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Association of UV radiation with Parkinson disease incidence: A nationwide French ecologic study

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ABSTRACT

Background: Vitamin D is thought to contribute to brain health, but it is unclear whether low vitamin D levels are associated with increased incidence of Parkinson's disease (PD). Using ultraviolet B (UV-B) as a surrogate for vitamin D levels, we conducted a nationwide ecologic study in France in order to examine the association of UV-B with PD incidence.

Methods: We used French national drug claims databases to identify PD cases using a validated algorithm. UV-B data from the solar radiation database were derived from satellite images. We estimated PD incidence (2010–2012) at the canton level (small administrative French unit) and used multilevel Poisson regression to examine its association with UV-B (2005 annual average), after adjustment for age, sex, deprivation index, density of neurologists, smoking, proportion of agricultural land, and vitamin D supplementation.

Results: Analyses are based on 69,010 incident PD patients. The association between UV-B and PD incidence was quadratic ($P < 0.001$) and modified by age ($P < 0.001$). Below 70y, incidence was higher in the bottom quintile (relative risk, $RR_{Q1:45\text{-}49y}$=1.18, 95% CI=1.08–1.29) compared with the middle UV-B quintile, and lower in the top quintile ($RR_{Q5:45\text{-}49y}$=0.85 [0.77–0.94]). An opposite pattern was observed in older subjects ($RR_{Q1:85\text{-}89y}$=0.92 [0.89–0.96]; $RR_{Q5:85\text{-}89y}$=1.06 [1.02–1.11]). Analysis based on continuous UV-B yielded similar conclusions.

Conclusions: In this nationwide study, there was an age-dependent quadratic association between UV-B and PD incidence. This study suggests that reasonable UV-B exposure is associated with lower PD risk in younger persons and that future studies should examine dose-response relations and take age into account.

1. Introduction

In addition to regulating calcium homeostasis and bone metabolism, vitamin D is involved in multiple biological pathways. Lower vitamin D is associated with increased mortality (Garland et al., 2014), in particular from some cancers (Zittermann et al., 2012; Moukayed and Grant, 2013), and there is increasing evidence that it may play a role in brain health (Holick, 2015). Recent epidemiological studies consistently point towards an inverse association of vitamin D with dementia and Alzheimer's disease (Afzal et al., 2014; Littlejohns et al., 2014), including a Mendelian randomization study that supports a causal link with Alzheimer's disease (Mokry et al., 2016). Other studies have also shown inverse associations with cognitive decline (Annweiler et al., 2015) and multiple sclerosis (Mokry et al., 2015).

Parkinson's disease (PD) is a neurodegenerative disorder resulting from loss of dopaminergic neurons in the *substantia nigra*. A high prevalence of vitamin D deficiency in PD patients was first reported in the late 1990's, and corroborated in several studies that also showed an inverse association between PD severity and serum vitamin D (Peterson, 2014). Although lower vitamin D may be a consequence of the disease, due to the patients' limited mobility and digestive symptoms, several lines of evidence suggest that vitamin D deficiency may also be implicated in PD etiology (Peterson, 2014; Newmark and Newmark, 2007). However, few studies have investigated this hypothesis, and the epidemiological evidence in favour of an association of vitamin D deficiency with PD risk remains limited (Knekt et al., 2010;

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Wang et al., 2015).

Skin exposure to sunlight is the major vitamin D source and a good surrogate marker of vitamin D levels both in population settings (Glerup et al., 2000) and PD patients (Wang et al., 2016). We have previously shown that drug claims databases can be used to identify PD patients (Moisan et al., 2011). We have used this approach to estimate PD incidence in France, and obtained estimates that were consistent with other European countries (Moisan et al., 2016). Our objective was to conduct a nationwide ecologic study to examine the association of ultraviolet B (UV-B) exposure with PD incidence in France using national drug claims databases. We hypothesized that regions with lower UV-B exposure are characterized by higher PD incidence.

2. Methods

2.1. Parkinson's disease

Data are drawn from the French National Health Insurance (*Système National d'Information Inter-Régimes de l'Assurance Maladie*, SNIIRAM), which contains information on drug reimbursements for > 97% of French population. SNIIRAM contains data on type of drugs, prescription and reimbursement date, total number of boxes, tablets dosage, and medical specialization of prescribers. Demographic characteristics (age, sex, place of residence) are available (Tuppin et al., 2010).

PD cases were identified using SNIIRAM, based on a prediction model that estimates the probability of being treated for PD in a given year through drug claims (Moisan et al., 2011, 2016). Predictors include: cumulative dose or ever use between January 1st and December 31st of antiparkinsonian drugs (levodopa, dopamine agonists - pramipexole, ropinirole, pergolide, apomorphine, bromocriptine, lisuride -, selegiline/rasagiline, piribedil, anticholinergics, COMT inhibitors), proportion of the aforementioned time-frame treated, number of neurologist/general practitioner's visits, and sex. This approach identifies cases with 92.5% sensitivity and 86.4% specificity (Moisan et al., 2011).

We identified persons with at least one antiparkinsonian drug reimbursement between 2009–2012, and excluded those < 20y, women < 50y reimbursed for bromocriptine alone (lactation suppression), and persons only on anticholinergics and neuroleptics (drug-induced Parkinsonism). We applied the prediction model for years 2010, 2011, and 2012; incident cases for a given year were identified by the model as cases that year without any antiparkinsonian drug reimbursement during the previous year. Finally, we computed the annual number of incident cases corrected by the model's sensitivity and specificity (Moisan et al., 2016; Couris et al., 2002).

PD incidence rates for the combined years 2010–2012 were computed by sex and 5-year age groups at the canton level, as population data were available at this level for all three years (Insee, 2016). Cantons (n=3,689) represent small administrative units with a median area of 147 km^2 (interquartile range [IQR]=142; min=1, max=972) and a median population size of 10,271 inhabitants in 2010 (IQR=14,253; min=138, max=2,243,833). In each strata, we divided the corrected number of incident cases (2010–2012) by the corresponding number of person-years.

2.2. Ultraviolet B exposure

UV exposure was computed using total available solar irradiance data from the online HelioClim-3 database (Wald, 2016; Qu et al., 2014; SoDa (Solar Radiation Data) SSfIaR, 2016). Data are produced by the processing of satellite images, largely from the Meteosat series of satellites, that are available for Europe. The SoDa UV modules have been shown to produce realistic results for incident UV radiation (Kift et al., 2006). This database has been previously used to show that UV-B (280–320 nm) radiation is associated with lower MS prevalence rates in France (Orton et al., 2011). Only UV-B was examined due to its biological role in vitamin D synthesis (Glerup et al., 2000). Monthly UV-B data (2005–2009) were available at the canton level. Mean annual and seasonal UV-B levels were calculated. Mean (SD) annual UV-B canton levels ranged between 18.2 (1.6) in 2008 and 18.9 (1.6) in 2009. To account for the PD latency period, we used the earliest available data (2005) for our main analyses as an estimate of historical UV-B exposure.

2.3. Covariates

2.3.1. Smoking

Based on age- and sex-specific proportions of ever-smokers in each French *région* from national surveys (2005, 2010) (Inpes, 2016), we estimated age- and sex-standardized rates of ever-smoking in each canton by assuming the same distribution of ever-smoking in all cantons that were part of a *région* (median of 164 cantons per *region*; IQR=59; min=43, max=313).

2.3.2. Proportion of agricultural land

It was estimated using the French agricultural census (1988) by dividing the cantons' area devoted to agriculture by their total area (Agreste, 2016).

2.3.3. Vitamin D supplementation

In each canton, we obtained from SNIIRAM the proportion of persons using vitamin D supplements by sex/5-year age groups (2012), and estimated age- and sex-standardized rates of vitamin D supplementation. Because data were not available for earlier years, we assumed no major spatial disparities in time-trends of vitamin D use.

2.3.4. Deprivation index (FDep99)

It summarizes four dimensions of socioeconomic level (median household income, percentage of high school graduates, percentage of blue-collar workers in the active population, unemployment rate) and was used as a marker of spatial socioeconomic heterogeneity (Rey et al., 2009).

2.3.5. Density of neurologists

In each *département* (median of 36 cantons per *département*; IQR=11; min=20, max=86), we obtained the number of neurologists and divided it by the population, to obtain the density of neurologists per inhabitant.

2.3.6. Air pollution

There is increasing interest on potential associations between air pollution and the etiology of neurodegenerative diseases. Although the evidence in favour of an association between $PM_{2.5}$ and PD incidence remains controversial (Kirrane et al., 2015; Palacios et al., 2014; Liu et al., 2016), we examined whether air pollution may act as a confounder. The average annual concentration of $PM_{2.5}$ was assessed at a 2 km resolution throughout France from 1989 to 2008 using the CHIMERE chemistry-transport model, mesh refinement, and data assimilation with geostatistical analyses (Bentayeb et al., 2014, 2015). Emission data were taken from the European monitoring and evaluation program emission cadastre (EMEP: http://www.emep.int/index.html), the Interprofessional Technical Centre for Studies on Air Pollution (CITEPA:http://www.citepa.org/en) and European Environment Agency (EEA: http://www.eea.europa.eu). For our analyses, we used the average concentration of $PM_{2.5}$ in 2005 at the canton level.

2.4. Statistical analysis

PD incidence rates were tabulated overall and by UV-B quintiles. PD incidence rates, UV-B exposure, and standardized rates of vitamin