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Effect of heat waves on morbidity and mortality due to Parkinson's disease in Madrid: A time-series analysis

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ABSTRACT

Background: Parkinson's disease (PD) is one of the factors which are associated with a higher risk of mortality during heat waves. The use of certain neuroleptic medications to control some of this disease's complications would appear to be related to an increase in heat-related mortality.
Objective: To analyse the relationship and quantify the short-term effect of high temperatures during heat wave episodes in Madrid on daily mortality and PD-related hospital admissions.
Methods: We used an ecological time-series study and fit Poisson regression models. We analysed the daily number of deaths due to PD and the number of daily PD-related emergency hospital admissions in the city of Madrid, using maximum daily temperature (°C) as the main environmental variable and chemical air pollution as covariates. We controlled for trend, seasonalities, and the autoregressive nature of the series.
Results: There was a maximum daily temperature of 30 °C at which PD-related admissions were at a minimum. Similarly, a temperature of 34 °C coincides with an increase in the number of admissions. For PD-related admissions, the Relative Risk (RR) for every increase of 1 °C above the threshold temperature was 1.13 IC95%:(1.03–1.23) at lags 1 and 5; and for daily PD-related mortality, the RR was 1.14 IC95%:(1.01–1.28) at lag 3.
Conclusion: Our results indicate that suffering from PD is a risk factor that contributes to the excess morbidity and mortality associated with high temperatures, and is relevant from the standpoint of public health prevention plans.

1. Introduction

Parkinson's disease (PD) is the second leading degenerative disease in the population and entails a high economic cost, particularly at advanced stages of the disease (Rodríguez-Blázquez et al., 2015; Reese et al., 2012; Mateus and Coloma, 2013). Suffering from a neurodegenerative disorder such as PD is one of the factors which, at an individual level, are associated with a higher risk of mortality during heat waves (Ministerio Sanidad Servicios Sociales e Igualdad, 2015). Moreover, the use of certain neuroleptic medications to control some of this disease's complications would appear to be related to an increase in heat-related mortality, as indeed occurred in the heat wave in France in 2003 (Stöllberger and Finsterer, 2007). Suffering from PD is thus a risk factor that contributes to the excess morbidity and mortality associated with high temperatures, and is relevant for public health prevention purposes.

From an environmental stance, some risk factors have been linked to development of PD, with pesticides (herbicides, insecticides, and fungicides) being the pre-eminent agents. Certain occupations (farming, welding, mining, painting) and circumstances (e.g., rural lifestyle, well-water use) have been related to an increased risk of suffering from PD, possibly associated with exposure to paraquat, rotenone, maneb, metals such as iron and manganese, organic solvents, or other products that are potentially toxic for the central nervous system and, specifically, for the substantia nigra. These agents presumably act by causing oxidative stress, inflammation, mitochondrial dysfunction, inhibition of proteasome and other disorders which culminate in cell death (Wirdefeldt et al., 2011; Campdelacreu, 2014; Agim and Cannon, 2015). Nevertheless, the evidence supporting such proposals is limited or inconsistent, and until now, only MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) has been shown to give rise to a PD-like disorder in the human being (Baltazar et al., 2014; Kieburtz and Wunderle, 2013; Chin-Chan et al., 2015).

Recently, there has been a shift in the approach taken to the participation of certain environmental factors in the aetiology of PD (and of other neurodegenerative diseases, such as Alzheimer's disease).

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According to this, it is not merely that exposure to environmental factors affects a selected population sample such as workers and the above-described population groups, but rather that factors to which the entire population is exposed, such as traffic-related air pollution (Ritz et al., 2015), are related to the aetiology or exacerbation of neurodegenerative diseases.

As regards the effect of high temperatures on PD, it is not suggested that high temperatures are related to a higher prevalence of the disease by participating in its aetiology. Instead, it is argued that -whether by virtue of a biological mechanism such as dopamine deficit linked to hyperthermia in heat waves (Finsterer et al., 2011) or by virtue of the effect of neuroleptic use during heat waves on persons over the age of 70 years (Stöllberger and Finsterer, 2007)- the effect of high temperatures may translate as disease exacerbations, which in turn have an impact on traditional health indicators, such as daily mortality or hospital admissions. Accordingly, the aim of this study was to establish the link between and quantify the short-term effect of high temperatures during heat waves in Madrid on daily PD-related mortality and hospital admissions. We conducted a novel analysis in this area of research, by means of an ecological time-series study. This study is especially pertinent, bearing in mind that the over-75 age group, in which the highest PD incidence is found (Huse et al., 2005), is also the age group to which the highest heat-wave mortality is attributed in Madrid (Díaz et al., 2015a), and that this is an environmental risk which, in the context of climate change, is destined to become ever more frequent and more intense (IPCC, 2014).

2. Methods

2.1. Study population

The city of Madrid is a densely populated metropolitan area situated in the central region of Spain. In the period 2001–2009, it had a mean population of 3,116,897 and of this total, 284,929 persons (9%) were aged 75 years or over (INE, 2014).

2.2. Outcomes

The following two data sources were used to obtain the main variables of analysis:

- *Number of daily deaths due to PD* (International Classification of Diseases 10th Revision (ICD-10); (ICD-10: G20-G21) in the city of Madrid from 01 to 01-2001 to 31-12-2009, based on data furnished by the National Statistics Institute to the Carlos III Institute of Health (Ministry of Economic Affairs & Competitiveness/*Ministerio de Economía and Competitividad*), for the purpose of undertaking a “Study of influenza-related mortality in Spain”.
- *Number of daily PD-related emergency admissions* (ICD-10: G20-G21) to municipal hospitals in Madrid from 01 to 01-2008 to 31-12-2009, obtained from the Minimum Basic Data Set (MBDS) (*Conjunto Mínimo Básico de Datos*) compiled by the Ministry of Health, Social Services & Equality.

2.3. Exposure

As the main environmental variable in the analysis we used *maximum daily temperature* (°C), since it displays the closest relationship with heat-wave-related morbidity and mortality in Spain (Díaz et al., 2015b). The maximum daily temperature data for the above time periods correspond to readings taken at the Madrid Retiro observatory, situated in the centre of the city of Madrid, and were furnished by the State Meteorological Agency (*Agencia Estatal de Meteorología/AEMET*).

To assess whether there was a functional relationship between maximum daily temperature and PD, and if so of what type, we plotted scatterplot diagrams. These diagrams furnish information on the type of relationship that exists (linear or otherwise) between mortality, hospital admissions and maximum temperature during the period analysed. In these diagrams, the value of mortality or the value of PD-related admissions corresponds to the mean value taken by this variable for each 2 °C interval between the minimum and maximum values of maximum temperature. If, as generally happens with all-cause morbidity and mortality (Díaz et al., 2002; Linares and Díaz, 2008), there is a temperature point above which the dependent variable analysed increases, this is called the “Threshold temperature (Tthreshold)” and is calculated by linear-type adjustment with loess smoothing. In the process of modelling and quantification of risk, the non-linear character of this maximum temperature-PD relationship is then taken into account as follows:

$$T_{cal} = 0 \qquad \text{if } T_{max} < \text{Tthreshold}$$

$$T_{cal} = T_{max} - \text{Tthreshold} \qquad \text{if } T_{max} > \text{Tthreshold}$$

where Tcal is the variable that determines the existence of the effect of a heat wave on PD-related morbidity and mortality. Given that the effect of a heat wave on PD may not be immediate, the following lagged variables were calculated: T_{cal} (lag 1), which takes into account the effect of the temperature on day “d” on mortality, one day later, “d + 1”; T_{cal} (lag 2), which takes into account the effect of the temperature on day “d” on mortality, two days later, “d + 2”; and so on successively. The number of lags were selected on the basis of the literature, which establishes that the effect of heat on total mortality is short-term (T_{cal}: lags 1–5) (Alberdi et al., 1998).

2.4. Covariates

2.4.1. Other meteorological variables

In addition, we considered the mean daily air pressure (Pa) and mean daily relative humidity (Hr) corresponding to the same study period, as recorded at the Madrid-Retiro observatory and furnished by *AEMET*. Previous studies conducted in Madrid have already shown the influence of these meteorological parameters on all-cause morbidity and mortality both in heat and in cold waves (González et al., 2001; Díaz et al., 2002).

2.4.2. Variables of chemical air pollution

Based on previous studies on PM_{10}, $PM_{2.5}$ and NO_2 (Jiménez et al., 2009), the relationship with morbidity and mortality was assumed to be linear, with the effect on the latter being felt until lag 5, with the corresponding lagged variables being created until this lag in the same way as for temperature. In the case of ozone (O_3), the functional relationship obtained by other studies was quadratic (Díaz et al., 1999) with an effect felt as far as lag 9. We worked with mean daily concentrations (μg/m^3), obtained as the overall mean value for the grid of stations which routinely measure chemical air pollution in Madrid. The data were supplied by the Madrid Municipal Air Pollution Monitoring Grid (*Red de Vigilancia de la Contaminación Atmosférica del Ayuntamiento de Madrid*).

2.4.3. Other control variables

In addition to the above-mentioned variables, we also controlled for trend, annual, six-monthly and weekly seasonalities, the autoregressive nature of the series, and days of the week.

2.5. Statistical analysis

To calculate the impact of heat waves on PD-related morbidity and mortality, generalised linear models (GLMs) were constructed with the Poisson regression link. This made it possible to obtain the estimator to calculate the relative risk (RR) of both daily mortality and non-emergency hospital PD admissions associated with an increase of 1 °C