A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP11745.

Large-Scale Analysis of the Association between Air Pollutants and Leucocyte Telomere Length in the UK Biobank

Vasiliki Bountziouka,[1,2] Anna L. Hansell,[3,4] Christopher P. Nelson,[1,2] Veryan Codd,[1,2] and Nilesh J. Samani[1,2]

[1]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[2]National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK
[3]Centre for Environmental Health and Sustainability, University of Leicester, Leicester, UK
[4]NIHR Health Protection Research Unit in Environmental Exposures and Health, University of Leicester, Leicester, UK

https://doi.org/10.1289/EHP11745

Introduction

Shorter telomere length (TL) and air pollution are both associated with higher risk of aging-related diseases.[1,2] Oxidative stress may mediate the adverse effects of air pollution and also accelerate telomere attrition. Therefore, some of the adverse effects of air pollution could be mediated through an effect on TL. A few small studies, summarized in a recent systematic review and meta-analysis,[3] suggested a possible association of exposure to particulate matter (PM) with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$) with shorter leukocyte TL (LTL), but overall findings were inconclusive.[4] Here, we have leveraged our recent measurement of LTL in over 474,000 participants in the UK Biobank (UKB)[5] and available individual-level estimates of exposures to particulates [$PM_{2.5}$; $PM_{2.5-10}$, PM with an aerodynamic diameter range of from 2.5 to 10 μm (referred to as PM_{coarse}); PM_{10}, PM with an aerodynamic diameter of $\leq$10 μm; $PM_{2.5absorbance}$, a proxy for elemental carbon] and gaseous [nitrogen oxides (NO_x) and nitrogen dioxide (NO_2)] air pollutants in UKB participants[4] to undertake a large-scale study of the associations of air pollutants with LTL.

Methods

Recruitment and phenotyping of UKB participants have been described in detail previously.[6] LTL was measured using a quantitative polymerase chain reaction method and expressed as a ratio (the T/S ratio) between the telomere repeat copy number (T) and that of a single copy gene (S). Details of the LTL measurements (UKB field code 22192) and their quality control are reported in full elsewhere.[5] Air pollution estimates for the year 2010 were modeled for each address using land use regression models developed and validated as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE).[7,8] The data are available in the following UKB field codes: 24006 ($PM_{2.5}$), 24007 ($PM_{absorbance}$), 24008 (PM_{coarse}), 24005 (PM_{10}), 24004 (NO_x), and 24003 (NO_2).

From the participants with LTL measurements in the UKB (n = 474,074), we excluded participants without information on ethnicity, or white blood cell (WBC) count (n = 14,836) and randomly excluded one of any genetically related (Kinship $K > 0.088$) participant pairs (n = 36,441). Of the remaining 422,797 participants, complete data on air pollution markers, socioeconomic status (SES) indicators and smoking variables were available in 299,786 participants (the available data). Those with complete data tended to be younger, male, of White ethnic background, and have longer LTL than those without. To account for any selective bias, we undertook analyses in imputed data generated through multiple imputation by chained equations (MICE)[9] with 10 imputed data sets (n = 422,927; the imputed data).

Correlation coefficients between air pollutants and with SES were assessed with Pearson's correlation coefficient (r). The association between each individual pollutant with LTL was investigated using linear regression models in R (version 4.2.1; R Development Core Team), adjusted for age, sex, ethnic background [defined by the UKB as Asian (including Asian or Asian British, Indian, Pakistani, Bangladeshi, and any other Asian background), Black (including Black or Black British, Caribbean, African, and any other Black background), Chinese, Mixed (including White and Black African, White and Black Caribbean, White and Asian, and any other Mixed background), Other, and White (including British, Irish, and any other White background)], and WBC (all determinants of LTL[6]; i.e., the base model). Nonlinearity was assessed via the inclusion of a quadratic term for the pollutant.

The fully adjusted model was additionally adjusted for the area-level Townsend deprivation index (UKB field code 189), annual gross family income (738), ever smoked (20160) and passive smoking (1269 and 1279), using UKB-defined category levels, and for highest educational level (6138), which was recategorized into None (no qualification), Compulsory (O-levels/CSE/GCSE), Advanced (A-levels/nonvocational/other professional), and Degree (university/college degree). To avoid the potential for collider bias between LTL and air pollution with SES, we further examined the association between individual air pollutants and LTL within substrata of the Townsend index. The UKB has ethical approval from the North West Centre for Research Ethics Committee (application 11/NW/0382), which covers the UK. The UKB obtained informed consent from all participants. The generation and analysis of the data presented in this paper was approved by the UK Biobank access committee under UK Biobank application no. 6007.

Results

Participants were 40–69 years of age at recruitment [mean ± standard deviation (SD) = 56.3 ± 8.0 y] with more women (52.3%) and predominantly of White ethnic background (95.2%). Mean ± SD exposures for NO_2, NO_x, PM_{10}, $PM_{2.5}$, and PM_{coarse} were 26.3 ± 7.6, 43.4 ± 15.5, 16.2 ± 1.9, 10.0 ± 1.1, and 6.4 ± 0.90 $\mu g/m^3$, respectively, and 1.2 ± 0.27 $\times 10^{-5}$/m for $PM_{2.5}$ absorbance. There was a strong correlation (r = 0.92) between NO_2 and NO_x levels. The correlations between the gaseous pollutants and the particulate pollutants ranged from r = 0.24 between NO_2 and PM_{coarse} to r = 0.87 between NO_2 and $PM_{2.5}$. Among the particulate pollutants, the correlations ranged from r = 0.22 between PM_{coarse} and $PM_{2.5}$ to r = 0.82 between PM_{coarse} and PM_{10} (all $p < 1 \times 10^{-300}$).

Accounting for all major determinants of LTL, there was a nominal (p = 0.03) inverse association of $PM_{2.5}$ with LTL

Address correspondence to Nilesh J. Samani, Department of Cardiovascular Sciences, University of Leicester, British Heart Foundation Cardiovascular Research Centre, Glenfield Hospital, Groby Rd., Leicester, UK. Telephone: 44 116 2044758. Email: njs@le.ac.uk

The authors declare they have nothing to disclose.

Table 1. Association of individual air pollution markers with leukocyte telomere length using the complete available data ($n = 299{,}786$).

	Base model		Fully adjusted model		
Exposure response estimate per 1 SD	Beta (95% CI)	p-Value	Beta (95% CI)	p-Value	$p_{Interaction}$
NO_2, per 7.6 μg/m^3	−0.001 (−0.004, 0.003)	0.71	−0.004 (−0.011, 0.002)	0.18	8.25×10^{-4}
NO_x, per 15.5 μg/m^3	−0.003 (−0.006, 0.001)	0.11	−0.005 (−0.011, 0.002)	0.15	0.004
PM_{10}, per 1.9 μg/m^3	−0.001 (−0.005, 0.002)	0.47	−0.002 (−0.008, 0.003)	0.41	0.11
$PM_{2.5}$, per 1.1 μg/m^3	−0.004 (−0.007, 0.000)	0.03	−0.004 (−0.011, 0.003)	0.27	0.19
$PM_{2.5absorbance}$, per 0.27×10^{-5}/m	0.003 (−0.001, 0.006)	0.15	−0.007 (−0.014, 0.000)	0.05	1.33×10^{-6}
PM_{coarse}, per 0.9 μg/m^3	−0.002 (−0.005, 0.002)	0.31	−0.004 (−0.009, 0.002)	0.20	0.03

Note: The base linear regression model was adjusted for age, sex, ethnicity, and white blood cell count. The fully adjusted model was further adjusted for markers of socioeconomic status (SES) and smoking. SES includes quintiles of the 2011 Townsend deprivation index, gross annual family income, and higher educational qualifications. Smoking factors include ever and passive smoking. $p_{Interaction}$ gives the global p-value for interaction, obtained through a Wald-test, where terms of pollution markers with SES markers were tested. In the presence of a pollution marker × Townsend interaction index, the interactions with income and education were not significant and removed from the models. CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5absorbance}$, a proxy for elemental carbon; PM_{coarse}, particulate matter with an aerodynamic diameter range of from 2.5 to 10 μm; SD, standard deviation.

(Table 1, base models). However, allowing for multiple testing (Bonferroni $p = 0.008$), no pollutant showed a significant association with LTL in the available data. The findings were unchanged after adjustment for SES indicators and smoking (Table 1, adjusted models). In the imputed data, there was a small but significant inverse association of $PM_{2.5}$ and NO_2 with LTL in the base models that became nonsignificant when adjusted for SES and smoking (Table 2). There was no strong evidence of nonlinear associations between the air pollutants and LTL or evidence of a threshold effect.

As expected, there were highly significant correlations (all $p < 1 \times 10^{-300}$) between air pollution markers and the Townsend index (NO_2: 0.496; NO_x: 0.436; PM_{10}: 0.219; $PM_{2.5}$: 0.448; $PM_{2.5absorbance}$: 0.406; and PM_{coarse}: 0.111). In analyses stratified by level of deprivation, higher $PM_{2.5absorbance}$, NO_x, and NO_2 concentrations were positively associated with LTL in the most deprived areas in the base model (Figure 1). However, further adjustment for additional SES factors and smoking attenuated the observed associations.

Discussion

In this large-scale analysis in a contemporary cohort, we found no evidence for a significant association between several air pollutants and LTL, with similar findings in both available and imputed data. The findings are surprising given prior, albeit weak, evidence suggesting that higher air pollution levels are associated with shorter LTL.[3] Furthermore, in the same data set we have been able to replicate associations of several traits with LTL and identify novel associations.[5,10] Similarly, the ESCAPE air pollution models have been extensively used, including in >60 studies in the UKB, demonstrating adverse associations with air pollution.[4]

Given that air pollution exposure is strongly linked with SES, as we also show here, we further examined the association between air pollution markers and LTL in groups stratified by the Townsend index, but this did not alter the findings.

Although our findings suggest that it is unlikely that the adverse health effects of several major air pollutants are substantially mediated through accelerated attrition of TL, several limitations of our study need to be considered. First, the analyses were cross-sectional owing to the availability of only single time point measurements for both LTL and air pollution. Second, we have analyzed only a single cohort, albeit large, of predominantly White ethnicity, living in a high-income country with lower ambient air pollution. Therefore, our findings may not be generalizable to other settings. Furthermore, for the particulate pollutants, because only particle concentrations are available, we are unable to evaluate any association between LTL and particle composition or toxicity. Finally, our study does not exclude the possibility that exposure to other pollutants, including those from indoor exposures, affect TL.

Acknowledgments

V.C., A.L.H., and N.J.S. conceived the project; V.C., C.P.N., and N.J.S. secured funding for the LTL measurements and oversaw the generation and curation of the LTL measurements; V.B. and C.P.N. developed the analysis plan; V.B. performed the analysis; V.B., A.L.H., and N.J.S. drafted the manuscript; and all authors revised the manuscript and approved the submitted version.

This work was funded by the UK Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council and British Heart Foundation (BHF) through MRC grant MR/M012816/1 (to N.J.S., V.C., and C.P.N.). V.B., V.C., C.P.N., and N.J.S. are supported by the National Institute for Health Research

Table 2. Association of individual air pollution markers with leukocyte telomere length using the imputed data ($n = 422{,}797$).

	Base model		Fully adjusted model		
Exposure response estimate per 1 SD	Beta (95% CI)	p-Value	Beta (95% CI)	p-Value	$p_{Interaction}$
NO_2, per 7.6 μg/m^3	−0.003 (−0.006, 0.000)	0.02	−0.002 (−0.008, 0.004)	0.46	0.0105
NO_x, per 15.5 μg/m^3	−0.005 (−0.008, −0.002)	3.74×10^{-4}	−0.003 (−0.009, 0.003)	0.30	0.04
PM_{10}, per 1.9 μg/m^3	−0.002 (−0.005, 0.002)	0.32	−0.001 (−0.006, 0.004)	0.65	0.04
$PM_{2.5}$, per 1.1 μg/m^3	−0.006 (−0.009, −0.003)	5.62×10^{-5}	−0.001 (−0.007, 0.005)	0.70	0.47
$PM_{2.5absorbance}$, per 0.27×10^{-5}/m	0.000 (−0.003, 0.003)	0.86	−0.006 (−0.013, 0.000)	0.04	1.38×10^{-6}
PM_{coarse}, per 0.9 μg/m^3	−0.002 (−0.005, 0.001)	0.27	−0.004 (−0.009, 0.001)	0.11	0.02

Note: The base linear regression model was adjusted for age, sex, ethnicity, and white blood cell count. The fully adjusted model was further adjusted for markers of socioeconomic status (SES) and smoking. SES includes quintiles of the 2011 Townsend deprivation index, gross annual family income, and higher educational qualifications. Smoking factors include ever and passive smoking. $p_{Interaction}$ gives the global p-value for interaction, obtained through a Wald-test, where terms of pollution markers with SES markers were tested. In the presence of a pollution marker × Townsend index interaction, the interactions with income and education were not significant and removed from the models. Imputed data were generated through multiple imputation by chained equations (MICE)[9] with 10 imputed data sets ($n = 422{,}927$). CI, confidence interval; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; $PM_{2.5absorbance}$, a proxy for elemental carbon; PM_{coarse}, particulate matter with an aerodynamic diameter range of from 2.5 to 10 μm; SD, standard deviation.

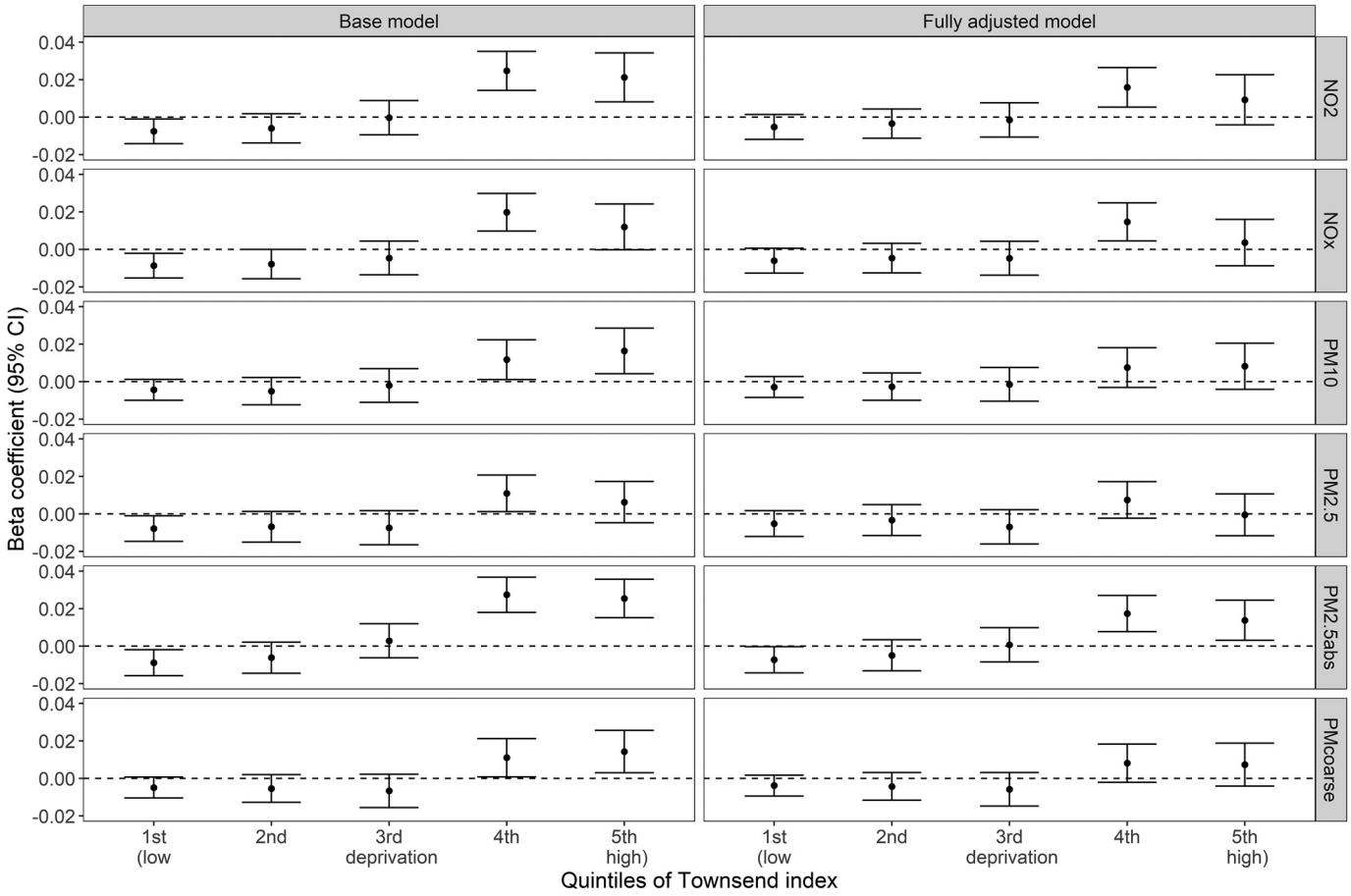

Figure 1. Association between leukocyte telomere length and air pollutants, stratified by quintiles of deprivation. Data are split into quintiles using the Townsend deprivation index, with the first quintile representing the least deprived and the fifth quintile, the most deprived. Beta estimates and 95% confidence intervals (CIs) were obtained from models run within strata. The base model was adjusted for age, sex, ethnicity, and WBC count. The fully adjusted model was further adjusted for markers of socioeconomic status (income and education) and smoking (both ever and passive smokers). Note: NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with an aerodynamic diameter of $\leq$2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of $\leq$10 μm; $PM_{2.5absorbance}$, a proxy for elemental carbon; PM_{coarse}, particulate matter with an aerodynamic diameter range of from 2.5 to 10 μm; WBC, white blood cell.

(NIHR) Leicester Cardiovascular Biomedical Research Centre (BRC–1215–20010). C.P.N. is funded by the BHF (SP/16/4/32697). A.L.H. acknowledges funding from the NIHR Health Protection Research Unit in Environmental Exposures and Health at the University of Leicester, a partnership between the UK Health Security Agency, the Health and Safety Executive, and the University of Leicester. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, the Department of Health and Social Care, or the UK Health Security Agency.

All data used in this study, including telomere length measurements, are available through application to the UK Biobank. Further information on registration to access the data can be found at http://www.ukbiobank.ac.uk/register-apply/.

References

1. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389(10082):1907–1918, PMID: 28408086, https://doi.org/10.1016/S0140-6736(17)30505-6.
2. Codd V, Wang Q, Allara E, Musicha C, Kaptoge S, Stoma S, et al. 2021. Polygenic basis and biomedical consequences of telomere length variation. Nat Genet 53(10):1425–1433, PMID: 34611362, https://doi.org/10.1038/s41588-021-00944-6.
3. Miri M, Nazarzadeh M, Alahabadi A, Ehrampoush MH, Rad A, Lotfi MH, et al. 2019. Air pollution and telomere length in adults: a systematic review and meta-analysis of observational studies. Environ Pollut 244:636–647, PMID: 30384069, https://doi.org/10.1016/j.envpol.2018.09.130.
4. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, et al. 2019. Air pollution, lung function and COPD: results from the population-based UK Biobank study. Eur Respir J 54(1):1802140, PMID: 31285306, https://doi.org/10.1183/13993003.02140-2018.
5. Codd V, Denniff M, Swinfield C, Warner SC, Papakonstantinou M, Sheth S, et al. 2022. Measurement and initial characterization of leucocyte telomere length in 474,074 participants in UK Biobank. Nat Aging 2(2):170–179, https://doi.org/10.1038/s43587-021-00166-9.
6. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. 2018. The UK Biobank resource with deep phenotyping and genomic data. Nature 562(7726):203–209, PMID: 30305743, https://doi.org/10.1038/s41586-018-0579-z.
7. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO_2 and NO_X land use regression models for estimating air pollution exposure in 36 study areas in Europe—the ESCAPE project. Atmos Environ 72:10–23, https://doi.org/10.1016/j.atmosenv.2013.02.037.
8. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.
9. White IR, Royston P, Wood AM. 2011. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 30(4):377–399, PMID: 21225900, https://doi.org/10.1002/sim.4067.
10. Bountziouka V, Musicha C, Allara E, Kaptoge S, Wang Q, Angelantonio ED, et al. 2022. Modifiable traits, healthy behaviours, and leucocyte telomere length: a population–based study in UK Biobank. Lancet Healthy Longev 3(5):e321–e331, PMID: 35685390, https://doi.org/10.1016/S2666-7568(22)00072-1.