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Robbie M Parks

Post-doctoral research fellow
Earth Institute, Columbia University
robbie.parks@columbia.edu
www.robbiemparks.github.io

Dr Timothy L. Lash,
Editor-in-Chief, *Epidemiology*

Dear Dr Lash:

On behalf of my co-authors, I would like to submit our paper “*Long-term traffic-related air pollutant exposure and amyotrophic lateral sclerosis diagnosis in Denmark: A Bayesian hierarchical analysis*” for consideration in *Epidemiology* as an Original Research Article.

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease, currently without a cure. Approximately half of patients die within three years of symptom onset. Annually, there are nearly 30,000 cases of ALS in Europe and over 200,000 worldwide. Known inherited genetic variants only account for 5–10% of ALS cases. Environmental factors, therefore, are likely important in ALS pathogenesis. Ambient air pollution, especially urban air pollution, is a ubiquitous exposure that has been associated with several other neurodegenerative disorders, and is consistently linked to systemic inflammation, oxidative stress, and neuroinflammation, all of which, in turn, have been reported as key pathways to ALS pathogenesis. Despite the compelling plausibility, few studies to date have evaluated the association between air pollution and ALS.

With this study, *the largest case-control study of ALS and air pollution to date*, we used data on 3,939 ALS cases from the Danish National Patient Register diagnosed between 1989 – 2013 and matched on, sex, year of birth and vital status to 19,298 population-based controls free of ALS at index date. We used predictions of nitrogen oxides (NO_x), carbon monoxide (CO), elemental carbon (EC), and fine particles (PM_{2.5}) from validated spatio-temporal models to assign 1-, 5-, and 10-year average exposures pre-ALS diagnosis at present and historical residential addresses of study participants. Although the last year of data in our analyses is from eight years ago (2013), our findings remain timely due to the uniquely large number of ALS cases we have collected, that air pollution remains so pervasive, and that ALS prevalence is projected to increase nearly 70% by 2040.

We found that an increase in the joint exposure to traffic-related pollutants was associated with an increase in odds of ALS diagnosis, significant for elemental carbon for a 1-year average standard deviation increase, though not significant at the 95% credible interval level for other pollutants. Our results indicate that sources of air pollution with elemental carbon, such as diesel engines and woodburning stoves, might contribute to development of ALS.

This manuscript has not been previously published and is not under review in any other journal. All authors have contributed to the paper, have approved its submission, and take responsibility for its contents. The authors have no actual or potential competing financial interests. There is no closely related paper included with this submission.

The following people are qualified to assess its contents and their implications, and are independent of this work:

1) Dr Aisha Dickerson (environmental risk factors; amyotrophic lateral sclerosis)
Johns Hopkins University
E-mail: adicke10@jhu.edu

2) Dr Maciej Strak (air pollution; environmental epidemiology)
Utrecht University
E-mail: m.m.strak@uu.nl

3) Dr Orla Hardiman (neurological disease; neurology)
Trinity College Dublin
E-mail: hardimao@tcd.ie

4) Dr Ioannis Bakolis (biostatistics; environmental epidemiology)
King's College London
E-mail: ioannis.bakolis@kcl.ac.uk

5) Dr Marta Blangiardo (Bayesian statistics; hierarchical models)
Imperial College London
E-mail: m.blangiardo@imperial.ac.uk

6) Dr Erika Garcia (biostatistics; environmental epidemiology)
University of Southern California
E-mail: garc991@usc.edu

7) Dr Howard Chang (biostatistics; environmental health)
Emory University
E-mail: howard.chang@emory.edu

8) Dr Michela Cameletti (biostatistics; Bayesian statistics)
University of Bergamo
E-mail: michela.cameletti@unibg.it

We look forward to your response and would be happy to answer any questions that you may have on this paper.

Sincerely,



Robbie M. Parks, PhD