cycle of the DNA replication (44). TL is approximately 30–100 bp shorter during each cell division process and can act as a senescent marker (45). The components of human telomeres are thousands of TTAGGG nucleotide repeats and protein (46). This special sequence TTAGGG makes telomeres have high content of guanine and are sensitive to oxidative stress (47). The damage caused by oxidative stress can be accumulated and lead to telomere erosion during the lifetime of cell. The shortening of telomere gradually

Table 3 Quality assessment of included study

Author	Year	Selection	Comparability	Outcome	Number of stars
Bassig <i>et al.</i> (16)	2014	★★★	★★	★	6
Bijnens <i>et al.</i> (17)	2015	★★	★★	★	5
Bin <i>et al.</i> (18)	2010	★★	★★	★	5
De Felice <i>et al.</i> (19)	2012	★★★★	★★	★	7
Dioni <i>et al.</i> (20)	2011	★★	★	★	4
Eshkoor <i>et al.</i> (21)	2011	★	★★	★	4
Hou <i>et al.</i> (22)	2012	★★	★★	★	5
Hoxha <i>et al.</i> (23)	2009	★★	★★	★	5
Lee <i>et al.</i> (24)	2017	★★★	★★	★	6
Li <i>et al.</i> (25)	2015	★★	★★	★	5
Li <i>et al.</i> (26)	2011	★★	★★	★	5
Lin <i>et al.</i> (27)	2017	★★★	★★	★	6
Lin <i>et al.</i> (28)	2013	★★	★★	★	5
Ling <i>et al.</i> (29)	2016	★★	★★	★★★★	7
McCracken <i>et al.</i> (30)	2010	★★	★★	★★★★	7
Pavanello <i>et al.</i> (31)	2010	★★	★★	★	5
Pawlas <i>et al.</i> (32)	2015	★★	★★	★★★★	7
Pieters <i>et al.</i> (33)	2015	★★	★★	★	5
Shan <i>et al.</i> (34)	2014	★★★★	★★	★	7
Walton <i>et al.</i> (35)	2016	★★★	★★	★★★★	8
Ward-Caviness <i>et al.</i> (36)	2016	★★★	★★	★★★★	8
Wong <i>et al.</i> (37)	2014	★★	★★	★★★★	7
Wu <i>et al.</i> (38)	2012	★★	★★	★	5
Xia <i>et al.</i> (39)	2015	★★★	★★	★★★★	8
Zota <i>et al.</i> (40)	2015	★★★	★★	★★	7

The scale contains eight items which has three main aspects: selection, comparability and outcome. Assessment result is demonstrated by the number of stars (★) the study obtained. A maximum of nine stars can be given for each study.

progresses after each DNA replication cycle and accelerate the cell aging. The most important oxidative stress substance is reactive oxygen species (ROS). ROS easily reacts with nucleic acids, protein and lipids. If the cells do not have enough ability to detoxify these ROS, telomere erosion will happen. Interestingly, Telomere shortening is not an irreversible process. For example, a study of lifestyle intervention demonstrated lengthening of telomeres in the

intervention group that persisted 5 years post intervention (48).

In studies included in this review, shorter leucocyte TL was common in people with polluted working or living conditions. Long-term accumulation of air pollution seems to lead to attrition of TL. A cross-sectional study of workers in a battery plant found that body lead burden, measured from 24 h urine, had stronger inverse association with leucocyte TL than blood lead levels (38). Lead can deposit

in bone which act as an effective body barrier to decrease the lead in bioavailable blood. There was only one study that did not find an association between short-term PM exposure and leucocyte TL (39). The subjects included in this study were all patients with type 2 diabetes and their telomere dynamics in response to acute stressors such as air pollution may not be generalizable to the wider population.

Every article, identified through our systematic review, used Cawthon's protocol. This technique was first proposed in 2002 and requires tiny amount of DNA to perform PCR for TL assessment (42). Smaller amounts of DNA requirement make this method easily applied to epidemiological studies that usually have large sample size (49). In 2009, Cawthon revised the original version of the method to avoid the methodological shortcoming and named it monochrome multiplex quantitative PCR (41). Due to this development of the method over time, 6 of 20 studies in this systematic review followed Cawthon's 2009 version method (16,17,27,33,35,38), while remaining articles still measured TL through Cawthon's initial method. It seems these two versions of protocol are similar for identified articles in this systematic review and the results are rarely affected by the version they used.

Five types of human tissues were used for TL measurements. A total of 10,568 people in these studies were examined using leukocyte TL, 450 with placenta TL, 444 with sperm TL, 333 with salivary TL and 263 with buccal cell TL. Although TLs in different tissue resources are inconsistent, the attrition rates of TL are similar for adult somatic tissue (50). Leucocytes are widely used for TL measurement because they are easy to extract from blood samples. However, buccal or salivary cells are easier to obtain, the technique is not as invasive, or expensive. The use of placental tissue is limited to research focusing on pregnant women and their offspring. Sperm TL is targeted to investigate male reproductive health.

Air pollutants have various forms including PM, liquids and gases (51,52). The composition and duration of the exposure to air pollutants influences the potential mechanism of action in affecting TL. Many different sources of PM have been shown to induce oxidative stress (53-55), including ambient PM_{0.25}, PM_{2.5}, BC, particle-bound metals and PAHs. Two studies (33,37) found the inverse relationship between PM_{2.5} and LTL: one reported with each increase of 1 mg/m³ per hour for cumulative PM_{2.5} exposure in the past month, TL decreased 0.04 units relatively, while the other found associations with annual average PM_{2.5} concentrations.

Metals can contribute to telomere disorders in multiple ways. Cadmium can accelerate the production of ROS and disturb the antioxidative response (56). It also prevents the function of DNA mismatch repair systems (57). Other metals provoke the release of inflammatory cytokines (58). One study found longer TL in steel workers exposed to metal-rich PM for 3 working days compared with their TL on the first day before working (20).

Five papers reported the relationship between PAHs exposure and TL of which 3 indicated shorter LTL and 1 with shorter sperm TL. PAHs are a group of organic compounds comprised of multiple benzene rings which can be produced by incomplete combustion (59). Among the studies focused on LTL, Lee *et al.* (24) chose the level of ambient PAHs with 4, 5 or 6 benzene rings as exposure estimate, while the other two measured urinary metabolite 1-hydroxypyrene (1-OHPyr) to reflect PAHs level. Although 1-OHPyr is regarded as a reliable biomarker (59), it is difficult to determine the specific species of PAHs exposure in these articles and we can't make a quantitative analysis.

Two reports demonstrated longer TL in acute phases after exposure to pollutants. Workers exposed to benzene for 5 separate days during a 2-week period (16), and truck drivers with short-term ambient PM pollution (22) both had longer TL compared with control groups. Little is known about the underlying mechanisms of longer TL in those exposed. Because of the discrepancy to other reports and of uncertainty, further researches are warranted to determine true effect size of air pollution on TL.

Recently, another study has been published after we finished this systematic review (60). It examined the TL from cord blood of newborns and also found shorter TL was associated with prenatal exposure to PAH. The comparison was between two groups of neonates born before and after the closure of the coal burning power plant, which indicated the benefits of reducing air pollution on children's health.

We followed the PRISMA guideline when performing this systematic review, but prospective register with the PROSPERO database of systematic reviews was not successful during data extraction stage. Despite different sources of TL and various air pollutants were obtained through comprehensive search in multiple databases, the heterogeneity among these studies did not allow us to do meta-analysis to make a quantitative inference. All studies were observational and thus have an inherent risk of selection bias.

Conclusions

Most of the studies support the association between air pollution exposure and shortened TL. Uniform reporting format would be required to enable combined estimates of the magnitude of the effect size of the impacts of air pollution on TL.

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Footnote

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Search criteria

PubMed

(telomer*) AND (((particulate AND matter*)) OR (air AND pollution*)) OR (air AND pollutant*))

Results: 62 articles

Scopus

((ALL (particulate) AND ALL (matter*)) OR ((ALL (air) AND ALL (pollution*)) OR ((ALL (air) AND ALL (pollutant*)))) AND (ALL (telomer*)))

Results: 1,426 articles

Embase

1 telomer*

2 ('air'/exp OR air AND pollution*) OR ('air'/exp OR air AND pollutant*) OR (particulate AND matter*)

3 #1 AND #2

Results: 81 articles

Web of Science

1 # 1

TOPIC: (particulate) AND TOPIC: (matter*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

2 # 2

TOPIC: (air) AND TOPIC: (pollution*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All

years

3 # 3

TOPIC: (air) AND TOPIC: (pollutant*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

4 # 4

#3 OR #2 OR #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

5 # 5

TOPIC: (telomere*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

6 # 6

#5 AND #4

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Results: 45 articles

Ovid

1 (pollutant* and air).af.

2 (pollution* and air).af.

3 (matter* and particulate).af.

4 1 or 2 or 3

5 telomer*.af.

6 4 and 5

Results: 537 articles

Last search: 16 August 2017