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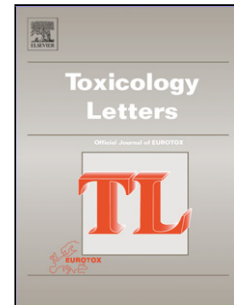
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# Ageing at the level of telomeres in association to residential landscape and air pollution at home and work: a review of the current evidence

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## Highlights

- Telomere lengths are cellular memories of exposures to inflammation and oxidative stress.
- Residential green space, low traffic exposure, and long-term lower exposure to particulate air pollution are associated with longer telomeres.
- Adverse environmental exposures may have a long lasting molecular footprint on the ageing process, as reflected by shorter telomere length.
- Shorter telomeres reflect higher disease susceptibility and a potential shorter life expectancy.
- Adequate reductions in, and protections against, pollutants may lead to decreased comorbidities and increased life-expectancy.

## Abstract

Studies suggest that leukocyte telomere length is an index of systemic ageing. Here, we discuss telomere length as a marker of biological ageing in relation to residential landscape (greenness), residential air pollution and work related exposures. Telomere lengths are memories of cumulative oxidative and inflammatory stress, and show to have inverse associations with the risk of non-communicable diseases. For this reason, telomeres are considered as markers of biological ageing. Studies at birth, in children, young adulthood, and elderly show that residential green space, lower traffic exposure and long-term lower exposure to particulate air pollution are associated with longer telomeres. Work related exposures including exposure to toxic metals, polycyclic aromatic hydrocarbons and particulate matter are associated with shorter telomeres for a given age. In contrast to chronic exposures, evidence is present of the observation that recent exposure is associated with longer telomeres. Our overview shows that the magnitude of residential and work related environmental factors on telomere length are often as important as many classical life-style factors.

**Keywords:** telomeres, telomere length, air pollution, particulate matter, polycyclic aromatic hydrocarbons, residential greenness, toxic metals

## Introduction

Air pollution is a complex mixture of different pollutants having both anthropogenic and natural origins. Important air pollutants include carbon monoxide and dioxide (CO, CO<sub>2</sub>), sulfur oxides (SO<sub>x</sub>), nitrogen oxides (NO<sub>x</sub>), volatile organic compounds (VOCs), ozone, metals, and particulate matter (PM). Awareness concerning the human health effect impact of air pollution exposures has led to major large population-based studies evaluating health effects of air pollution and with a stringent focus on the health related effects of ambient PM exposure. In the recent 2016 update of the Global Burden of Disease Study, ambient PM was ranked as the 6<sup>th</sup> and 7<sup>th</sup> of the most leading risk factors influencing public health worldwide in women and men, respectively. Besides PM, household air pollution was ranked 10<sup>th</sup> and 8<sup>th</sup>, respectively.<sup>1</sup> Ambient PM exposure is associated with a high risk for developing cardiovascular and respiratory diseases and with early mortality.<sup>2-4</sup> A recent U.S.<sup>4</sup> study including 60,925,443 individuals showed that an increase of 10 µg/m<sup>3</sup> in PM<sub>2.5</sub> increased the risk of death by 13.6% (95% CI, 13.1 to 14.1) for individuals having an exposure below the primary standard of the annual mean concentration of 12 µg/m<sup>3</sup> in PM<sub>2.5</sub>. A reduction of 10 µg/m<sup>3</sup> in fine PM<sub>2.5</sub> has been related to an increase in the mean (SD) life expectancy up to 7.3 (2.4) months.<sup>5</sup> The underlying biological mechanisms by which air pollution may affect human health is via inflammatory and immune related responses and via generation of oxidative stress.<sup>6,7</sup> In addition to air pollution, a growing body of evidence has linked exposure to residential

landscape (also referred to as green space or natural environments) with health outcomes, including mortality,<sup>8-11</sup> well-being and mental health<sup>12-15</sup>.

Telomere shortening is a primary hallmark of ageing and telomere length (TL) shortens with age and reflects the cellular replicative capacity. In addition, TL shortens due to DNA damaging effects and it is believed that therefore TL provides a cellular memory of exposures to oxidative stress and inflammation besides cellular replication. In this review, we summarize additional and new evidence on the air-pollution induced telomere-mitochondrial ageing hypothesis. This hypothesis states that TL may provide a potential biological mechanism by which air pollution affects ageing, health, and disease.<sup>16</sup> We focus on current findings of TL in relation with residential landscape, PM, and polycyclic aromatic hydrocarbons (PAH) exposure.

## **Telomeres, telomerase and age-related diseases**

Telomeres are ribonucleoprotein complexes that cap the end of chromosomes protecting them from degradation and end-to-end fusion, which ensures genome stability and prevents the loss of genetic information.<sup>17</sup> Human telomeres consist of several kilobase (kb) tandem repeated TTAGGG sequences.<sup>18</sup> Telomeres shorten after each cellular division due to the end-replication problem.<sup>19</sup> A yearly telomeric loss between 32.2 and 45.5 bp has been estimated based on longitudinal population-based studies.<sup>20,21</sup>

Telomerase is a ribonucleoprotein that is able to maintain TL by adding the telomeric repeat sequences to the ends of the chromosomes.<sup>22</sup> Telomerase contains a RNA template (TERC) and a reverse transcriptase (TERT) and is mainly active in germ, stem, and immortal cells, but is mainly repressed in somatic cells.

Telomere length is highly variable between same-aged persons and this variation has been attributed by genetics, lifestyle, behavioral and environmental factors. The heritability of TL varies between 36% and 82%.<sup>21,23-26</sup> In general, telomeres are longer in women than in men,<sup>27</sup> tend to be longer in African-Americans and Hispanics compared with Non-Hispanic Whites,<sup>28</sup> and are longer in offspring of older fathers.<sup>29,30</sup> Different adverse lifestyle, behavioral, and environmental exposures have been associated with a shorter TL. Indeed shorter telomeres are observed in smokers,<sup>31</sup> and in overweight and obese persons.<sup>32</sup> Adherence to the Mediterranean diet,<sup>33,34</sup> increased physical activity<sup>35</sup> and both sleep duration and quality are associated with longer telomeres.<sup>36,37</sup> Sociodemographic parameters, including low educational level is associated with shorter TL for a given age.<sup>38</sup> Persons exposure to life stress events have been related with shortened telomeres, and life stress may influence telomerase activity.<sup>39,40</sup> Interesting in this regard is that most of these described factors relate to some extent to the oxidative and inflammatory state of humans, which may directly act on the telomeric DNA, resulting in DNA damage and DNA breakage, and leading to a rapid erosion of telomeres.

The ageing process runs in parallel with increased chronic, low-grade systemic inflammation and has led to the definition of the term "Inflamm-aging".<sup>41</sup> As TL is proposed to be a marker of biological ageing

and may capture inflammation related conditions, TL may therefore be a morbidity-related endophenotype (i.e. intermediate phenotypes common to several diseases). Indeed large epidemiological studies have evaluated the role of TL as a potential biological mechanism underlying diverse age-related diseases and age-related health conditions. In this regard, studies show that a short TL in leukocytes independently of age is associated with following age-related conditions, including hypertension,<sup>42,43</sup> atherosclerosis,<sup>44,45</sup> myocardial infarction,<sup>46,47</sup> coronary heart and cerebrovascular disease,<sup>48</sup> stroke,<sup>47,49</sup> insulin resistance,<sup>50</sup> type 2 diabetes mellitus,<sup>51</sup> Alzheimer's disease<sup>52</sup> and retinal arteriolar narrowing.<sup>53</sup> Telomere length is associated with cancer incidence risks, however both short TLs<sup>51</sup> and long TLs<sup>54</sup> have been described in this association. Lastly, increased all-cause mortality rates are observed in association with shorter TL in small (n=143) and large population (n=64,637) cohorts with hazard ratios of 1.86 and 1.40, respectively.<sup>55,56</sup> Observational studies as presented above cannot prove a causative role of TL in disease development. It might also that TL is a biomarker of the ageing process it-self. However, Sahin *et al.*<sup>57</sup> demonstrated in *Tert*<sup>-/-</sup> mouse models of ageing that dysfunctional telomeres are causally involved in inducing age-related pathways and cardiovascular ageing. Finally, an animal based study,<sup>58</sup> studied zebra finches from birth to death and observed a clear relation between the initial TL (at 25 days after birth) and the lifespan of these birds. All together, these studies and evidences underscore the importance of TL in relation to life expectancy and a healthy or diseased phenotype. Identification of external factors, such as air pollution exposure, that associate with TL may provide evidence of the biological underlying mechanisms explaining disease- and mortality air pollution induced related outcomes.

### **Telomere length, oxidative stress, and inflammation**

Experimental studies have shown that cultivating human fibroblasts under hyperoxia conditions (represented as a state of oxidative stress) indeed shorten telomeres.<sup>59</sup> The underlying mechanism by which reactive oxygen species (ROS) induce DNA damage and shorten telomeres is by the accumulation of single-strand nicks in the telomere DNA stretches, which are less well repaired than other regions in the genome.<sup>60</sup> Especially, the G-rich parts of the telomere sequence (TTAGGG) and not the G-rich single stranded overhang are highly sensitive for DNA damage, in human fibroblasts, induced by oxidative stress conditions (after exposure to H<sub>2</sub>O<sub>2</sub>, an NO-generating agent and a O<sub>2</sub><sup>-</sup> generating system).<sup>61,62</sup>

Next to oxidative stress, an experimental study<sup>63</sup> recently unraveled the role of chronic inflammation on the telomere system. Jurk *et al.*<sup>63</sup> showed that mouse models (*nfkb1*<sup>-/-</sup>) of chronic inflammation displayed increased telomere dysfunction due to increased oxidative stress, partially by the activation of cyclooxygenase COX-2. Inflammation may induce telomere shortening by increasing cell turnover and by the induction of ROS that can damage telomeric DNA. Accelerated shortening of telomeres, and as such, senescence of cells may be an important pathway by which oxidative stress and inflammation may accelerate biological ageing and the resultant development of ageing-related morbidity, including cardiovascular disease.<sup>45,47</sup>

## **Toxicological properties of particulate matter and its relation to oxidative stress, inflammation, and the ageing process**

Particulate matter is a complex mixture of particles and these are classified based on size into i) coarse particles with aerodynamic diameter between 10 and 2.5  $\mu\text{m}$  ( $\text{PM}_{10}$  to  $\text{PM}_{2.5}$ ), ii) fine particles with aerodynamic diameter between 2.5 and 0.1  $\mu\text{m}$  ( $\text{PM}_{2.5}$  to  $\text{PM}_{0.1}$ ), and iii) ultrafine particles with aerodynamic diameter  $\leq 0.1$   $\mu\text{m}$  (UFP). However, independent of particulate mass concentration the composition and potential toxicity of particulate matter may greatly differ, depending on the origins.<sup>64,65</sup> Direct formation of ROS on the particle surface via Fenton reactions, or indirect formation via altered function of NADPH-oxidase, mitochondria and activation of inflammatory cells may lead to high oxidative stress which directly damage proteins, lipids, membranes and DNA.<sup>64,66</sup> Besides, it has been shown that increased exposure may have systemic toxic effects, involving an increased inflammatory response including NF- $\kappa$ B related inflammatory and cytokine gene expression.<sup>65,67</sup> As stated previously, both ROS and inflammation may target telomeres which may lead to dysfunctional telomeres and may induce the ageing mechanism. This has led to our recently proposed “air-pollution telomere-mitochondrial ageing hypothesis”,<sup>16</sup> with its fundamentals based on the experimental studies of Sahin *et al.*<sup>57</sup> that unveiled a fascinating connection between the nuclear and mitochondrial ageing processes. The current accepted experimental model proposes that DNA damage to telomeres leads to dysfunctional telomeres, which in turn activates the p53 pathway and represses the SIRT1 cascade. Both p53 and SIRT1 can alter the “master regulators” of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma co-activator 1 alpha and beta (PGC-1 $\alpha,\beta$ ). Repression of PGC-1 $\alpha,\beta$  leads to mitochondrial dysfunction, increased ROS production and alteration in the glucose pathways, resulting in the induction of cell cycle arrest and senescence. Senescence, apoptosis and growth arrest in tissues and stem cells correspond directly to the ageing phenotype.<sup>57,68,69</sup> This experimental model is in line with human observations. Among 166 elderly, TL and SIRT1 gene expression were found to be intermediate mechanisms between PM air pollution exposure and mtDNA alterations. Formal mediation analysis indicated that the effect of long-term PM air pollution on mtDNA content was mediated by SIRT1 expression.<sup>70,71</sup>

### ***In vitro* and *in vivo* studies on air pollutant exposures and telomere length**

Evidence of the impact of air pollution related compounds on the telomere biology system firstly came from *in vitro* and *in vivo* cigarette smoke and cigarette smoke condensate (CSC) exposure studies. A first study showed alterations in the telomere biology system from CSC treated (0.2 mg/ml CSC containing 10.80mg of total particulate matter/cigarette) fibroblasts compared with controls, and observed an abnormal number of telomeres in 29.4% of treated cells compared with 16.7% in control cells ( $P=0.0001$ ).<sup>72</sup> In an *in vivo* exposure experiment, telomere shortening was observed in embryos from smoke or CSC exposed mice.<sup>73</sup> In addition, Huang and colleagues,<sup>74</sup> showed in an early mouse embryo *in vitro* model that exposure to CSC (0.02 mg/ml) and cadmium (5-100  $\mu\text{M}$ ) resulted in shorter embryonic

TLs. In an embryonic stem cell model, chronic long-term exposure (2 weeks) to a low dose of CSC (0.02 mg/ml) or cadmium (5  $\mu$ M) resulted in significant shorter embryonic stem cell telomeres. Telomeres in the CSC exposed embryonic stem cell were shorter than telomeres from control embryonic stem cells ( $P < 0.05$ ), and the shortest telomeres ( $P < 0.0001$ ) were observed in the cadmium exposed group.<sup>75</sup> In a recent experiment,<sup>76</sup> the effect of particulate matter exposure ( $PM_4$ ) on TLs from both normal human bronchial epithelial cells (NHBE) and chronic obstructive pulmonary disease (COPD)-diseased human bronchial epithelial (DHBE) cells was evaluated. A three times repeated exposure of 4 hours (with intervals of 24 hours) to 5  $\mu$ g/cm<sup>3</sup> of  $PM_4$  resulted in a significant shortening of TL and an increase in telomerase activity in both NHBE and COPD-DHBE cells comparing with non-exposed cells. The strongest effects were observed in COPD-DHBE cells. In a comparable study exposing NHBE and COPD-DHBE cells with sampled  $PM_{2.5}$  air pollution from two different seasons (autumn-winter and spring-summer season) revealed shorter TLs and an increase in telomerase activity in a concentration- and exposure-dependent manner.<sup>77</sup> A single exposure of 4 hours to 2 or 10  $\mu$ g/cm<sup>3</sup> of  $PM_{2.5}$  did not alter TL and telomerase activity in both NHBE and COPD-DHBE cells compared with controls. However a three times repeated exposure of 4 hours to a concentration of 2 or 10  $\mu$ g/cm<sup>3</sup> of  $PM_{2.5}$  significantly shortened TL and increased telomerase activity in NHBE and COPD-DHBE cells compared with controls. In this latter exposure experiment a stronger TL decrease and increased telomerase activity was observed when using the highest concentration of  $PM_{2.5}$  (10  $\mu$ g/cm<sup>3</sup>) compared with the lower  $PM_{2.5}$  concentration (2.5  $\mu$ g/cm<sup>3</sup>). Lastly, umbilical vein endothelial cells exposed for 4 hours to 1  $\mu$ g/cm<sup>2</sup> ultrafine carbon black particles resulted in a significant decrease in telomerase activity. Comparable results were observed for 4 hours exposed lung epithelial cell lines to 10  $\mu$ g/cm<sup>2</sup> of ultrafine carbon black particles.<sup>78</sup>

### Residential landscape and telomere length

Research suggests that residential greenness is protective against adverse mental health outcomes, cardiovascular disease, and mortality, partly by reducing air pollution but also via increasing physical activity, and well-being. We summarized studies evaluating the association between residential landscape and TL in Table 1. A first report of the effects of residential greenness and the presence of green spaces on TL was conducted in a Hong Kong study of 976 men aged over 65 years. Results showed longer TLs in persons residing in a newly built area including green parks compared with persons residing in older high densely parts of the city.<sup>79</sup> In addition to this, Bijnens *et al.*<sup>80</sup> found that placental TL at birth was related to residential landscape, with longer newborn TL in association with higher maternal exposure to residential greenness. A doubling in the distance to a major road and an IQR increase in maternal residential surrounding greenness were associated with 5.32% (95% CI: 1.90, 8.86%,  $P = 0.003$ ) and 3.62% (95% CI: 0.20, 7.15%,  $P = 0.04$ ) longer placental telomeres, respectively.<sup>80</sup> Interestingly, the association between the distance that pregnant mothers lived to a major road and TL persisted when telomeres in buccal cells were evaluated from the same individuals but now during young adulthood (mean age (SD) of 22.6 (3.1) years).<sup>81</sup> An Italian study<sup>82</sup> evaluated TL and telomerase hTERT gene-



expression in 50 pregnant women living near hazardous-waste landfill sites in the Campania region in comparison with 50 pregnant women living in a non-polluted area. Both TL and hTERT expression were significantly decreased in pregnant women residing in the polluted area compared with controls (both models  $P < 0.001$ ). Finally, a recent interesting study<sup>83</sup> on nestling great tits (*Parus major* L.) evaluated the effect of being raised in an urban or rural area on TL evaluated at 25 days after birth from cross-fostered urban and rural birds. Independent of birthplace (urban or rural), birds grown up in urban areas had 10.7% shorter TL than birds grown up in the rural area. Factors explaining this observation include the higher urban pollution levels, environmental stress related to habitat quality, and dietary differences. Although limited studies evaluated the effects of residential landscape and TL, the evidence till now supports the idea that residential greenness or rural environments are associated with longer telomeres, and may increase molecular longevity. The independence from other factors such as air pollution should be further unraveled

### **Telomere length and particulate matter related air pollution exposure**

Evidence of occupational and environmental exposures (based on the home address) to chemicals and air pollutants in relationship with TL have been documented before.<sup>16,84</sup> However, in this review we add newly identified studies that extend the evidence of the association between TL and particulate matter exposure as previously reviewed by Martens and Nawrot.<sup>16</sup> Both general population (Table 2) and occupational (Table 3) studies evaluating particulate matter exposure or related compounds including black carbon (BC) or elemental carbon (EC) are summarized. The reported studies are based on air pollution concentrations estimated using spatio-temporal models with air pollution monitoring stations in combination with land-use regression models, or based on actual personal and/or local air pollution sampling and recording at the home or work address. Based on all reviewed studies (Tables 2 and 3), TL was negatively associated with long-term air pollution exposure, whereas TL tends to be positively associated with short-term exposure.

#### **i) Telomere length and particulate matter exposure at home**

Studies evaluating long-term and short-term exposures to ambient particulate matter or BC estimated at the home address in relation to TL are listed in Table 2. In elderly aged men of the Normative Aging Study (NAS), an annual increase of  $0.25 \mu\text{g}/\text{m}^3$  in BC was associated with 7.6% ( $P = 0.008$ ) shorter leukocyte telomere length (LTL).<sup>85</sup> Pieters *et al.*,<sup>70</sup> showed that a long-term increment of  $5 \mu\text{g}/\text{m}^3$  in residential  $\text{PM}_{2.5}$  exposure was associated with 16.8% ( $P = 0.0005$ ) shorter LTL, whereas exposure during the month prior blood draw was associated with 17.5% ( $P = 0.0001$ ) longer LTL in an elderly population in Flanders, Belgium. Recently, in the KORA F4 study<sup>86</sup> a significant interaction between BC exposure and sex ( $P$ -interaction = 0.008) in relation with LTL was observed. Shorter telomeres in men were observed in association with annual exposure to BC ( $P = 0.005$ ), whereas no associations were observed for women ( $P = 0.44$ ). These authors could replicate the results in the NAS study including all male veterans ( $n = 496$ ), where shorter telomeres were observed in association with both higher annual  $\text{PM}_{2.5}$  and BC exposures

(both  $P < 0.0001$ ).<sup>86</sup> Investigators of the Belgian ENVIRONMENTAL influence ON early AGEing (ENVIRONAGE) birth cohort<sup>87</sup> studied TL at the beginning of life, and revealed that prenatal  $PM_{2.5}$  exposure was associated with newborn TL measured both in cord blood and placental tissue. A  $5 \mu\text{g}/\text{m}^3$  increase in  $PM_{2.5}$  exposure during the entire pregnancy was associated with 8.8% (95%CI; -14.1 to -3.1%) shorter cord blood and 13.2% (95%CI, -19.3 to -6.7%) shorter placental TL with the strongest effects during second trimester.<sup>87</sup> Interestingly, also a positive association was observed between cord blood TL and  $PM_{2.5}$  exposure late in gestation (32-34 weeks), this adding to the evidence of short-term exposure in relation with longer TL. Up to now, only one study evaluated TL during childhood in relation with PM exposure.<sup>88</sup> In this United Kingdom based study including 333 children aged 8.9 years, surprisingly, a significantly positive association was found between saliva TL and long-term (annual) exposures to  $PM_{2.5}$  and  $PM_{10}$  (all models  $P < 0.0001$ ). The latter study provided for the first time puzzling evidence of long TL in association with long-term air pollution exposure. In this regard, we need to remark that the use of saliva as a matrix studying TL perhaps requires a good evaluation (e.g. technical variation aspects, and measurement errors as well as correlations studies with TL obtained for other matrices) as to compare the observed effects with the effects observed from studies using LTL. To our knowledge, only one study in 137 cancer-free non-smokers evaluated TL and indoor air pollution exposure estimated based on a face-to-face interview questionnaire (not included in Tables). This study observed that cumulative exposure to solid fuel usage for cooking was negatively associated with LTL ( $P = 0.01$ ).<sup>89</sup>

## ii) Telomere length and particulate matter exposure at work

Studies evaluating PM related exposures at work confirm the observation of long TL in association with short-term exposures (Table 3). In 57 steel workers, longer telomeres were observed in association with high short-term exposure (3-days) to  $PM_1$  and  $PM_{10}$ .<sup>90</sup> This is in line by the study of Hou *et al.*,<sup>91</sup> who observed that LTL was positively associated with increased personal  $PM_{2.5}$ , personal EC and ambient  $PM_{10}$  on the day of examination in truck drivers and office workers in Beijing, China. Wong *et al.*,<sup>92</sup> however showed that LTL in boilermakers decreased with cumulative  $PM_{2.5}$  exposure in the month prior follow-up. Long-term exposure reflected by a career cumulative exposure to  $PM_{2.5}$  showed a negative although non-significant trend with LTL. Finally, a strong difference in exposure to respirable dust was observed in 101 welders compared with 127 controls ( $1.2 \text{ mg}/\text{m}^3$  vs  $< 0.1 \text{ mg}/\text{m}^3$ ;  $P < 0.0001$ ), and relative LTL tended, but no significant, to be shorter in welders compared with controls (0.86 vs 0.88;  $P = 0.090$ ). However, each working year as a welder was significantly associated with 0.0066 units shorter LTL ( $P = 0.033$ ) (Table 3).<sup>93</sup>

## iii) Potential mechanisms for positive air pollution telomere length associations and blood cell compositions

Positive associations between LTL and current or short-term air pollution exposure may be indicative of a potential compensatory or over-compensatory mechanism in response to the air pollution-induced higher oxidative or inflammatory state. Short-term exposures may reflect acute exposure-induced inflammatory

responses which result in the recruitment of less mature leukocytes that migrate from the bone marrow into the blood circulation.<sup>90</sup> The less mature leukocytes have undergone fewer cell divisions, which exhibit therefore longer telomeres. It is known that different subpopulations of B and T cells have different TLs. Clonal expansion of subpopulations of cells with longer telomeres following acute exposure may reflect the finding of longer telomeres in association with air pollution exposure.<sup>90,94,95</sup> A second suggested mechanism is the activity of telomerase in lymphocytes upon exposure. It has been shown that antigen challenge activates CD4<sup>+</sup> T-cells, which in turn induces telomerase expression.<sup>94</sup> If for instance air pollution particles act as an antigen and thereby challenging T-cells this may result in high telomerase activity. Indeed small air pollution particles such as ultrafine particles (UFP) with a diameter <0.1  $\mu\text{m}$  (<100 nm) are able to cross the airway barrier and may enter the blood stream and then may be transported to different body compartments influencing local inflammatory processes.<sup>96-98</sup>

As stated, studies have indicated that TL may vary between different leukocyte subtypes, and for this reason TL assessment in studies may be potentially affected by the compositional proportion of these subtypes.<sup>99,100</sup> In this regard, some studies, although not all, adjusted to some extent for white blood cell count or blood cell differentials. We indicated these studies in Tables 2 and 3.

### **Telomere length and PAH and VOC exposures at home and work**

In Table 4 we summarize studies reporting on a negative association between TL and PAH exposures across different age groups, and both observed in the general population and in occupational settings. Additionally, studies reporting on associations between TL and exposures to VOC are included in Table 4. Most studies estimated PAH exposure by urinary concentrations of PAH metabolites, or by PAH-DNA adducts. One study, however, used a land use-regression model to estimate ambient PAH exposure.<sup>101</sup> Main routes of environmental exposures to PAH are via inhalation through air, cigarette smoke, but also via intake of PAH contaminated water and food or via food PAH generating food processing processes such as smoking, baking, boiling, and frying.<sup>102</sup> As PAH may enter the human body via the respiratory tract, gastrointestinal tract or via skin contact, urinary PAH metabolites may reflect a good measure of internal exposure and can be used as a sensitive biomarker of the overall environmental exposure to PAH.<sup>103</sup> Most of the studies reporting on associations between TL and PAH-exposures clearly identified an air pollution related source of PAH, including coke-ovens, coal burning factories, and rubber factories. Nevertheless, the results obtained with urinary PAH measures or PAH-DNA-adducts should be interpreted keeping in mind that other exposure sources of PAH, besides the air pollution related exposures, may add to the observed effects.

Pavanello *et al.*,<sup>104</sup> reported on significant shorter TL in highly PAH exposed coke-oven workers compared with controls ( $P=0.038$ ). Although no direct associations of urinary PAH measurements and PAH-DNA adducts were observed in relationship with TL in coke-oven workers, TL was inversely associated with the amount of years working in the cookery ( $\beta=-0.027$ ;  $P=0.018$ ). In a second study, shorter telomeres ( $P=0.026$ ), higher levels of both airborne benzene and urinary-1-hydroxypyrene were

observed in coke-oven workers when compared with controls.<sup>105</sup> However, whether a direct association exists between PAH concentrations and TL could not be confirmed after reviewing this study. A Swedish study<sup>106</sup> evaluated TL in 166 rubber factory workers from 8 rubber industries in association with different occupational and potential carcinogenic related exposures (including aromatic amines, N-nitrosamines and PAH). In this study, personal air sampling of N-nitrosamines (n=60) and urinary measures of 1-hydroxypyrene and toluidine were carried out (n=157). Telomere length was inverse associated with N-nitrosamines (P=0.046). Additionally, a significant decrease in TL was observed with higher urinary p-toluidine levels (P=0.021), but not with urinary 1-hydroxypyrene. Ling *et al.*,<sup>107</sup> evaluated 8 different urinary PAH metabolites in association with male reproductive viability as potentially explained by TL in sperm. In this population of young male adults, a significant shorter sperm TL was observed with increased urinary concentrations of 1-hydroxypyrene and 1-hydroxynaphthalene after adjustment of potential other sources of PAH including smoking and baked food consumption. Interestingly, these authors provided experimental evidence of their population-based findings by exposing rats with benzo[a]pyrene for four weeks, and observed that both TL and the expression of TERT protein decreased significantly (P<0.0001) in testes derived germ cells from highly exposed rats (10 mg/kg) compared with control, non-exposed rats. Recently, a pilot study<sup>101</sup> including 14 children found that ambient exposure to PAH was negatively associated with childhood TL. In addition, even at birth, PAH exposure is related with cord blood TL. Perera *et al.*<sup>108</sup> studied cord blood PAH-DNA adducts in relation with newborn TL before and after the closure of a coal burning power plant, which was identified as the primary source of PAH exposure. In this study longer newborn telomeres were observed after closure of the coal burning power plant, and in addition a shorter TL was observed in association with higher cord PAH-DNA adducts (P=0.003).

### **Telomere length and environmental metal pollution related studies**

Telomere length in association with toxic metal exposures (mostly focused on cadmium, lead and arsenic) have been studied in occupational settings and in some general population studies. Placental levels of cadmium negatively associates with newborn TL ( $r = -0.138$ ;  $P = 0.013$ ).<sup>109</sup> In the NHANES (1999-2002) study (participants aged >20 years) high blood and urine cadmium concentrations were associated with -5.54% and -4.50% shorter LTL, respectively, but no association with blood lead was observed.<sup>110</sup> Similar results were observed in another NHANES subset in which each 1 mg/L increase in blood cadmium was associated with 3.74% shorter LTL.<sup>111</sup> In addition, also in young adulthood (participants aged 12-16 years), salivary TL negatively associates with urinary cadmium.<sup>112</sup> Short TL in both battery plant workers and lead smelters with increasing levels of blood-lead has been reported.<sup>113,114</sup> In 8-year old children a similar negative association was observed between TL and blood lead concentrations.<sup>115</sup> Different studies associating TL with increased arsenic (mostly by drinking water contamination) concentrations observe positive associations.<sup>112,116-119</sup>

## Conclusions

Telomere length provides an underlying mechanism by which a wide range of environmental exposures including residential landscape, and air pollutants in the general and work related environment may influence ageing and may relate to the early development of age-related diseases and increased mortality. Telomeres might behave as endophenotype linking exposures to early development in different age-related diseases. Further, as memories of the cumulative inflammatory and oxidative stress exposure telomere length can be considered as marker of the exposome. Both in the residential and work environment adequate reductions in, and protections against, pollutants may lead to decreased comorbidities and increased life-expectancy.

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ACCEPTED MANUSCRIPT

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**Table 1. Association between TL and residential landscape**

Authors	Study Population	n	Age, y	% Men	Method and tissue	Exposure	Association
Woo et al., 2009 <sup>79</sup>	Elderly population, Hong Kong	976	65	100%	qPCR, peripheral blood	Region of residence in Hong Kong. Inhabitants of four densely populated regions (Kowloon City, Wong Tai Sin, Sham Shui Po and Yau Tsim Mong) are compared with inhabitants of the new region Shatin. The Shatin region includes buildings close to rivers and many parks.	OR (95%CI): Shatin: Ref Kowloon City: 0.50 (0.30-0.83) Wong Tai Sin: 0.59 (0.37-0.94) Sham Shui Po: 0.38 (0.24-0.60) Yau Tsim Mong: 0.48 (0.29–0.78)
De Felice et al., 2012 <sup>82</sup>	Pregnant women in polluted and non-polluted areas, Campania, Italy	100	< 30 y: 48% 30-35 y: 44% > 35 y: 8%	0%	qPCR, TRF peripheral blood	50 pregnant women living in north-east Naples, characterized by atmospheric pollution and intense environmental pressure due to hazardous-waste sites, are compared with 50 pregnant women living in non-polluted areas.	Mean relative TL women from polluted area vs control: 1.27 vs 3.11; P<0.001  Correlation for distance from polluted area and relative TL in exposed women: r=0.954; P<0.05
Bijnens et al., 2015 <sup>80</sup>	East Flanders Prospective Twin Survey, Belgium	211	0	43%	qPCR, placenta	Traffic indicators: - Distance to major road - Distance weighted traffic density  Land use indicators: - Semi-natural, forested and agricultural area - Residential area - Industrial area	% change; P value for 2-fold change: Distance major road: 5.23%, P=0.003 Distance weighted traffic density 100m buffer: -3.78%; P=0.05  % change; P value for IQR increase with 5000 m buffer: Semi-natural, forested and agricultural area: 3.62%; P=0.04 Residential area: -3.41%; P=0.03 Industrial area: -4.90%; P=0.04

OR: odds ratio; qPCR: quantitative polymerase chain reaction; TRF: terminal restriction fragment; IQR: interquartile range; TL: telomere length

**Table 2. Association between TL and particulate matter related air pollution at home**

Authors	Study Population	n	Age, y	% Men	Method and tissue	Exposure period	Exposure, concentration in $\mu\text{g}/\text{m}^3$	% change or $\beta$ , P value
McCracken et al., 2010 <sup>85</sup>	Normative Aging Study (NAS): Population of males, all never smokers, Massachusetts, USA	165	73.6 $\pm$ 7.1 <sup>a</sup>	100%	qPCR, WBC	365 days before each blood drawn	Annual BC: 0.32 $\pm$ 0.2 <sup>a</sup>	% change for 0.25 $\mu\text{g}/\text{m}^3$ increase: -7.6 %; P=0.008*
Shan et al., 2014 <sup>120</sup>	Population of females, Sichuan, China	21	59 (38-85) <sup>b</sup>	0%	qPCR, buccal cells	24-h personal exposure	24-h PM <sub>2.5</sub> in low vs high exposed: 39 $\pm$ 11 <sup>a</sup> vs 101 $\pm$ 37 <sup>a</sup> 24-h BC in low vs high exposed: 2.6 $\pm$ 1.8 <sup>a</sup> vs 14.9 $\pm$ 11.2 <sup>a</sup>	Low vs high exposed group: -43%; P=NS
Xia et al., 2015 <sup>121</sup>	Type 2 diabetes patients, Shanghai, China	35	65 $\pm$ 8 <sup>a</sup>	49%	qPCR, WBC	Lag 0, 1, 2, 3 and 4-7 days prior blood drawn	24-h PMC: PMC < 1 $\mu\text{m}$ : 39.6 $\pm$ 21.7 <sup>a</sup> PMC 1-2.5 $\mu\text{m}$ : 6.6 $\pm$ 4.5 <sup>a</sup> PMC 2.5-10 $\mu\text{m}$ : 21.1 $\pm$ 18.5 <sup>a</sup>	All lags not significant PM <sub>2.5</sub> : 0.11%; P=NS for each IQR increase in 24-h average air pollutant
Pieters et al. 2016 <sup>70</sup>	Population of elderly, all non-smokers, Belgium	166	70.6 $\pm$ 4.7 <sup>a</sup>	46%	qPCR, WBC	One year exposure, last month and last week	Annual PM <sub>2.5</sub> : 21.1 $\pm$ 1.76 <sup>a</sup>	% change for 5 $\mu\text{g}/\text{m}^3$ increase: Last year: -16.8%; P=0.0005* Last month: 17.5%; P=0.0001* Last week: NS
Walton et al., 2016 <sup>88</sup>	Children from the Exploration of Health and Lungs in the Environment (EXHALE) study, UK	333	8.9 $\pm$ 0.3 <sup>a</sup>	55%	qPCR, saliva	One year exposure, last week and last day	Annual concentrations: PM <sub>2.5</sub> : 13.70 $\pm$ 0.82 <sup>a</sup> PM <sub>10</sub> : 23.36 $\pm$ 1.53 <sup>a</sup>	% change for 1 $\mu\text{g}/\text{m}^3$ increase: Last year: 11.6% for PM <sub>2.5</sub> and 4.7% for PM <sub>10</sub> , all P<0.001 Last week: 1.3% for PM <sub>2.5</sub> and 1.0% for PM <sub>10</sub> all P<0.05. Last day: NS
Ward-Caviness et al., 2016 <sup>86</sup>	Populations from the Cooperation for Health Research in the Region of Augsburg (KORA F4) cohort, Germany and from NAS, USA	1777 in KORA F4 496 in NAS	61 $\pm$ 8.9 <sup>a</sup> in KORA F4 74 $\pm$ 6.8 <sup>a</sup> in NAS	52% in KORA F4 0% in NAS	qPCR, WBC	Annual exposures for KORA F4 and NAS	Annual concentrations in KORA: BC: 1.7 $\pm$ 0.17 <sup>a</sup> PM <sub>2.5</sub> : 14 $\pm$ 0.84 <sup>a</sup> PM <sub>10</sub> : 20 $\pm$ 2.4 <sup>a</sup> Annual concentrations in NAS: BC: 0.53 $\pm$ 0.2 <sup>a</sup> PM <sub>2.5</sub> : 11.1 $\pm$ 1 <sup>a</sup>	TeloAA in KORA F4: All participants no associations Male participants: $\beta$ = -0.28; P=0.005 for BC, no other associations  TeloAA in males in NAS: $\beta$ = -0.49; P<0.0001 for PM <sub>2.5</sub> and $\beta$ = -0.40; P<0.0001 for BC
Martens et al., 2017 <sup>87</sup>	Prospective birth cohort, ENVIRONAGE, Belgium	641	0	50%	qPCR, cord blood and placenta	Weeks during pregnancy, trimester specific and entire pregnancy exposure	Weekly mean PM <sub>2.5</sub> during pregnancy: 13.4 (4.3-32.5) <sup>c</sup>	% change for 5 $\mu\text{g}/\text{m}^3$ increase during entire pregnancy: Cord blood: -8.8%; P=0.003 Placenta: -13.2%; P<0.0001

<sup>a</sup>Mean  $\pm$  SD; <sup>b</sup>Mean (range); <sup>c</sup>Mean (5<sup>th</sup>-95<sup>th</sup> percentile); \*studies adjusting for white blood cell count or blood cell differentials; IQR: interquartile range; NS: not significant; TeloAA: telomere length based age acceleration; PM<sub>2.5</sub>: particulate matter  $\leq$ 2.5  $\mu\text{m}$ ; PM<sub>10</sub>: particulate matter  $\leq$ 10  $\mu\text{m}$ ; BC: black carbon; PMC: particulate mass concentration; WBC: white blood cell; qPCR: quantitative polymerase chain reaction

**Table 3. Association between TL and particulate matter related air pollution at work**

Authors	Study Population	n	Age, y	% Men	Method and tissue	Exposure period	Exposure, concentration in $\mu\text{g}/\text{m}^3$	% change or $\beta$ , P value
Dioni et al., 2011 <sup>90</sup>	Population of steel workers, Brescia, Italy	57	44 (27-55) <sup>b</sup>	100%	qPCR, WBC	PM <sub>10</sub> and PM <sub>1</sub> exposure for 3 days	PM <sub>10</sub> : 262 $\pm$ 272 <sup>a</sup> PM <sub>1</sub> : 8.0 $\pm$ 7.7 <sup>a</sup>	PM <sub>10</sub> : $\beta$ = 0.30; P=0.002 for 285 $\mu\text{g}/\text{m}^3$ increase* PM <sub>1</sub> : $\beta$ = 0.29; P=0.042 for 11.05 $\mu\text{g}/\text{m}^3$ increase*
Hou et al., 2012 <sup>91</sup>	The Beijing Truck Driver Air Pollution Study, Beijing, China	120	Truck drivers: 33.5 $\pm$ 5.7 <sup>a</sup> Office workers: 30.27 $\pm$ 7.96 <sup>a</sup>	67%	qPCR, WBC	Personal PM <sub>2.5</sub> and EC exposure for 8-h Ambient PM <sub>10</sub> exposure: Examination day, 1day, 1-2 days, 1-5 days, 1-7 days, 1-10 days, 1-14 days	Truck drivers vs office workers: Personal PM <sub>2.5</sub> : 126.8 $\pm$ 68.8 <sup>a</sup> vs 94.6 $\pm$ 64.9 <sup>a</sup> Personal EC: 17.3 $\pm$ 6.7 <sup>a</sup> vs 13.1 $\pm$ 4.0 <sup>a</sup> Ambient PM <sub>10</sub> : - Examination day: 116.7 $\pm$ 50.2 <sup>a</sup> vs 123.5 $\pm$ 50.1 <sup>a</sup> - 1-day: 121.5 $\pm$ 47.8 <sup>a</sup> vs 119.5 $\pm$ 51.2 <sup>a</sup> - 1-2 days: 121.6 $\pm$ 38 <sup>a</sup> vs 119.3 $\pm$ 40.3 <sup>a</sup> - 1-5 days: 119.5 $\pm$ 26.9 <sup>a</sup> vs 118.2 $\pm$ 25.6 <sup>a</sup> - 1-14 days: 119.9 $\pm$ 18.7 <sup>a</sup> vs 121.7 $\pm$ 17.8 <sup>a</sup>	% change for IQR increase: PM <sub>2.5</sub> : 5.2%; P=0.007 EC: 4.9%; P=0.01 for PM <sub>10</sub> : Examination day: 7.7% P<0.001 1-day: 8.4%; P<0.001 1-2 days: 8.1%; P=0.002 1-5 days: -1.3%; P=0.64 1-14 days: -9.9%; P=0.02
Wong et al., 2014 <sup>92</sup>	Boilermakers Study: Population of males, Massachusetts, USA	48	39.3 $\pm$ 12.8 <sup>a</sup> at baseline	100%	qPCR, WBC	Career exposure, last year and last month exposure	Career cumulative PM <sub>2.5</sub> : 713.7 $\pm$ 1457.9 <sup>a</sup> mg/m <sup>3</sup> hr Year cumulative PM <sub>2.5</sub> : 74.0 $\pm$ 77.3 <sup>a</sup> mg/m <sup>3</sup> hr Month cumulative PM <sub>2.5</sub> : 8.5 $\pm$ 10.2 <sup>a</sup> mg/m <sup>3</sup> hr	Career: $\beta$ = -0.021; P>0.05* Year: $\beta$ = -0.022; P>0.05* Month: $\beta$ = -0.04; P≤0.05*
Li et al., 2015	Population of welders, southern Sweden	228	Welders: 41 (23-60) <sup>c</sup> Controls: 43 (23-56)	100%	qPCR peripheral blood	Respirable dust particles, during a workday measured for 53 welders and 19 controls. Exposure estimated for other workers	Welders: 1.2 $\pm$ 3.3 <sup>a</sup> mg/m <sup>3</sup> Controls: <0.1 mg/m <sup>3</sup>	TL in welders compared with controls: $\beta$ = -0.053; P=0.083

<sup>a</sup>Mean  $\pm$  SD; <sup>b</sup>Mean (range); <sup>c</sup>Median (5<sup>th</sup>-95<sup>th</sup> percentile); \*studies adjusting for white blood cell count or blood cell differentials; IQR: interquartile range; PM<sub>1</sub>: particulate matter  $\leq$ 1  $\mu\text{m}$ ; PM<sub>2.5</sub>: particulate matter  $\leq$ 2.5  $\mu\text{m}$ ; PM<sub>10</sub>: particulate matter  $\leq$ 10  $\mu\text{m}$ ; EC: elemental carbon; WBC: white blood cell; qPCR: quantitative polymerase chain reaction

**Table 4. Occupational and general population based studies exploring the association between TL and PAH or VOC exposures**

Authors	Study Population	n	Age, y	% Men	Method and tissue	Exposures, periods	Exposure concentration	% change or $\beta$ , P value
Hoxha et al., 2009 <sup>122</sup>	Population of street traffic officers and office workers (referents), Milan, Italy	134	< 30 y: 39% 30-40 y: 37% > 40 y: 24%	63%	qPCR, WBC	Benzene and toluene during one work shift (7 hours)	Referents vs traffic workers: - Airborne benzene: 13.0 (2.0-115.1) <sup>b</sup> vs 31.8 (9.0-315.7) <sup>b</sup> $\mu\text{g}/\text{m}^3$ - Airborne toluene: 43.4 (6.0-368.0) <sup>b</sup> vs 128.7 (24.4-1710.7) <sup>b</sup> $\mu\text{g}/\text{m}^3$	% change for IQR increase: Benzene: -6.4% P=0.004 Toluene: -6.2% P=0.008
Pavanello et al., 2010 <sup>104</sup>	Population of non-current smoking coke-oven workers and gender/ethnicity matched controls, Poland	92	Workers: 36 (20-59) <sup>d</sup> Controls: 38 (21-58) <sup>d</sup>	100%	qPCR, WBC	Urinary 1-pyrenol and anti-benzo[a]pyrene-diolepoxide (anti-BPDE)-DNA adduct	Workers vs controls: - 1-pyrenol : 3.09 (0.41-7.48) <sup>d</sup> vs 0.09 (0.01-0.40) <sup>d</sup> $\mu\text{mol}/\text{mmol}$ creatinine - anti-BPDE-DNA adduct: 5.06 (0.90-12.24) <sup>d</sup> vs 0.21 (0.125-5.56) <sup>d</sup> $10^{-8}$ nucleotides	Median TL in workers vs controls: 0.99 vs 1.20; P=0.038  No associations between TL and 1-pyrenol or anti-BPDE-DNA adducts
Bin et al., 2010 <sup>105</sup>	Population of coke-oven workers and non-exposure control group	213	NP	NP	qPCR, peripheral blood	Airborne benzene-soluble matter and particulate-phase sampling, Urinary 1-hydroxypyrene	Workers vs controls (median concentration): - Airborne benzene: 328.6 vs 97.8 $\mu\text{g}/\text{m}^3$ - Particulate phase: 926.9 vs 49.1 $\text{ng}/\text{m}^3$ - 1-hydroxypyrene: 12.2 vs 0.7 $\mu\text{mol}/\text{mol}$ creatinine	TL in workers vs controls: 1.10 vs 1.43; P=0.026  Specific associations NP
Li et al., 2011 <sup>106</sup>	Population of rubber industry workers, Southern Sweden	157	38 (19-65) <sup>d</sup>	49%	qPCR, peripheral blood	Urinary 1-hydroxypyrene, TTCA, and Orto (o-), meta (m-), and para (p-) toluidine in all participants  3 hours air sampling of N-nitrosamines for 60 participants, and based on this estimated N-nitrosamine values for the other participants	Concentration ( $\mu\text{mol}/\text{mol}$ creatinine): - 1-hydroxypyrene: 0.14 (0.0020-0.85) <sup>d</sup> - TTCA: 24 (1.7-690) <sup>d</sup>  Concentration (ng/ml): - o-toluidine: 0.46 (0.025-108) <sup>d</sup> - m-toluidine: 0.15 (0.025-3.8) <sup>d</sup> - p-toluidine: 0.090 (0.025-4.7) <sup>d</sup>  Concentration ( $\mu\text{g}/\text{m}^3$ ): - Estimated N-nitrosamines: 1.3 (0.1-22) <sup>d</sup> - Measured N-nitrosamines: 1.07 (0.07-35.5) <sup>d</sup>	p-toluidine: $\beta$ = -0.028; P=0.021  Estimated N-nitrosamines: $\beta$ = -4.4; P=0.042  Measured N-nitrosamines: $\beta$ = -8.1; P=0.046  No other associations

Ling et al., 2016 <sup>107</sup>	Prospective cohort study, the Male Reproductive Health in Chongqing College Students (MARHCS) study, China	666	21.4 ± 1.2 <sup>a</sup>	100%	qPCR, sperm	Exposure reflected by 8 urinary PAH concentrations	Metabolite concentration (µg/g creatinine): - 2-hydroxyfluorene: 0.413 ± 1.838 <sup>c</sup> - 1-hydroxypyrene: 0.020 ± 4.065 <sup>c</sup> - 1-hydroxynaphthalene: 0.068 ± 7.195 <sup>c</sup> - 2-hydroxynaphthalene: 0.650 ± 2.099 <sup>c</sup> - 1-hydroxyphenanthrene: 0.084 ± 3.986 <sup>c</sup> - 2-hydroxyphenanthrene: 0.175 ± 1.838 <sup>c</sup> - 3-hydroxyphenanthrene: 0.190 ± 1.856 <sup>c</sup> - 4-hydroxyphenanthrene: 0.007 ± 4.393 <sup>c</sup>	1-hydroxypyrene: β= -0.414; P=0.024  1-hydroxynaphthalene: β= -0.081; P=0.018  No other associations
Lee et al., 2017 <sup>101</sup>	Population of children from the study of asthma in Fresno, CA, USA	14	14 ± 2.11 <sup>a</sup>	NP	qPCR, PBMC	Outdoor residential 24-hour exposure of PAH	24-hour concentration: PAH456: 2.98 ± 0.58 <sup>a</sup> ng/m <sup>3</sup>	TL decreased with -0.14 units P=0.01 per 1 ng/m <sup>3</sup> increase in PAH456
Perera et al., 2018 <sup>108</sup>	Prospective cohort study in the Tongliang County, Chongqing Municipality, China	255	0	54%	qPCR, cord blood	Cord blood Benzo[a]pyrene (B[a]P)-DNA adducts as proxy for PAH-DNA adduct in 133 newborns from 2005, after closure of coal burning facility vs 122 newborns from 2002 before closure	Before vs after closure: - Cord adduct: 0.33 ± 0.140 <sup>a</sup> vs 0.20 ± 0.081 <sup>a</sup> 10 <sup>-8</sup> nucleotides	SD increase in cord PAH-DNA adducts: β= -0.019; P=0.003

<sup>a</sup>Mean ± SD; <sup>b</sup>Mean (range); <sup>c</sup>Geometric mean ± SD; <sup>d</sup>Median (range); IQR: interquartile range; PAH: polycyclic aromatic hydrocarbons; WBC: white blood cell; PBMC: peripheral blood mononuclear cell; TTCA: 2-thiothiazolidine-4-carboxylic acid; NP: not provided; qPCR: quantitative polymerase chain reaction