Letters

COMMENT & RESPONSE

Trends in the Incidence of Parkinson Disease

To the Editor We read with interest the article by Savica et al,[1] who described an increase in the incidence rate of parkinsonism in the Rochester Epidemiology Project between 1976 and 2005. This finding contradicts our recently reported observation that the incidence rate of parkinsonism was lower in a subcohort of the Rotterdam Study that was followed up between 2000 and 2011 compared with a subcohort that was followed up between 1990 and 2000.[2] Similarly, a UK primary care study previously reported a significant decline in Parkinson disease (PD) incidence rates between 1999 and 2009.[3]

Savica et al[1] hypothesized that the changes observed in the Rochester Epidemiology Project could be attributed to a decrease in the prevalence of smoking in the second half of the 20th century, but they were unable to test this hypothesis in their cohort. Within the Rotterdam Study, we assessed smoking habits at baseline of both subcohorts (1990 and 2000). As expected, we observed that the age- and sex-adjusted prevalence of current smoking was lower across all ages (55-106 years) in the subcohort that started in 2000.[2]

During follow-up, incident parkinsonism was diagnosed in 182 of 6752 persons in the subcohort that started in 1990, and in 28 of 2440 persons in the subcohort that started in 2000. The age- and sex-adjusted incidence rate (IR) of parkinsonism for smokers was similar in both subcohorts (IR, 0.63; 95% CI,0.43-0.91 in the 1990 subcohort; IR, 0.61; 95% CI, 0.27-1.44 in the 2000 subcohort). The age- and sex-adjusted incidence rate ratio (IRR) for parkinsonism of persons in the 2000 subcohort vs the 1990 subcohort was 0.55 (95% CI, 0.36-0.81). After additional adjustment for smoking status, the IRR remained virtually unchanged (IRR, 0.57; 95% CI, 0.37-0.84). Unfortunately, the small number of PD cases in the 2000 subcohort prevented PD-specific analyses on the effect of smoking. We conclude that it is unlikely that the decline in smoking prevalence drove a change in the incidence of parkinsonism in the Rotterdam Study.

The discrepant findings of the study by Savica et al[1] compared with previous studies, including the Rotterdam Study, highlight the lack of insight on causality of risk factors for parkinsonism and PD. For smoking in particular, causality of its inverse association with the risk for parkinsonism and PD remains highly contentious,[4] and the inference that the increase in parkinsonism incidence in the Rochester Epidemiology Project can be attributed to a decline in smoking may shift focus from other putative etiological factors. To better understand factors that drive differential trends in the incidence of parkinsonism across populations, there is an urgent need for cross-cohort collaboration, similar to recently initiated efforts for dementia.[5]

Sirwan K. L. Darweesh, MD, MSc
Peter J. Koudstaal, MD, PhD
M. Arfan Ikram, MD, PhD

Author Affiliations: Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands (Darweesh, Ikram); Department of Neurology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands (Koudstaal).

Corresponding Author: M. Arfan Ikram, MD, PhD, Department of Epidemiology, Erasmus MC University Medical Center, Dr Molewaterplein 50, 3015 GE, Rotterdam, the Netherlands (m.a.ikram@erasmusmc.nl).

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1. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time trends in the incidence of Parkinson disease. *JAMA Neurol*. 2016;73(8):981-989.

2. Darweesh SK, Koudstaal PJ, Stricker BH, Hofman A, Ikram MA. Trends in the incidence of Parkinson disease in the general population: the Rotterdam Study. *Am J Epidemiol*. 2016;183(11):1018-1026.

3. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. *J Neurol*. 2013;260(5):1351-1357.

4. Hershey LA, Perlmutter JS. Smoking and Parkinson disease: where there is smoke there may not be fire. *Neurology*. 2014;83(16):1392-1393.

5. Orrell M, Brayne C; INTERDEM (early detection and timely INTERvention in DEMentia); Alzheimer Europe; Alzheimer's Disease International; European Association of Geriatric Psychiatry. Dementia prevention: call to action. *Lancet*. 2015;386(10004):1625.

To the Editor In a study published in *JAMA Neurology*, Savica et al[1] aimed to investigate the incidence of Parkinson disease (PD) through a retrospective study related to the 30-year period between 1976 and 2005. Interestingly, they found a statistically significant increment of the incidence of PD in men 70 years or older. However, the increment was not significant in the women's group. This finding is in line with the previous prediction of an increase of incidence of PD in the United States as a consequence of the reduction of smoking considered a protective risk factor.[2] However, Rocca et al[3] did not find a particular trend in a previous US PD population investigated over a 15-year period (1976-1990). On the contrary, Horsfall et al[4] found a 6% decline in incidence in a UK PD population between 1999 and 2009. However, the authors were cautious in the interpretation of their surprising results because there is the possibility that they represented changes in diagnosis and/or coding rather than a true decline in incidence. Of note, the only epidemiological data consistent over these different studies is the sex difference with the higher representation of male patients. The conflicting results in the same country as well as in a different population clearly show to scientists and clinicians that other potential environmental and genetic factors may be responsible for the incidence of PD and the explanation cannot be restricted just to smoking. Indeed,

a number of environmental risk factors have been previously pointed out including alcohol, elevated urate level, pesticides, and head injury.[5]

Overall, the findings of Savica et al[1] may be explained with an improved diagnostic process in the contest of the neurodegenerative disease but the higher incidence is found in the male group compared with the female group in the same population, and this is completely in line with the previous literature. These data supported a genuine trend of the incidence, which cannot be supported with the improved diagnostic tools. However, it should be confirmed in other populations in the European Union and United States with a systematic investigation of related sociodemographic and geographic factors.

What is behind the incidence of PD? This is the question for future investigation in PD research. Detailed multicenter assessments of the different factors involved in the pathogenesis of neurodegeneration of PD as well as the development of biomarkers for early diagnosis are needed to resolve the remaining conundrums.

Antonella Macerollo, MD
Jui-Cheng Chen, MD, PhD

Author Affiliations: Sobell Department, Institute of Neurology, University College of London, London, England (Macerollo); School of Medicine, College of Medicine, China Medical University, Taichung City, Taiwan (Chen); Neuroscience Laboratory, Department of Neurology, China Medical University Hospital, Taichung, Taiwan (Chen).

Corresponding Author: Antonella Macerollo, MD, Sobell Department, Institute of Neurology, University College of London, 33 Queen Square, London, England (a.macerollo@ucl.ac.uk).

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1. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time trends in the incidence of Parkinson disease. *JAMA Neurol*. 2016;73(8):981-989.

2. Morozova N, O'Reilly EJ, Ascherio A. Variations in gender ratios support the connection between smoking and Parkinson's disease. *Mov Disord*. 2008;23(10):1414-1419.

3. Rocca WA, Bower JH, McDonnell SK, Peterson BJ, Maraganore DM. Time trends in the incidence of parkinsonism in Olmsted County, Minnesota. *Neurology*. 2001;57(3):462-467.

4. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. *J Neurol*. 2013;260(5):1351-1357.

5. Noyce AJ, Lees AJ, Schrag AE. The prediagnostic phase of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2016;87(8):871-878.

In Reply We appreciate the comments expressed by Darweesh and colleagues and by Macerollo and Chen concerning our article on time trends for Parkinson disease (PD) in Olmsted County, Minnesota.[1] Both groups of authors challenged the attribution of the increasing trend in the incidence of PD to a declining trend in cigarette smoking over time. They also called for an international collaborative research effort to identify risk and protective factors for PD.

The contrasting findings from the Rotterdam Study and from our study suggest that the risk factors for PD may vary across countries, by sex, and over time.[2] To complicate the landscape, 1 additional study in the United Kingdom and 1 in Taiwan suggested a possible decline in the risk for PD.[3,4] By contrast, a second study in Taiwan showed an increase in the incidence rate between 2002 and 2009.[5] At this point, we have 5 studies from 4 distinct countries and 3 continents showing results in either direction.

Our study combined 2 incidence studies conducted in the same population for 1976 to 1990 (earlier study) and 1991 to 2005 (more recent study). We have conducted extensive studies of risk and protective factors in the earlier segment of the incidence study (1976-1990).[6] However, because of insufficient funding, we were unable to collect data on smoking, pesticide exposure, or other risk factors in the more recent segment of our study (1991-2005). Therefore, at this time, we are unable to link patients with incident PD to specific risk or protective factors over the entire 30 years of the combined study.

We agree that the association between smoking and reduced risk for PD may not be causal. Avoidance of smoking initiation early in life or ease of smoking cessation later in life may be markers of a preexisting predisposition to PD (cause-effect inversion). Therefore, other environmental risk factors (eg, pesticides and air, water, or soil pollutants) or behavioral risk factors (eg, alcohol, coffee, diet, exercise, or head trauma) may be more important. Interestingly, most of these environmental or behavioral risk factors have a different frequency or a different effect in men and women.[6]

Our finding of a birth cohort effect may also be of interest in interpreting the trend. Men born in the decade from 1915 to 1924 experienced an increased risk for PD compared with men born in other birth decades, both before and after. A similar trend was also observed for women, but the analyses did not reach statistical significance.[1] This birth cohort effect is probably not in support of an effect of smoking on the trend, but it may instead suggest exposures that took place during intrauterine life or in early childhood (eg, infections, toxic exposures, or dietary deficiencies).[1] We agree with Darweesh and colleagues and with Macerollo and Chen that new studies are needed to clarify the risk or protective factors for PD, recognizing that these factors may vary across populations, by sex, and over time. We also note that it is currently difficult to obtain funding for studies investigating epidemiologic patterns.

Walter A. Rocca, MD, MPH
Rodolfo Savica, MD, PhD
Brandon R. Grossardt, MS

Author Affiliations: Division of Epidemiology, Departments of Health Sciences Research and Neurology, College of Medicine, Mayo Clinic, Rochester, Minnesota (Rocca, Savica); Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, Minnesota (Grossardt).

Corresponding Author: Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (rocca@mayo.edu).

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1. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time trends in the incidence of Parkinson disease. *JAMA Neurol*. 2016;73(8):981-989.

2. Darweesh SK, Koudstaal PJ, Stricker BH, Hofman A, Ikram MA. Trends in the incidence of Parkinson Disease in the general population: the Rotterdam Study. *Am J Epidemiol*. 2016;183(11):1018-1026.

3. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. *J Neurol*. 2013;260(5):1351-1357.

4. Liu WM, Wu RM, Lin JW, Liu YC, Chang CH, Lin CH. Time trends in the prevalence and incidence of Parkinson's disease in Taiwan: a nationwide, population-based study. *J Formos Med Assoc*. 2016;115(7):531-538.

5. Liu CC, Li CY, Lee PC, Sun Y. Variations in incidence and prevalence of Parkinson's disease in Taiwan: a population-based nationwide study. *Parkinsons Dis*. 2016;2016:8756359.

6. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Risk factors for Parkinson's disease may differ in men and women: an exploratory study. *Horm Behav*. 2013;63(2):308-314.

Plasma Coenzyme Q10 Levels and Multiple System Atrophy

To the Editor We read with interest the study by Mitsui and colleagues[1] who found decreased levels of plasma coenzyme Q10 (CoQ10) in patients with multiple system atrophy (MSA) regardless of the *COQ2* genotype. Mutations in CoQ2 (which encodes an essential enzyme in the biosynthetic pathway of CoQ10) have previously been shown to be associated with MSA.[2] Mitsui et al[1] found a lower plasma CoQ10 level in those with MSA compared with controls (95% CI, 0.10; range, 0.02-0.66) (P = .02). Owing to the small sample size, the reference level of plasma CoQ2 used in the comparison had a major influence in the conclusion.

The mean (SD) plasma CoQ10 level reported in the study was 0.51 (0.22) vs 0.72 (0.42) µg/mL in patients with MSA and healthy controls, respectively. While the authors highlighted that this was comparable with the mean (SD) serum CoQ10 level of 985.3 (939.4) nmol/L (equal to 0.85 [0.81] µg/mL; n = 18) by Kasai et al[3] and mean (SD) plasma CoQ10 level of 757 (247) nM (equal to 0.65 [0.21] µg/mL; n = 20) by Sohmiya et al[4] in healthy Japanese controls, the sample sizes of all these studies were rather small. We would like to draw the authors' attention to a recent study by Iwasaki and colleagues[5] who reported the median plasma CoQ10 in healthy Japanese individuals from Tokyo to be 1.02 µg/mL (range, 0.93-1.11 µg/mL). This level gathered from a much larger sample size (n = 141)[5] was much higher than the level in the controls in the study by Mitsui et al.[1] This suggests that the plasma CoQ2 level in healthy controls may be 2 times higher than in patients with MSA in the Japanese population. The magnitude of this difference certainly elevates the clinical relevance and significance of the conclusions by Mitsui et al.[1]

The authors have prudently excluded potential confounding variables (such as dyslipidemia and some drugs that potentially interact with CoQ10) in their study participants. Cholesterol influences CoQ10 levels by creating a conjugated form in blood,[3] but this is not an "all or nothing" interaction. Hence, we think that measurements of the cholesterol levels in both patients with MSA and healthy controls should have been taken into account in the analysis using a multivariate regression model.

If CoQ10 levels are indeed consistently low in patients with MSA, the more challenging question is whether CoQ10 supplementation in patients with MSA with low CoQ2 level will be able to improve clinical symptoms or retard disease progression. We await with great interest for future studies to address this.

Yin Xia Chao, MD, PhD
Zhidong Zhou, PhD
Eng-King Tan, MD

Author Affiliations: Department of Neurology, Singapore General Hospital, Singapore (Chao, Tan); Duke-NUS Graduate Medical School, Singapore (Chao, Tan); National Neuroscience Institute, Singapore (Chao, Zhou, Tan); Department of Clinical Research, Singapore General Hospital, Singapore (Tan).

Corresponding Author: Eng-King Tan, MD, Department of Neurology, Singapore General Hospital, Outram Road, Singapore 169108 (gnrtek@sgh.com.sg).

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1. Mitsui J, Matsukawa T, Yasuda T, Ishiura H, Tsuji S. Plasma coenzyme Q10 levels in patients with multiple system atrophy. *JAMA Neurol*. 2016;73(8):977-980.

2. Multiple-System Atrophy Research Collaboration. Mutations in COQ2 in familial and sporadic multiple-system atrophy. *N Engl J Med*. 2013;369(3):233-244.

3. Kasai T, Tokuda T, Ohmichi T, et al. Serum levels of coenzyme Q10 in patients with multiple system atrophy. *PLoS One*. 2016;11(1):e0147574.

4. Sohmiya M, Tanaka M, Suzuki Y, Tanino Y, Okamoto K, Yamamoto Y. An increase of oxidized coenzyme Q-10 occurs in the plasma of sporadic ALS patients. *J Neurol Sci*. 2005;228(1):49-53.

5. Iwasaki M, Franke AA, Hamada GS, et al. Comparison of plasma levels of nutrient-related biomarkers among Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA. *Eur J Cancer Prev*. 2015;24(2):155-161.

In Reply We thank Chao and colleagues for their comments regarding our article.[1] Referring to the recent article that showed the median plasma coenzyme Q10 (CoQ10) level in 141 healthy Japanese individuals to be 1.02 µg/mL,[2] which was much higher than that in our study (0.72 µg/mL), they suggested that the difference in the plasma CoQ10 level between patients with multiple system atrophy (MSA) and controls may be much larger than previously reported. To date, 2 groups from Japan have shown decreased plasma CoQ10 levels in patients with MSA.[1,3] As noted by Chao and colleagues, the sample sizes in those studies were relatively small; hence, it will be important to determine plasma CoQ10 levels in much larger sample sizes. They also mentioned that cholesterol levels should be taken into account in evaluating CoQ10 levels because plasma cholesterol levels affect CoQ10 levels by forming a conjugated form. We admit that we did not include plasma cholesterol levels in our study. However, Kasai et al[3] reported that the CoQ10 to total cholesterol ratios are significantly decreased in patients with MSA (mean [SD], 3.04 [1.23]) compared with those in controls (mean [SD], 5.92 [5.88]). Furthermore, 2 groups from the United Kingdom and United States have reported decreased CoQ10 levels in the cerebellum of patients with MSA.[4,5] Thus, decreased CoQ10 levels in patients with MSA are consistent findings. Although the association of the *COQ2* V393A variant with MSA has been demonstrated in