



Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study

Hong Chen, Jeffrey C Kwong, Ray Copes, Karen Tu, Paul J Villeneuve, Aaron van Donkelaar, Perry Hystad, Randall V Martin, Brian J Murray, Barry Jessiman, Andrew S Wilton, Alexander Kopp, Richard T Burnett

Summary

Background Emerging evidence suggests that living near major roads might adversely affect cognition. However, little is known about its relationship with the incidence of dementia, Parkinson's disease, and multiple sclerosis. We aimed to investigate the association between residential proximity to major roadways and the incidence of these three neurological diseases in Ontario, Canada.

Methods In this population-based cohort study, we assembled two population-based cohorts including all adults aged 20–50 years (about 4·4 million; multiple sclerosis cohort) and all adults aged 55–85 years (about 2·2 million; dementia or Parkinson's disease cohort) who resided in Ontario, Canada on April 1, 2001. Eligible patients were free of these neurological diseases, Ontario residents for 5 years or longer, and Canadian-born. We ascertained the individual's proximity to major roadways based on their residential postal-code address in 1996, 5 years before cohort inception. Incident diagnoses of dementia, Parkinson's disease, and multiple sclerosis were ascertained from provincial health administrative databases with validated algorithms. We assessed the associations between traffic proximity and incident dementia, Parkinson's disease, and multiple sclerosis using Cox proportional hazards models, adjusting for individual and contextual factors such as diabetes, brain injury, and neighbourhood income. We did various sensitivity analyses, such as adjusting for access to neurologists and exposure to selected air pollutants, and restricting to never movers and urban dwellers.

Findings Between 2001, and 2012, we identified 243 611 incident cases of dementia, 31 577 cases of Parkinson's disease, and 9247 cases of multiple sclerosis. The adjusted hazard ratio (HR) of incident dementia was 1·07 for people living less than 50 m from a major traffic road (95% CI 1·06–1·08), 1·04 (1·02–1·05) for 50–100 m, 1·02 (1·01–1·03) for 101–200 m, and 1·00 (0·99–1·01) for 201–300 m versus further than 300 m (p for trend=0·0349). The associations were robust to sensitivity analyses and seemed stronger among urban residents, especially those who lived in major cities (HR 1·12, 95% CI 1·10–1·14 for people living <50 m from a major traffic road), and who never moved (1·12, 1·10–1·14 for people living <50 m from a major traffic road). No association was found with Parkinson's disease or multiple sclerosis.

Interpretation In this large population-based cohort, living close to heavy traffic was associated with a higher incidence of dementia, but not with Parkinson's disease or multiple sclerosis.

Funding Health Canada (MOA-4500314182).

Introduction

Dementia, Parkinson's disease, and multiple sclerosis are among the most common neurodegenerative diseases, with devastating effects on individuals, families, and society. Globally, about 55 million people have these disorders, with rising numbers expected given increasing longevity.^{1,2} Without cures, identification of modifiable risk factors is important.

Despite the mounting global effect of these neurodegenerative diseases, their cause remains largely unknown.^{3–5} Concern is growing that exposures associated with traffic such as air pollution and noise might contribute to neurodegenerative pathology.^{6,7} Results of studies showed that air pollutants and diesel exhaust induce oxidative stress and neuroinflammation,⁸ activate microglia,⁹ and stimulate neural antibodies.¹⁰ Exposure to

more noise also impairs cognitive abilities in rats.¹¹ Similarly, a few epidemiologic studies^{12–14} linked traffic-related noise and air pollution to cognitive decline and increased incidence of Parkinson's disease¹⁵ and Alzheimer's disease.¹⁶ Traffic exposure might affect various neurodegenerative processes.

Studies also showed that living near roads was associated with reduced white matter hyperintensity volume¹⁷ and cognition,^{18,19} but its effect on the incidence of dementia, Parkinson's disease, and multiple sclerosis is unknown. Living near traffic is a multifaceted exposure representing heightened exposure to nitrogen oxides, ultrafine particles, fine particulate matter (≤ 2.5 μm in diameter or $\text{PM}_{2.5}$), heavy metals, polycyclic aromatic hydrocarbons, volatile organic compounds, noise, and other factors. Because hundreds of millions of people

Lancet 2017; 389: 718–26

Published Online

January 4, 2017

[http://dx.doi.org/10.1016/S0140-6736\(16\)32399-6](http://dx.doi.org/10.1016/S0140-6736(16)32399-6)

See [Comment](#) page 675

Public Health Ontario,

Toronto, ON, Canada

(H Chen PhD, J C Kwong MD,

R Copes MD); Institute for

Clinical Evaluative Sciences,

Toronto, ON, Canada (H Chen,

J C Kwong, K Tu MD,

A S Wilton MSc, A Kopp BA);

Dalla Lana School of Public

Health, University of Toronto,

Toronto, ON, Canada (H Chen,

J C Kwong, R Copes,

P J Villeneuve PhD); Department

of Family and Community

Medicine, University of

Toronto, Toronto, ON, Canada

(J C Kwong, K Tu); Department of

Health Sciences, Carleton

University, Ottawa, ON, Canada

(P J Villeneuve); Department of

Physics and Atmospheric

Science, Dalhousie University,

Halifax, NS, Canada

(A van Donkelaar PhD,

Prof R V Martin PhD); College of

Public Health and Human

Sciences, Oregon State

University, Corvallis, USA

(P Hystad PhD);

Harvard-Smithsonian Centre

for Astrophysics, Cambridge,

MA, USA (Prof R V Martin);

Division of Neurology,

Department of Medicine,

Sunnybrook Health Sciences

Centre, University of Toronto,

Toronto, Canada

(B J Murray MD); and Population

Studies Division, Health

Canada, Ottawa, ON, Canada

(B Jessiman MSc,

R T Burnett PhD)

Correspondence to:

Hong Chen Public Health Ontario,

Toronto, Ontario M5G 1V2

hong.chen@oahpp.ca

Research in context

Evidence before this study

We searched the MEDLINE and Embase databases for epidemiological studies of the associations between exposure to roadway traffic and the risk in adults (older than 18 years of age) of developing dementia, Parkinson's disease, or multiple sclerosis. Studies published in the peer-review literature up to Feb 1, 2016, were included, regardless of the language of publication. We perused the bibliographies of these articles and of previously published reviews. We searched the bibliographic databases using the keywords traffic exposure, mobile source, roadway, proximity or near, air pollution, and with the following health outcomes: dementia; Alzheimer's disease; cognition; Parkinson's disease; multiple sclerosis. A few studies found an association between living close to major roadways and cognitive decline and changes in the brain structure. There is also some evidence linking traffic-related noise and air pollution to cognitive decline and the incidence of dementia, and to a lesser degree, Parkinson's disease. No study has so far investigated the onset of all three major neurodegenerative diseases (dementia, Parkinson's disease, and multiple sclerosis) in association with near-road exposure. Moreover, the few existing studies involved relatively small study populations and nearly half were cross-sectional.

Added value of this study

We report that living close to heavy traffic is associated with increased incidence of dementia. Using the same populations and methods, however, we did not find an association between residential proximity to traffic and Parkinson's disease or multiple sclerosis.

The cause of these major neurodegenerative diseases remains largely unclear. This study sheds important insights into a possible role of near-road exposure on the development of dementia. Our study overcomes several limitations of previous studies, since it has large cohorts comprising almost the entire adult population in Ontario, the most populous province in Canada, and lagged exposure up to 10 years to reduce concerns about reverse causality. With demographic characteristics similar to the USA and many European countries, findings from this study will be highly generalisable to populations in many other regions.

Implications of all the available evidence

Increasing population growth and continuing urbanisation globally has placed many people close to heavy traffic. With the widespread exposure to traffic and growing population with dementia, even a modest effect from near-road exposure can pose an enormous public health burden. This study suggests that improvements in environmental health policies and land use planning aimed at reducing traffic exposure can have considerable potential for prevention of dementia, which would lead to a broad public health implication. This study adds weight to previous observations suggesting that roadway traffic is an important source of environmental stressors that could give rise to neurological disorders and that future investigation targeting the effects of different aspects of traffic such as traffic-related air pollutants and noise on neurological health is merited.

worldwide live close to major roads, we sought to investigate the association between exposure to traffic, measured by residential proximity to major roadways, and the incidence of dementia, Parkinson's disease, and multiple sclerosis in a large population-based cohort in Ontario, Canada.

Methods

Study design

We did a population-based cohort study of all Ontario adults to determine the incidence of dementia, Parkinson's disease, and multiple sclerosis. Eligible participants were, as of April 1, 2001, Ontario residents for 5 years or longer, aged 20–85 years, and Canadian-born. We created the study population using Ontario's Registered Persons Database, a registry of all residents who have ever had health insurance. This database covers virtually all Ontario residents.²⁰

Because dementia and Parkinson's disease onset occurs predominantly in people aged 55 years or older, whereas multiple sclerosis onset is most common in adults younger than 50 years, we separated the study population into two analytical cohorts: individuals aged 20–50 years (multiple sclerosis cohort); and individuals

aged 55–85 years (dementia or Parkinson's disease cohort). We further excluded individuals with any of these three disorders at baseline, yielding a total of 4 372 720 and 2 165 268 participants in each cohort.

The Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, approved the study.

We ascertained incident diagnoses of dementia, Parkinson's disease, and multiple sclerosis using validated databases (see appendix). Details of these databases are available elsewhere.²⁰ These databases have been validated previously using chart review, with sensitivity of 78–84% and specificity of 99–100%.^{21–23} They were created using hospital discharge abstracts from the Canadian Institute for Health Information, physician service claims from the Ontario Health Insurance Plan database, and prescription medication claims from the Ontario Drug Benefits programme database. Hospital, laboratory, and physician services in Ontario are funded by the provincial government through a single-payer universal medicare system that covers virtually all residents.²⁰ Drug coverage is provided to those aged 65 years or older, and social assistance recipients. We linked the cohorts to these databases using encrypted unique identifiers to ascertain incident cases.

See Online for appendix

Residential proximity to roads

We calculated residential proximity to major roadways or highways based on 6-character postal-code addresses in 1996, 5 years before cohort inception. Postal codes in urban areas represent the centroid of the blocks or single large buildings in which cohort members lived. Distance (m) was measured using ArcGIS. Major traffic roads include primary urban roads and arterial roads (ie, a major thoroughfare with medium to large traffic capacity with a combination of controlled access and intersections at grade level) whereas highways include expressways and primary and secondary highways, according to Ontario Government Road Network Data Standards. Consistent with previous studies,^{17,24} we created five distance categories: less than 50 m from major traffic road, 50–100 m, 101–200 m, 201–300 m, and more than

300 m. We also considered a continuous measure of distance.

Covariates

We selected accepted or suspected risk factors for neurodegenerative pathology, including age, sex, pre-existing comorbidities, and socioeconomic status.^{3–5} The comorbidities included traumatic brain injury, diabetes, hypertension, stroke, coronary heart disease, congestive heart failure, and arrhythmia. We ascertained the presence of comorbidities at baseline using hospital discharge abstracts, physician service claims, and validated chronic disease databases (appendix).

Several individual-level socioeconomic status and behavioural factors, such as education, smoking, and physical activity are also implicated in neurological health,^{3–5} but were unavailable. Since neighbourhood-level socioeconomic status is strongly associated with these factors,^{25,26} we derived four neighbourhood-level variables: income quintile, a measure of relative household income accounting for household size and community; percentage of population aged 15 years or older with less than high school education; unemployment rate; and percentage of recent immigrants, using 2001 Canadian Census dissemination area data. A dissemination area (with 400–700 people) is the smallest census geographic area for which census data are disseminated. We further derived neighbourhood-level deprivation based on the Ontario Marginalization Index that quantifies the degree of marginalisation in health and social wellbeing (appendix).

To control for regional differences in the incidence of dementia, Parkinson's disease, and multiple sclerosis, we created a variable for urban residence (yes/no), density of neurologists using the ICES Physician Database to represent accessibility to neurological care, and the latitude of residence given the reported latitude gradient with multiple sclerosis.³ Additionally, we created a dichotomous variable classifying Ontario into the Greater Toronto Area, a densely-populated urban mega-region, and all other areas. Toronto tends to differ from other areas with respect to sociodemographic characteristics, health care access, and population health status.

To explore whether exposure to air pollutants, especially nitrogen dioxide (NO₂) and PM_{2.5} might explain the roadway proximity-outcome association, we obtained long-term measures of PM_{2.5} and NO₂ for all participants (appendix). Briefly, estimates of ground-level concentrations of PM_{2.5} were derived from satellite observations of aerosol optical depth in combination with outputs from a global atmospheric chemistry transport model (GEOS-Chem CTM).²⁷ The PM_{2.5} estimates were further adjusted using information on urban land cover, elevation, and aerosol composition using a geographically weighted regression. We used estimates between 1998 (the earliest year with available data) and 2001 (the year of cohort inception), thus producing four-year mean concentration of PM_{2.5} at a spatial resolution of 1×1 km and covering all North America

	Multiple sclerosis cohort* (n=4 372 720)		Dementia/Parkinson's disease cohort* (n=2 165 268)	
	Subject count	%	Subject count	%
Age at entry (years); mean (SD)	35.9 (8.7)	..	66.8 (8.2)	..
20–29	1 198 499	27.4
30–39	1 475 303	33.7
40–50	1 698 918	38.9
55–64	978 235	45.2
65–74	731 685	33.8
75–85	455 348	21.0
Sex				
Male	2 178 448	49.8	1 013 010	46.8
Female	2 194 272	50.2	1 152 258	53.2
Pre-existing comorbidity†				
Coronary heart disease	21 957	0.5	213 071	9.8
Stroke	6 005	0.2	66 241	3.1
Congestive heart failure	4 687	0.1	120 550	5.6
Diabetes	105 088	2.4	323 544	15.0
Hypertension	295 996	6.8	1 038 119	48.0
Arrhythmia	11 717	0.3	93 495	4.3
Traumatic brain injury	302 869	6.9	90 694	4.2
Area-level risk factors‡				
Low-income cutoff quintile				
Lowest	784 958	18.0	400 839	18.5
Lower middle	867 694	19.8	447 184	20.7
Middle	903 386	20.7	437 336	20.2
Upper middle	915 524	20.9	420 427	19.4
Upper	901 158	20.6	459 482	21.2
Percentage of rural residents	724 024	16.6	410 575	19.0
Percentage of recent immigrants	..	3.6	..	3.3
Percentage ≥15 years of age with less than high school education	..	25.5	..	26.9
Percentage ≥15 years of age without employment	..	6.2	..	6.2

Data are n or %, unless otherwise specified. *Multiple sclerosis cohort comprised all adults aged 20–50 years and dementia/Parkinson's disease cohort comprised all adults aged 55–85 years in Ontario, Canada, in 2001. †In the 10 years before cohort onset. ‡From Canadian Census 2001, at the census dissemination area level.

Table 1: Baseline characteristics of the study population

	Incidence of dementia (n=243611)‡			Incidence of Parkinson's disease (n=31577)‡			Incidence of multiple sclerosis (n=9247)‡		
	HR	95% CI	P _{trend}	HR	95% CI	P _{trend}	HR	95% CI	P _{trend}
Distance† by category									
<50 m	1.07	1.06–1.08	0.0349	1.01	0.98–1.04	0.12	1.02	0.95–1.09	0.72
50–100 m	1.04	1.02–1.05	..	1.01	0.97–1.05	..	0.93	0.86–1.01	..
101–200 m	1.02	1.01–1.03	..	0.99	0.96–1.03	..	1.01	0.95–1.08	..
201–300 m	1.00	0.99–1.01	..	0.99	0.96–1.02	..	1.01	0.94–1.08	..
>300 m	Reference	Reference	Reference
Log(distance)§	0.91	0.89–0.92	..	0.99	0.97–1.01	..	1.00	0.98–1.02	..

Cox proportional hazards model with age as the time-scale, stratified by an indicator for living in the Greater Toronto Area or not, adjusted for sex, history of diabetes, hypertension, coronary heart disease, stroke, congestive heart failure, arrhythmia, and traumatic brain injury, income quintile, urban/rural indicator, census division-level unemployment rate, education, recent immigrants, as well as the subtraction of these variables at the census dissemination level from their census division. For multiple sclerosis, the model was also adjusted for latitude. †Major traffic roads include primary urban roads and arterial roads whereas highways include expressways and primary and secondary highways, as defined by Ontario Government Road Network Data Standards. ‡Incidence of dementia and Parkinson's disease was analysed among all adults aged 55–85 years (dementia/Parkinson's disease cohort) whereas incidence of multiple sclerosis was analysed among all adults aged 20–50 years (multiple sclerosis cohort). §Distance was fitted as a continuous variable, using natural logarithm of distance. Hazard ratios (HRs) expressed per IQR increase in distance (dementia/Parkinson's disease cohort: 310 m and multiple sclerosis cohort: 320 m).

Table 2: Hazard ratios and 95% CIs for the associations between residential proximity to major roadways in 1996 and the risks of incident dementia, Parkinson's disease, and multiple sclerosis in Ontario, during the follow-up period 2001–12

below 70°N, which includes all of Ontario. These satellite-based estimates of PM_{2.5} closely agree with ground measurements at fixed-site monitoring stations across North America (R² 0.82, n=1440).²⁷ Similarly, we derived long-term exposure to NO₂ from a national land-use regression (LUR) model developed from Environment Canada's National Air Pollution Surveillance Network monitoring data, 2005–11 satellite NO₂ estimates, area of industrial land use, road length, and mean summer rain fall.²⁸ The estimates were further calibrated by incorporating local-scale variations of NO₂ from vehicle emissions by applying spatially-varying multipliers that represented distance-decay gradient in NO₂. The final LUR model explained 73% of the variation in annual 2006 measurements of NO₂, with a root mean square error of 2.9 parts per billion (ppb).²⁸ The resulting LUR NO₂ estimates were available for each year between 1998 and 2001, after applying temporal adjustment.

Statistical analysis

We used Cox proportional hazards models with age as the time-scale to assess the relationship between residential proximity to major roadways and the incidence of dementia, Parkinson's disease, and multiple sclerosis. For each outcome, follow up time (in days) was measured from April 1, 2001 until diagnosis date, ineligibility for provincial health insurance, death, or March 31, 2012.

Separate models were developed for each disease. All models were stratified by region (living in Toronto or not), and adjusted for sex, comorbidities, urban residency, and neighbourhood-level income, education, unemployment, and immigration status. To adjust for regional variations in the neighbourhood-level variables across Ontario, we included them as the average for each census division (equivalent to county), and as the difference between the

values for each census dissemination area and the census division mean. We further adjusted for latitude for multiple sclerosis cohort. The analyses were repeated using distance as categorical and continuous variables.

We routinely tested for deviation from the proportional hazards assumption by adding the cross-product of each variable with the natural logarithm of the time variable, but we did not find any violation of this assumption (p>0.05). We calculated adjusted hazard ratios (HRs) and 95% CIs for each category of roadway proximity compared with the furthest category (>300 m). Linear trend was assessed by assigning the median distance (in natural log) to each category and fitting the term as a continuous variable in a regression model. In analyses with distance as a continuous variable, we considered the natural log of distance because this exposure has been linearly related to mortality and morbidity outcomes in Ontario and elsewhere.^{17,24}

Sensitivity analyses

We controlled for access to neurologists, deprivation index, and a North/South indicator (appendix). We also adjusted for a linear term for time to account for potential changes in the risk of the three disorders over time.

We assessed whether HR might be influenced by any spatial dependence among participants. We fitted models with a frailty term for census division (ie, county) to account for the possibility that participants in the same community could share similar risk factors than those living in different locations. We assumed a gamma distribution for the frailties, with an exchangeable correlation structure within county.

We assessed the potential influence of unmeasured individual-level socioeconomic status and behavioural variables, especially education, smoking, obesity, and

	Main model ‡		Indirectly adjusted for smoking		Further indirectly adjusted for BMI, physical activity		Further indirectly adjusted for education	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Distance† by category								
<50 m	1.07	1.06–1.08	1.06	1.05–1.08	1.06	1.05–1.08	1.06	1.05–1.08
50–100 m	1.04	1.02–1.05	1.03	1.02–1.05	1.03	1.02–1.05	1.04	1.02–1.06
101–200 m	1.02	1.01–1.03	1.01	1.00–1.02	1.01	1.00–1.03	1.02	1.01–1.04
201–300 m	1.00	0.99–1.01	1.00	0.98–1.01	1.00	0.99–1.02	1.01	0.99–1.03
>300 m	Reference	..	Reference	..	Reference	..	Reference	..
Log (distance)§	0.91	0.89–0.92	0.92	0.90–0.93	0.92	0.90–0.93	0.92	0.90–0.93

Indirect adjustment for smoking, body-mass index (BMI), physical activity, and attained education. Data of smoking, BMI, physical activity, and educational attainment were obtained from Ontario respondents to the 1996 cycle of National Population Health Survey and the 2000–01, 2003 cycles of Canadian Community Health Survey, and who were 50 to 85 years old at the time of the surveys (n=16 441). †Major traffic roads include primary urban roads and arterial roads whereas highways include expressways and primary and secondary highways, as defined by Ontario Government Road Network Data Standards. ‡Cox proportional hazards model with age as time axis, stratified by an indicator for living in the Greater Toronto Area or not, adjusted for sex, history of diabetes, hypertension, coronary heart disease, stroke, congestive heart failure, arrhythmia, and traumatic brain injury, income quintile, urban/rural indicator, census division-level unemployment, education, and recent immigrants, as well as the subtraction of these variables at the census dissemination level from their census division. §Distance was fitted as a continuous variable, using natural logarithm of distance. The hazard ratios were expressed per interquartile-range increase in distance (310 m).

Table 3: Hazard ratios and 95% CI for associations between residential proximity to major roadways in 1996 and the risk of incident dementia in Ontario during the follow-up period 2001–12

	Parkinson's disease				Multiple sclerosis			
	Main model‡		Indirectly adjusted for smoking and physical activity		Main model‡		Indirectly adjusted for smoking	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Distance† by category								
<50 m	1.01	0.98–1.04	1.01	0.98–1.05	1.02	0.95–1.09	1.00	0.93–1.07
50–100 m	1.01	0.97–1.05	1.02	0.98–1.06	0.93	0.86–1.01	0.93	0.86–1.01
101–200 m	0.99	0.96–1.03	0.99	0.96–1.03	1.01	0.95–1.08	1.00	0.93–1.06
201–300 m	0.99	0.96–1.02	1.00	0.97–1.03	1.01	0.94–1.08	1.00	0.93–1.07
>300 m	Reference	..	Reference	..	Reference	..	Reference	..
Log (distance)§	0.99	0.97–1.01	1.00	0.98–1.02	1.00	0.98–1.02	0.99	0.97–1.02

Indirect adjustment for smoking and physical activity for Parkinson's disease, and for smoking for multiple sclerosis. Data of smoking and physical activity were obtained from Ontario respondents to the 1996 cycle of National Population Health Survey and the 2000–01 and 2003 cycles of Canadian Community Health Survey. For Parkinson's disease, respondents aged 50–85 years at the time of the surveys were included (n=16 441) and for multiple sclerosis, those who were 20–55 years old were included (n=31 635). †Major traffic roads include primary urban roads and arterial roads whereas highways include expressways and primary and secondary highways, as defined by Ontario Government Road Network Data Standards. ‡Cox proportional hazards model with age as time axis, stratified by an indicator for living in the Greater Toronto Area or not, adjusted for sex, history of diabetes, hypertension, coronary heart disease, stroke, congestive heart failure, arrhythmia, and traumatic brain injury, income quintile, urban/rural indicator, census division-level unemployment, education, and recent immigrants, as well as the subtraction of these variables at the census dissemination level from their census division. For multiple sclerosis, the model was also adjusted for latitude. §Distance was fitted as a continuous variable, using natural logarithm of distance. HRs expressed per interquartile-range increase in distance (dementia/Parkinson's disease cohort: 310 m and multiple sclerosis cohort: 320 m). ||For Parkinson's disease, $p_{trend}=0.38$ and for multiple sclerosis, $p_{trend}=0.53$.

Table 4: Hazard ratios and 95% CI for associations between residential proximity to major roadways in 1996 and risk of incident Parkinson's disease and multiple sclerosis in Ontario, during the follow-up period 2001–12

physical activity on our results. To do this, we used a method to mathematically adjust HR for these variables while simultaneously controlling for all variables available in the model (ie, age, sex, comorbidities, and socioeconomic status; appendix). Details of this method are presented elsewhere.²⁹ Briefly, this method requires spatial associations between the unmeasured and observed variables from an auxiliary dataset. Following previous Canadian studies,³⁰ we obtained the relationships using data from the 1996–97 cycle of the National Population Health Survey and the 2000–01 and 2003 cycles of the Canadian Community Health Survey,

which constituted a representative sample of the study cohorts (appendix). This information along with estimated associations between these unmeasured variables and incident dementia, Parkinson's disease, and multiple sclerosis from the literature, were used to estimate their effect on HR. Based on systematic reviews of dementia, Parkinson's disease, and multiple sclerosis, we considered all four variables in our analysis with dementia, smoking and physical activity with Parkinson's disease, and smoking with multiple sclerosis (appendix). Furthermore, we additionally adjusted for PM_{2.5} and NO₂, excluded events occurring in the first 2 and 5 years

during follow-up to lag exposure up to 10 years, excluded people residing in long-term care facilities (often located near major roadways) at baseline, and restricted the dementia/Parkinson's disease cohort to those aged 65 years or older because drug information was unavailable for younger adults. Lastly, we further adjusted for rurality index and neighbourhood-level percentage of visible minority, and restricted the analysis to people who never moved since 1996, to urban residents, and to residents of six major urban centres in Ontario (Toronto, Hamilton, Ottawa, London, Windsor, and Sarnia) (appendix).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The multiple sclerosis cohort comprised 46.7 million person-years of observations and the dementia/Parkinson's disease cohort contributed 20.1 million person-years. At baseline, the mean age was 35.9 years (SD 8.7 years) for the multiple sclerosis cohort and 66.8 years (8.2 years) for the dementia/Parkinson's disease cohort (table 1). Of the multiple sclerosis cohort, 50% were male, 17% were rural residents, 2% had diabetes, and 7% had hypertension, whereas 47% of the dementia/Parkinson's disease cohort were male, 19% were rural residents, 15% had diabetes, and 48% had hypertension. Average unemployment among census dissemination areas was 6% and the mean percentage of population with less than high school education was about 26% in both cohorts.

Nearly half of the cohorts lived within 200 m from a major road and 95% were within 1000 m (appendix). Of the cohorts, the average concentration of $PM_{2.5}$ according to participants' residences in 1996, 5 years before cohort inception, was $9.7 \mu\text{g}/\text{m}^3$ (range $1.3\text{--}19.8 \mu\text{g}/\text{m}^3$), while the average concentration of NO_2 was 15.4 ppb ($2.2\text{--}62.0$ ppb). Between 2001–12, we identified 243611 incident cases of dementia, 31577 incident cases of Parkinson's disease, and 9247 incident cases of multiple sclerosis.

In both categorical and continuous analyses, living closer to a major road was associated with increased incidence of dementia, with fully adjusted HR of 1.07 (95% CI 1.06–1.08) for people living less than 50 m, 1.04 (1.02–1.05) for people living 50–100 m, 1.02 (1.01–1.03) for people living 101–200 m, and 1.00 (0.99–1.01) for people living 201–300 m away from a major roadway versus more than 300 m from a major roadway ($P_{\text{trend}}=0.0349$; table 2). An interquartile-range increase in residential proximity to a major road was associated with a 9% (95% CI 8–11%) lower incidence of dementia. In contrast, there was no

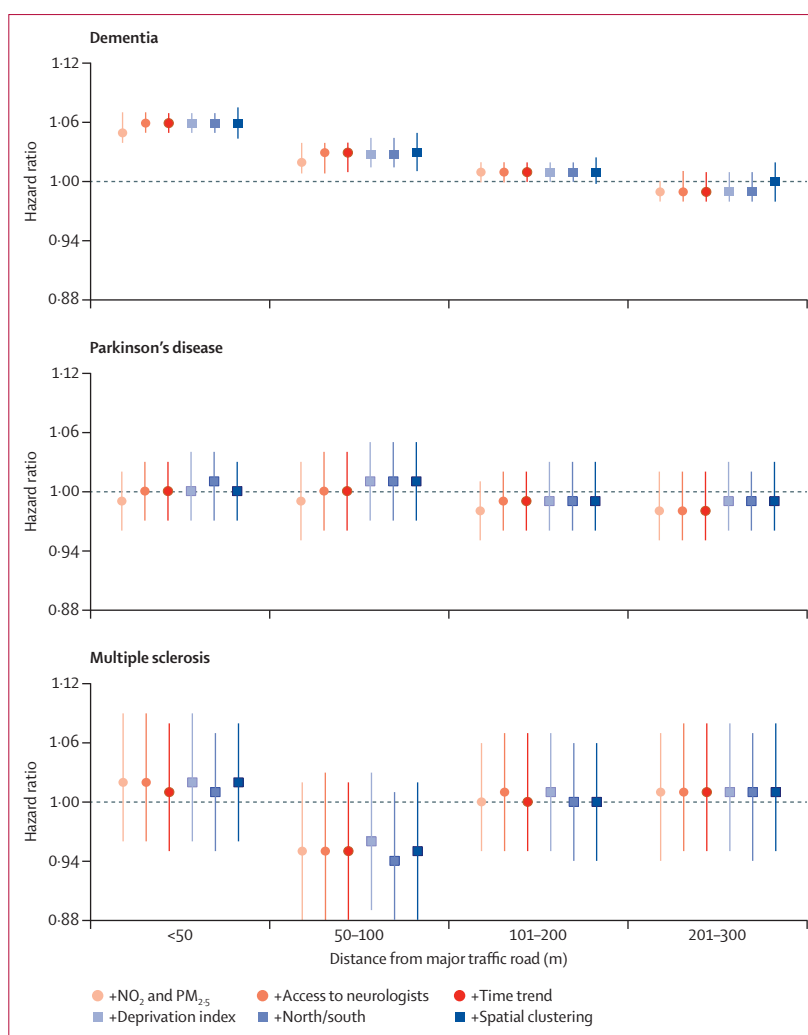


Figure 1: Estimated associations between residential proximity to major roadways in 1996 and the risk of incident dementia, Parkinson's disease, multiple sclerosis in Ontario, 2001–12

Measured by six sensitivity analyses to further control for potential confounding factors. Model further adjusted for exposure to NO_2 and $PM_{2.5}$, access to neurologists, time trend, deprivation, an indicator for North/South Ontario, and a frailty term to account for potential spatial clustering.

evidence linking traffic proximity to Parkinson's disease or multiple sclerosis (HR 1.00 for both; table 2).

The association between traffic exposure and dementia was insensitive to additional controls for smoking, obesity, physical activity, and education (HR 1.06 for living <50 m away from a major road, 1.04 for 51–100 m, and 1.02 for 101–200 m; table 3). Similarly, the associations between traffic exposure and Parkinson's disease and multiple sclerosis remained unchanged after adjusting for smoking and physical activity (table 4).

Further adjustment for access to neurologists, deprivation, time trend, and a North/South indicator did not alter the associations, nor did adding a frailty term in the survival model to account for potential spatial clustering (figure 1). Adjustment for NO_2 and $PM_{2.5}$ modestly attenuated the association between traffic

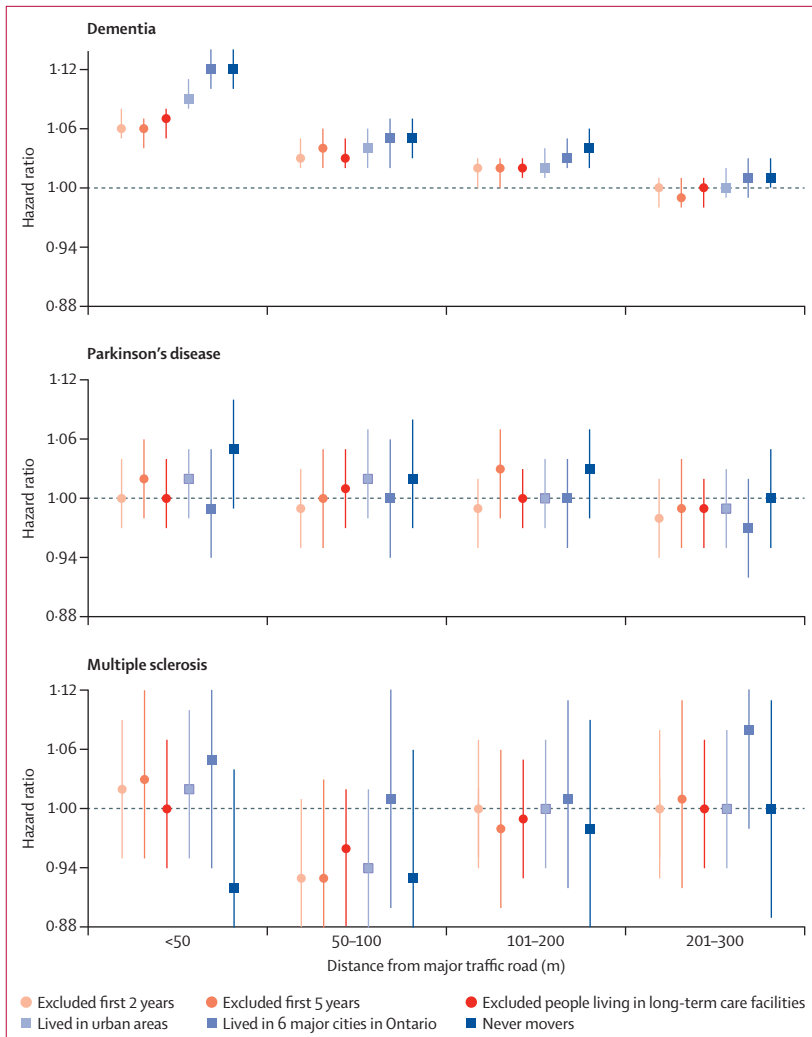


Figure 2: Association between residential proximity to major roadways in 1996 and the risk of incident dementia, Parkinson's disease, multiple sclerosis in Ontario, 2001-12

Hazard ratios and 95% CIs from six additional sensitivity analyses (excluding first 2 years of follow-up, excluding first 5 years of follow-up, excluding people living in long-term care facilities, restricting to urban residents, restricting to six major cities in Ontario, and restricting to those who did not move after 1996).

proximity and dementia (HR 1.05 for living <50 m away from a major road and HR 1.02 for 51–100 m away from a major road vs 1.07 and 1.04 without adjustment). Importantly, NO₂ was significantly associated with dementia, whereas PM_{2.5} was associated with both dementia and Parkinson's disease (appendix).

In sensitivity analyses, the magnitude of associations were similar after further excluding the first 2 and 5 years of follow-up, restricting to people aged 65 years or older, excluding those living in long-term care facilities, or considering other sensitivity analyses (figure 2 and appendix). However, the association between living less than 50 m from a major roadway and dementia appeared stronger among participants who lived in urban areas, who lived in one of the six major cities, or who never moved (HR 1.09–1.12, depending on the analysis).

Discussion

In this large population-based cohort, living near major roadways was associated with increased dementia incidence. The associations seemed stronger among urban residents, especially those living in major urban centres and those who never moved. Although the increase in risk might appear moderate (eg, HRs varied from 1.07–1.12 for living <50 m away from a major road, depending on the region), this translates to 7–11% of dementia cases in patients who live near major roads attributable to traffic exposure (appendix). The associations were robust to various sensitivity analyses, except for additional adjustment for PM_{2.5} and NO₂ which led to a modest attenuation. It is noteworthy that both NO₂ and PM_{2.5} were positively associated with dementia. Lastly, we found no association between roadway proximity and incidence of Parkinson's disease or multiple sclerosis.

To our knowledge, this is the first study to investigate the onset of three major neurodegenerative diseases in association with near-roadway exposure. Previous studies have linked living near roadways to cognitive decline in cohorts of older adults in Boston MA, USA¹⁸ and in the Ruhr area, Germany,¹⁹ and to smaller white matter hyperintensity volume in the Framingham Offspring cohort.¹⁷ Living near major roads substantially increases an individual's exposure to traffic-related air pollution (eg, ultrafine particles, nitrogen oxides, and particles from wear of tyres and friction materials), and noise.¹⁷ Although the mechanisms through which traffic exposure might affect brain health are unknown, systemic inflammation arising from traffic-related air pollution is probably important. In studies of both experimental animals and in autopsy samples of sudden accidental deaths in human beings, particulates and diesel exhaust provoke oxidative stress and systemic inflammatory responses, disrupt the blood-brain barrier, precipitate A β peptides, and activate microglia.^{8,9} Ultrafine particles have also been found in the olfactory bulb and the frontal cortical areas in the brain of highly exposed dogs and human beings.⁸ Furthermore, emerging epidemiologic evidence relates nitrogen oxides and black carbon, markers for traffic-related pollution, to dementia incidence¹² and cognitive impairment.¹⁴ We observed that exposures to NO₂ and PM_{2.5} were related to dementia and that adjusting for these two pollutants attenuated its association with roadway proximity, suggesting that the effect of traffic exposure might, at least in part, operate through this mechanism. Given the potentially significant implications of exposure to traffic-related pollutants on dementia risk, understanding their effects merit further investigation.

The fact that PM_{2.5} and NO₂ did not fully explain the near-road effect on dementia suggests that additional pollutants or other factors such as noise might play a role. Although we were unable to directly examine these factors, traffic-related noise has been linked to cognitive

impairment in a cohort in Germany.¹³ In rat models, noise exposure directly impaired cognition.¹¹ Additionally, sleep loss from noise contributes to sleep fragmentation, which is associated with reduced cognition.⁵ Living near busy roads might also reduce physical activity, which could subsequently affect neurological health. However, we found little change in our results after indirect adjustment for this variable.

Compared with dementia, less is known about the effect of traffic exposure on Parkinson's disease and multiple sclerosis. Only three studies have examined the relationship between traffic exposure and Parkinson's disease: a positive association between NO₂ and incident Parkinson's disease was reported in a case-control study in Denmark,¹⁵ whereas in another case-control study in the USA, no association with NO₂ was found.³¹ Additionally, in a cross-sectional study in Ontario, Parkinson's disease prevalence was not associated with roadway proximity nor NO₂.³² For multiple sclerosis, one time-series study found a relationship between daily hospital admissions and particulate pollution,³³ but no studies have assessed the effect of living close to traffic. In this study, we observed an association only between traffic proximity and dementia, which might be attributable to relatively few cases of Parkinson's disease and multiple sclerosis. Another possibility is that traffic exposure could augment neurodegeneration through pathways that are related to dementia but not Parkinson's disease or multiple sclerosis.³⁻⁵

Our study has some limitations. First, we could not identify undiagnosed cases of dementia, Parkinson's disease, and multiple sclerosis. However, the estimates were unchanged when we adjusted for access to neurologists, a North/South indicator, deprivation, and time trends. With universal health care in Ontario, incomplete diagnosis might lead to underestimation of the true effect because this measurement error was probably independent of the exposure.

Second, we did not have information on medications that might potentially influence dementia risk (eg, anti-inflammatory medication and NSAIDs), although it is unclear whether these factors would be associated with traffic exposure. Furthermore, we lacked information on individual socioeconomic status and behavioural variables. To control for these unmeasured variables, we adjusted for neighbourhood socioeconomic status and comorbidities. Since neighbourhood socioeconomic status is strongly associated with individual socioeconomic status and behavioural variables,^{25,26} and comorbidities and neurodegenerative diseases share some common behavioural factors, adjusting for these variables should reduce the influence of these unmeasured variables on HR (appendix). We further controlled indirectly for these variables, and found similar results. Although we cannot rule out residual confounding, the null findings for Parkinson's disease and multiple sclerosis do not support this possibility.

Third, our exposure assessment was based on postal-code addresses, which do not completely reflect personal exposure. PM_{2.5} is a complex mixture with a secondary aerosol component that might not originate from vehicle emissions. Finally, roadway proximity does not account for traffic density and meteorological conditions that might influence exposure to air pollution and noise. Given the inherent imprecision of this exposure, our assessment of near-road exposure was probably subject to non-differential misclassification that probably attenuated our results.

The strengths of this study include the large cohorts made up of almost the entire adult population in Ontario. The many cases ascertained from validated registries enabled us to investigate fine-scale changes in traffic exposure and to examine the effect from exposures lagged up to 10 years. Our study also benefited from quantifying and comparing the effects on three major neurodegenerative diseases from traffic exposures using the same methods. Furthermore, the availability of detailed information on medical and residential history allowed us to control for important risk factors (eg, head trauma) and assess the influence of residential mobility.

Conclusions

In this large cohort, living near major roadways was associated with higher incidence of dementia, but not Parkinson's disease or multiple sclerosis. Given the potentially significant implications of traffic exposure on dementia risk, understanding the effect of different aspects of traffic merits further investigation.

Contributors

HC, RTB, JCK, PJV, KT, BJM, RC, and BJ contributed to the study design. HC, ASW, and AK prepared and cleaned the data. HC, AvD, PH, and RVM contributed to the exposure assessment. RTB provided substantial scientific input in statistical methods and interpretation of the results. HC, RTB, JCK, PJV, KT, BJM, ASW, and AK contributed to the data analyses. HC took the lead in drafting the manuscript. All authors contributed to interpretation of data, provided critical revisions to the manuscript, and approved the final draft.

Declaration of interests

We declare no competing interests.

Acknowledgements

This study was supported by Public Health Ontario (PHO) and the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and information compiled and provided by Canadian Information Health Institute (CIHI). The opinions, results, and conclusions reported in this article do not necessarily represent the views of ICES, PHO, MOHLTC, or CIHI.

References

- 1 Prince M, Guerchet M, Prina M. The epidemiology and impact of dementia: current state and future trends. Geneva, World Health Organization, 2015. http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf (accessed June 18, 2016).
- 2 World Health Organization. Neurological disorders: public health challenges. Geneva, World Health Organization, 2006. http://www.who.int/mental_health/neurology/neurodiso/en/ (accessed June 18, 2016).

- 3 O'Gorman C, Lucas R, Taylor B. Environmental risk factors for multiple sclerosis: a review with a focus on molecular mechanisms. *Int J Mol Sci* 2012; **13**: 11718–52.
- 4 Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 2011; **26** (suppl 1): S1–58.
- 5 Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement* 2015; **11**: 718–26.
- 6 Block ML, Elder A, Auten RL, et al. The outdoor air pollution and brain health workshop. *Neurotoxicology* 2012; **33**: 972–84.
- 7 Tzivian L, Winkler A, Dlugaj M, et al. Effect of long-term outdoor air pollution and noise on cognitive and psychological functions in adults. *Int J Hyg Environ Health* 2015; **218**: 1–11.
- 8 Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* 2008; **36**: 289–310.
- 9 Block ML, Wu X, Pei Z, et al. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. *FASEB J* 2004; **18**: 1618–20.
- 10 Calderon-Garciduenas L, Vojdani A, Blaurock-Busch E, et al. Air pollution and children: neural and tight junction antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. *J Alzheimers Dis* 2015; **43**: 1039–58.
- 11 Cui B, Wu M, She X, Liu H. Impulse noise exposure in rats causes cognitive deficits and changes in hippocampal neurotransmitter signaling and tau phosphorylation. *Brain Res* 2012; **1427**: 35–43.
- 12 Oudin A, Forsberg B, Adolfsson AN et al. Traffic-related air pollution and dementia incidence in northern Sweden: a longitudinal study. *Environ Health Perspect* 2016; **124**: 306–12.
- 13 Tzivian L, Dlugaj M, Winkler A, et al. Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: a cross-sectional analysis of the Heinz Nixdorf recall study. *Environ Health Perspect* 2016; **124**: 1361–68.
- 14 Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A III, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect* 2011; **119**: 682–87.
- 15 Ritz B, Lee PC, Hansen J, et al. Traffic-related air pollution and Parkinson's disease in Denmark: a case-control study. *Environ Health Perspect* 2016; **124**: 351–56.
- 16 Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis* 2015; **44**: 573–84.
- 17 Wilker EH, Preis SR, Beiser AS, et al. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. *Stroke* 2015; **46**: 1161–66.
- 18 Wellenius GA, Boyle LD, Coull BA, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston Study. *J Am Geriatr Soc* 2012; **60**: 2075–80.
- 19 Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res* 2009; **109**: 1004–11.
- 20 Chen H, Kwong JC, Copes R, et al. Cohort Profile: The Ontario population health and environment cohort (ONPHEC). *Int J Epidemiol* 2016; published online April 20. DOI:10.1093/ije/dyw030.
- 21 Butt DA, Tu K, Young J, et al. A validation study of administrative data algorithms to identify patients with Parkinsonism with prevalence and incidence trends. *Neuroepidemiology* 2014; **43**: 28–37.
- 22 Jaakkimainen RL, Bronskill SE, Tierney MC, et al. Identification of physician-diagnosed Alzheimer's disease and related dementias in population-based administrative data: a validation study using family physicians' electronic medical records. *J Alzheimers Dis* 2016; **54**: 337–49.
- 23 Widdifield J, Ivers NM, Young J, et al. Development and validation of an administrative data algorithm to estimate the disease burden and epidemiology of multiple sclerosis in Ontario, Canada. *Mult Scler* 2015; **21**: 1045–54.
- 24 Chen H, Goldberg MS, Burnett RT, Jerrett M, Wheeler AJ, Villeneuve PJ. Long-term exposure to traffic-related air pollution and cardiovascular mortality. *Epidemiology* 2012; **24**: 35–43.
- 25 Janssen I, Boyce WF, Simpson K, Pickett W. Influence of individual- and area-level measures of socioeconomic status on obesity, unhealthy eating, and physical inactivity in Canadian adolescents. *Am J Clin Nutr* 2006; **83**: 139–45.
- 26 Gan WQ, Davies HW, Koehoorn M, Brauer M. Association of long-term exposure to community noise and traffic-related air pollution with coronary heart disease mortality. *Am J Epidemiol* 2012; **175**: 898–906.
- 27 van Donkelaar A, Martin RV, Spurr RJ, Burnett RT. High-resolution satellite-derived PM_{2.5} from optimal estimation and geographically weighted regression over North America. *Environ Sci Technol* 2015; **49**: 10482–91.
- 28 Hystad P, Setton E, Cervantes A, et al. Creating national air pollution models for population exposure assessment in Canada. *Environ Health Perspect* 2011; **119**: 1123–29.
- 29 Shin HH, Cakmak S, Brion O, et al. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. *Environ Res* 2014; **134**: 482–87.
- 30 Crouse DL, Peters PA, Hystad P, et al. Ambient PM_{2.5}, O₃, and NO₂ exposures and associations with mortality over 16 years of follow-up in the Canadian census health and environment cohort (CanCHEC). *Environ Health Perspect* 2015; **123**: 1180–86.
- 31 Liu R, Young MT, Chen JC, Kaufman JD, Chen H. Ambient air pollution exposures and risk of Parkinson disease. *Environ Health Perspect* 2016; published online June 10, 2016. DOI:10.1289/EHP135.
- 32 Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. *Environ Res* 2007; **104**: 420–32.
- 33 Angelici L, Piola M, Cavalleri T, et al. Effects of particulate matter exposure on multiple sclerosis hospital admission in Lombardy region, Italy. *Environ Res* 2016; **145**: 68–73.