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Research article

Evidence of climate change impact on Parkinson's disease

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ABSTRACT

Background: Climate change represents a threat to human health. In this research, we have investigated the sensitivity of Parkinson's disease (PD) to climate change, and assessed whether there is any detectable link between climate warming and key PD indices.

Methods: We contrasted variations between 1990 and 2016 of PD patients' indices (prevalence, deaths, and disability-adjusted life years) and climate indices (warming and annual average temperature) for 185 countries. Countries were clustered in four categories, depending on whether they had higher-than-median or lower-than-median warming, and higher-than-median or lower-than-median temperature. For all four clusters, we assessed the relationship between variations in PD patients' indices, and climate indices.

Findings: In the cluster of the 25 countries (home to about 900 million people) characterized by higher-than-average warming and higher-than-average temperature, we have found a positive correlation between more intense warming and higher variations in the PD indices: in other words, warmer countries that have experienced more intense warming have reported a larger increase in PD cases.

Interpretation: These results indicate that in warmer-than-average countries, i.e., countries that have in general a warmer climate, climate change has an impact on PD that depends on the intensity of the warming: the more intense the warming, the stronger the impact. In other worlds, climate change should be considered as one of the 'environmental factors' that can impact PD.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterized classically by tremor, bradykinesia-akinesia, rigidity, and balance deficit, that can eventually cause depression and cognitive and neurovegetative dysfunctions [1]. In 2016, PD worldwide affected more than 6 million individuals, over 2.5 times the value reported in 1990 (2.5 million), mainly because of an increase in the relative percentage of elderly people. This increase in prevalence also has been linked to environmental factors [2,3], with global warming potentially playing a pivotal role [4,5]. These findings highlight how heat waves might contribute to worsened neurological symptoms or be considered as a risk factor that influences both morbidity and mortality associated with PD at high temperatures.

Given these associations, an important question is whether there is any evidence that climate change can lead to an increase in PD cases. If this were the case, we should expect that countries with the highest temperature increases would display an enhanced increase in PD indices such as prevalence, deaths, and disability-adjusted life years. Human beings as living endothermic organisms have several features that can compensate for temperature changes; however, these are diminished in elderly or sick people [6]. PD patients may exhibit a spectrum of thermoregulatory dysfunctions that can be exacerbated by heat stress and heat waves [7,8], and thus further climate warming in areas already characterized by high temperatures could lead to increased health issues in PD patients.

The objective of this work was to investigate whether we could detect an association between climate change and PD indices. We concentrated on the period 1990–2016, and investigated whether among the countries characterized by high temperatures, the ones affected by more intense warming were the ones that showed higher increases in PD indices.

2. Data and method

2.1. Data

Epidemiological data were derived from Table 1 of Dorsey et al. (The Lancet, 2016, pg. 943–948; [2]), who listed the global, regional,

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Table 1
Distribution of the T2016 and the climate warming indices: the minimum and maximum values, the 5th and 75th percentiles and median of the distribution of T2016 and of the 1990–2016 warming indices of 185 countries.

	T2016	1990–2016 Warming Index
Min	−15.9	−0.3
25th	11.8	0.4
Median	23.2	0.7
75th	26.3	1.2
Max	29.1	1.8

and country-specific variations, between 1990 and 2016, of three epidemiological indices related to PD patients: prevalence, deaths, and disability-adjusted life years (DALYs). They reported an increase in all three indices between 1990 and 2016, and concluded that "the global burden of PD has more than doubled".

Climate data were extracted from the World Bank Climate Change Data Portal (freely available from The World Bank web site: https://data.worldbank.org/indicator), which includes, for almost all countries of the world, the monthly average temperature from 1990 to 2016. From these data, two climate indices were defined:

- The 2016 average temperature (T2016), computed as the annual mean 2-meter temperature.
- The 1990–2016 warming index, which is a function of the slope of the linear regression curve that fitted the monthly 2-m temperature data from January 1990 to December 2016; more precisely, this index has been defined as the average annual warming between 1990 and 2016, computed from the linear-fit curve (we used this index, rather than the difference between the annual average temperatures of 2016 and 1990, to represent in a more correct way the 26-year warming, and avoid the impact of annual variations). For example, a warming index of 0.05 °C degrees/year indicates a 1.3 °C degrees warming between 1990 and 2016.

According to these indices, countries with warmer climate have a higher value of T2016, and countries more affected by climate change have a higher warming index.

2.2. Method

Of the 194 countries listed in [2], we selected the 185 countries for which we could find monthly average temperature data in the World Bank Climate Change Data Portal. These 185 countries, once their climate indices were computed, were grouped in four clusters, by comparing their individual climate indices (warming and T2016) with the sample medians:

- High-temperature and high-warming (HT-HW).
- High-temperature and low-warming (HT-LW).
- Low-temperature and high-warming (LT-HW).
- Low-temperature and low-warming (LT-LW).

The characteristics of the distributions of the four clusters can be described by their means, medians and quartiles, and standard statistical methods can be applied (see, e.g., [16]) to assess the correlation between variables. When comparing two distributions, to assess whether they come from the same population, the student t-test has been applied. The student *t*-test provides the statistical significance of the validity of the null hypotheses that are posed throughout the analysis (for example, whether there is no distinction between the distribution of PD deaths for countries characterized by below-average climate conditions compared to those with above-average climate conditions).

To investigate whether there is any link between climate warming and PD indices, the following three key questions were addressed:

1. Is there a link between the average climate conditions, as represented by T2016, and the PD indices?
2. Is there is a link between climate warming and the variations of the PD indices?
3. Is there any statistically significant difference between the distribution of the PD indices of the HT-HW cluster from the other three clusters?

3. Results

For all 185 countries, the 2016 average temperatures (T2016) vary between −15.9 °C and 29.1 °C, with a median of 23.2 °C, and the 1990–2016 warming indices vary between −0.3 °C and 1.8 °C, with a median of 0.7 °C (see Table 1). Fig. 1. shows the scatter plot of the two climate indices, with the countries clustered in the four categories introduced above (Fig. 1). (The reader is referred to table A, reported in appendix, for the list of the two climate indices and the PD indices of all countries).

Let us now consider the first question posed in Section 2, i.e., whether there is any link between the average climate conditions, represented by T2016, and the PD indices. To answer it, firstly we have assessed whether there is a linear relationship between the PD-indices and the T2016 index. Results indicate very low correlation values between T2016 and the three PD indices: 2.4% for deaths, 1.1% for prevalence and 2.5% for DALY's. Then, we have clustered the countries accordingly to T2016 in high-temperature (HT) and low-temperature (LT) countries: if you consider Fig. 1, this clustering leads to a split the 185 countries into the ones to the right and to the left of the T2016 median value).

To compare the distributions of the HT and LT clusters, for each of them we computed the median, 25th and 75th percentiles of the PD-indices for the two clusters. Results (Table 2) indicate that the PD-indices are slightly higher for the HT countries, indicating that there is some sensitivity to the average climate. To assess how robust the difference is between the HT and the LT distributions, we computed the Student's *t*-test: results indicate that the probability that the HT

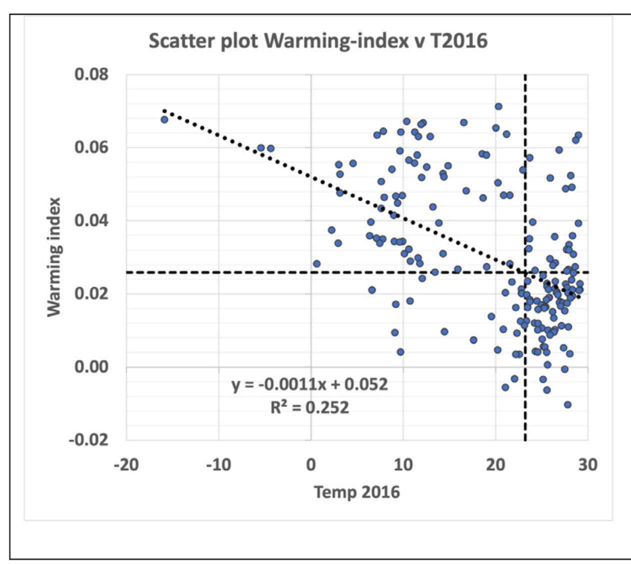

Fig. 1. Scatter diagram of the 1990–2016 warming index versus the T2016. Each symbol represents one of the 185 analysed countries (see Table in Appendix A). The horizontal and vertical lines divide the countries in the 4 categories high/low temperature, high/low warming. The dotted inclined line shows the linear fit of the warming index with respect to T2016 ().

Table 2
Statistics (median, 25th and 75th percentiles) **of the PD-indices** for the high-temperature (HT) and low-temperature (LT) countries: deaths (columns 2–3), prevalence (columns 4–5) and DALY's (columns 6–7).

	Deaths		Prevalence		DALY's	
	HT	**LT**	**HT**	**LT**	**HT**	**LT**
25th	0.14	0.085	0.14	0.087	0.15	0.09
Median	0.20	0.15	0.16	0.13	0.19	0.15
75th	0.30	0.25	0.25	0.20	0.29	0.24

distribution is indistinguishable from the LT distribution for deaths is 8%, for prevalence is 15%, and for DALY's is 6.0%. In other words, the null hypothesis that "warmer and colder countries have the same statistics of the PD indices" cannot be rejected with $p < 0.05$. These *t*-test results indicate that the climate of a country, as represented by T2016, plays only a minimal role.

Now, let us consider the second question posed in Section 2, i.e., whether there is a link between climate warming and the variations of the PD indices. To assess whether this is the case, we have further split the HT and LT clusters, and grouped the 185 countries in the following 4 clusters (Fig. 1):

- the HT-HW cluster, which includes the 25 countries with above median climate indices (the ones represented by the dots in the top-right quadrant of the scatter plot shown in Fig. 1);
- the HT-LW cluster, which includes 68 countries (the ones in the bottom-right quadrant of Fig. 1);
- the LT-HW cluster, which includes 68 countries (the ones in the top-left quadrant of Fig. 1);
- the LT-LW cluster, which includes 24 countries (the ones in the bottom-left quadrant of Fig. 1).

To assess whether there is any relationship between climate warming and variations in the PD indices, we have compared the correlation between the 1990–2016 variations of the PD indices and the 1990–2016 climate warming index for all the 185 countries, and for the 4 clusters. Results (Table 3) indicate that the correlation is considerably higher, above 25%, for the countries in the HT-HW cluster, while it is less than 1% for the countries in the other clusters. It is interesting to check the names of the 25 countries included in the HT-LW cluster: Algeria, Bahrain, Belize, Benin, Brazil, Chad, Djibouti, Egypt, Eritrea, Ethiopia, Guatemala, Kuwait, Mauritania, Mauritius, Niger, Nigeria, Oman, Qatar, Saudi Arabia, Seychelles, South Sudan, Sudan, Togo, United Arab Emirates, and Venezuela. Looking at this list, note that they are quite heterogenous in their environmental conditions and in the technological development of their medical equipment. This would exclude the possibility that other factors such as pollution and population exposure to toxins, or changes in the countries' capability to diagnose PD, could be responsible more than temperature of the link that between climate warming and the variation of PD indices. However, this result does not exclude that other environmental factors could also contribute to the variation s in PD indices, as reported, e.g., by Rong et al. (2021) [17], who indicated that in the US *'occupational exposures (including pesticides, herbicides, and heavy metal) and air pollution may increase risk of PD'*.

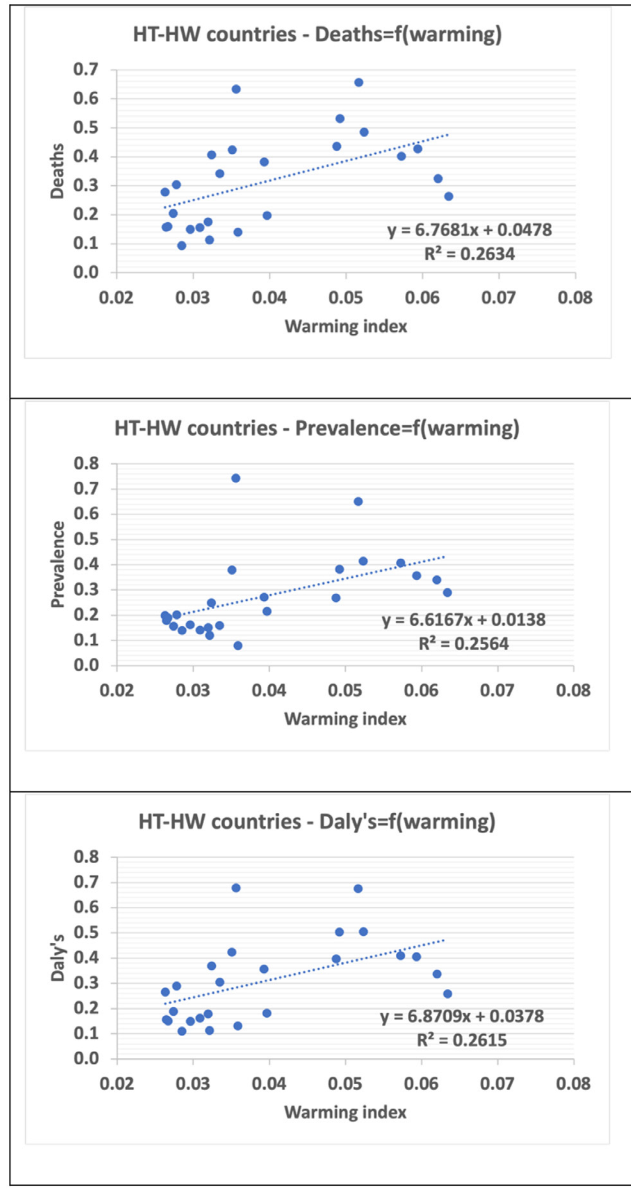

Fig. 2. Relationship, for the HT-HW countries, between the climate warming and the 1990–2016 variations of the PD indices and climate warming, for PD patients' deaths (top panel), prevalence (middle panel) and DALYs (bottom panel). Each dot represents one of the 25 HT-HW countries.

Fig. 2 shows, for the HT-HW countries, the scatter plot of the 1990 –2016 variations of the PD indices as a function of the warming

Table 3
Correlation coefficients between the 1990–2016 climate warming index and the 1990–2016 variations of the PD indices (deaths, prevalence and DALYs) for the countries in the 4 categories (HT-HW, HT-LW, LT-HW and LT-LW) and for all countries.

Category	Correlation of the 1990–2016 variation of the PD index and the climate warming index		
	Deaths	**Prevalence**	**DALYs**
HT-HW	26.3%	25.6%	26.1%
HT-LW	2.0%	1.6%	0.4%
LT-HW	0.5%	0.8%	0.4%
LT-LW	0.1%	4.1%	0.1%
ALL countries	0.2%	0.8%	0.02%

index. Note the positive slope for all 3 PD indices, indicating that for this cluster, the variations of the PD indices are higher for the countries that have experienced the most intense warming. For all three PD indices, the correlation between each index and the climate warming index is about 26%, a value that indicates that environmental factors linked to climate change contributed to the variations of the PD indices between 1990 and 2016.

The top panel of Fig. 2 shows that the linear regression curve between the PD deaths (y-axis) and the warming index (x-axis) is:

$$y = 6.77x + 0.05$$

where y is the variation in the annual deaths and x is the average annual warming due to climate change (please note that we have approximated the slope from 6.7681 to 6.77 and the intercept from 0.0478 to 0.05). This relationship indicates that between 1990 and 2016 (i.e., over 26 years), a country with an average annual warming of 0.05 °C (which translates into a warming between 1990 and 2016 of 1.3 °C), has detected an annual average increase of the percentage of PD deaths of 3.4% (i.e., 0.034 = 6.77 × 0.05). Similar considerations can be drawn for prevalence and DALY's, using the slopes of their relative linear regressions: a country with an average annual warming of 0.05 °C has detected an annual average increase of these two PD indices of, respectively, 6.62% and 6.87%. Similar considerations can be drawn by considering PD prevalence (Fig. 2, middle panel) of PD DALY's (Fig. 2, bottom panel).

Let us now consider the third question posed in Section 2, i.e., whether there is any statistically significant difference between the distribution of the PD indices of the HT-HW cluster from the other 3 clusters. Fig. 3 shows the median, the 25th percentile and the 75th percentile of the distributions of the PD indices for the 4 clusters. It indicates that, for all 3 PD indices, there is a clear difference between the percentiles of the HT-HW cluster, and the percentiles of the other 3 clusters. To assess the similarity between the distributions of the 1990–2016 variations of the PD indices of the HT-HW countries and the distributions of the other categories, the Student's *t*-test has been computed. Results (Table 4) indicate that the probability that the two distributions are similar is less than 9.7% for PD deaths, less then 4% for PD prevalence and less then 3.2% for PD DALY's. In other words, the null hypothesis that "there is no difference between the distribution of the PD indices of the HT-HW cluster from the other three clusters", can be rejected with $p < 0.05$ for all but for PD deaths between HT-HW and LT-LW (see Table 4).

As a final piece of our investigation, let us consider again the sensitivity of the variations of the PD indices to the average climate conditions (see Table 2 and the related discussion), and investigate how the explained variance of the PD-indices would change if we considered not only the climate warming index as independent variable, but also the T2016 indices. Focusing on the HT-HW countries, we have computed the explained variance of the PD-indices due to (a) only climate warming, (b) only the average climate conditions, and (c) both. Results reported in Table 5 indicate that the percentage of the explained variance is higher than 25% if we consider only climate warming, that it would be very low if we consider only T2016, and that it would increase to about 30% if we consider both the climate warming index and T2016. These correlations confirm that the climate warming index explains most of the variance, and that the average climate conditions play a marginal role: for deaths, for example, the % of the explained variance increases from 26.3% to 30.3% if we add T2016 to our linear analysis.

4. Discussion

The average age of the world population is increasing and with it all the diseases linked to aging, such as PD. Environmental temperatures are increasing too, and it is therefore important to assess whether there is a relationship between these events. In particular,

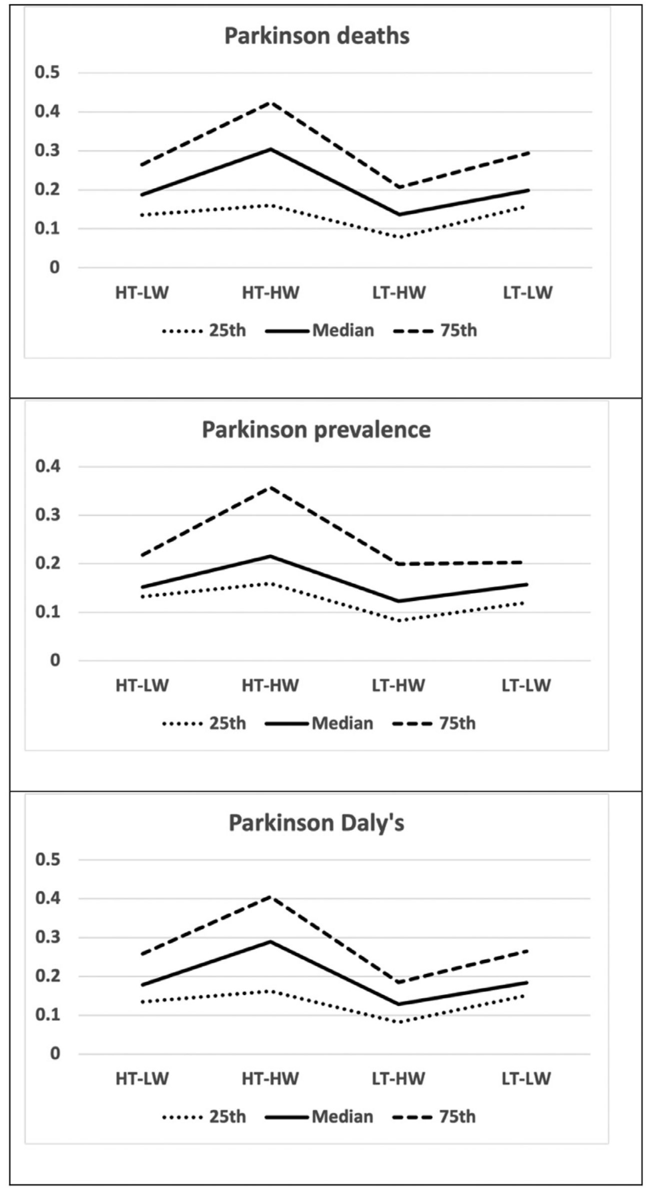

Fig. 3. Distribution of the climate warming index for the countries grouped in the four clusters. The top panel refers to the 1990–2016 variations of the PD patients' deaths: for each of the 4 categories of countries HT-LW; HT-HW, LT-HW; LT-LW the 25th percentile (dotted line), the median (solid curve) and the 75th percentile (dashed line). The middle and bottom panels show the same percentiles, for the PD prevalence (middle panel) and the PD patients' DALYs (bottom panel).

Table 4
Student's *t*-test computed to assess the difference between the PD indices of the HT-HW cluster and the other three clusters (HT-LW, LT-HW and LT-LW), for PD deaths, prevalence and DALYs. For example, the top-left value of 0.7% indicate that the null hypothesis that "there is no difference between the distribution of the PD indices of the HT-HW cluster and the distribution of the HT-LW cluster" can be rejected at the 0.7% level (i.e., with $p < 0.05$).

T-TEST	HT-HW		
	Deaths	**Prevalence**	**DALYs**
HT-LW	0.7%	0.0%	0.2%
LT-HW	0.5%	4.0%	0.9%
LT-LW	9.7%	0.1%	3.2%

Table 5
Percentage of variance of the variation of the Parkinson indices (deaths, prevalence and DALY's), explained by the warming index, by the climate index (T2016), and by the warming index and the climate index (T2016), for the high-temperature and high-warming countries.

% explained variance (r^2)	Deaths	Prevalence	DALY's
Warming index	26.3	25.6	26.1
T2016	1.7	4.1	1.9
Warming index and T2016	30.3	33.0	30.4

we focused on PD for 185 countries, and investigated whether we could detect any link between variations in three PD indices, deaths, prevalence, and disability-adjusted life years (DALY's) between 1990 and 2016, and two climate indices, climate warming. and the average climate conditions.

Results indicate that for the cluster of the 25 countries characterized by warmer-than-average climate conditions and more intense warming (the HT-HW cluster), there is a link between climate change-induced warming and PD patients' epidemiological data between 1990 and 2016. More precisely, results indicate that for these 25 countries, there is a significant correlation of about 25% between the warming index and the variations in the PD patients' epidemiological indices: the countries that show the largest variations of the PD indices between 1990 and 2016, are the ones that suffered the strongest warming.

This cluster is populated by developing and developed countries that are characterized by different levels of technological development, and thus we do not think that the link can be explained by an increase in pollution or by an increased capability to detect PD. Thus, how can we explain this result?

An average warming of few degrees implies that there is a higher probability of more intense and longer heat waves, that can have major impact on human health. For example, it is worth reminding the impact that the extended heat wave that hit Europe in the summer of 2003 had on mortality rates. For the future, a further warming of another 1−2° could mean more frequent summer-2003-type of summers, and thus more heat-induced deaths.

From our findings, chronic exposure to more intense warming in environments that are already warmer than average, correlates with the onset of neurodegenerative events of clinical relevance. It can be hypothesized that populations already exposed to high temperatures have a thermoregulation system more prone to develop neuroinflammatory events [10]. A plethora of both molecular and metabolic features related to organ homeostasis (e.g., hypothalamus control, hormonal networks, heat shock proteins) is activated in living endothermic organisms that can compensate for temperature changes. However, some of those features can be altered during aging, diseases or excessive heat exposure leading to a greater predisposition to aggravation of neurodegenerative disease. Moreover, when an already high external temperature increases further due to enhanced global warming, an acclimatization process begins [11] causing, if prolonged, the activation of biochemical pathways (such as oxidative stress and excitotoxicity) that can ultimately lead to neurodegeneration [12]. The main molecular pathways altered by temperature that can affect neuronal health, and can cause the onset of neurodegenerative diseases [13, 14], have been reported and discussed in a recent review by [10]. Moreover, these effects are particularly great in elderly people, whose thermoregulation is compromised.

Our results are very important since the 25 HT-HW countries are home of about 912 million people, i.e., of about 12% of the world population (based on 2020 data). With climate-induced warming projected to double in the next decades [9, 15] unless a drastic reduction in greenhouse gas emissions is achieved, these 25 and possibly even other countries that experience a warm climate and are subject to intense warming, could be affected by further increases in PD patients.

In the past decade, the average global average temperature has increased by about 0.2 °C, with hot-spot regions such as the countries facing the Mediterranean recording warmings of about 0.5 °C [9], which translates into an average annual warming due to climate change of about 0.05 °C. Although this value is very small, it is associated with an increased frequency of longer and more intense heat waves that impact human health. If we look forward in time and assume that the world continues to warm at the rate of the last decades, we can apply the linear regression curves detected to the HT-HW countries and calculate that in the next decades we could see further increases of all the PD-indices. For example, if we consider PD deaths, an HT-HW country that is affected by an average warming of about 0.05 °C could see an increase of about 3.5% per year.

More research to confirm our results is welcomed and should be funded welcomed. For example, our findings could be confirmed by studies based on larger diachronic databases relating to both climatic variations and epidemiological parameters of PD patients, and subjects suffering from other neurodegenerative diseases. These data may already exist but are not openly available to the whole scientific community, or if they do not exist prospective collection is recommended so a more detailed investigation of the link between climate change and neurodegenerative diseases can be performed.

5. Conclusions

We investigated whether there is any link between climate warming and PD indices by comparing the variations of three PD indices (deaths, prevalence, and disability-adjusted life years, DALY's) between 1990 and 2016, with two climate indices. One climate index, defined by the average temperature in 2016, characterizes the country climate conditions while the other one measures the warming between 1990 and 2016 due to climate change. The analysis was based on 185 countries. Three key questions have been addressed.

Firstly, results indicate a weak link between the average climate conditions, represented by the average annual temperature in 2016 (T2016), with warmer countries characterized by higher variations, and variations in the PD indices. Secondly, they indicate there is a link between climate warming and the variations of the PD indices between 1990 and 2016, for the countries in the cluster characterized by warmer-than-average climate and higher-than-average warming (the HT-HW cluster). For each of the three PD indices, a statistical analysis indicated a correlation of about 25% between climate warming and PD index variations, with countries with higher warming characterized by higher variations. The different behavior of the HT-HW countries from the others has been confirmed by the comparison of the distributions of the four clusters, and the application of Student's t-tests.

To our knowledge, this is the first time that a link between climate warming and variations in PD indices is reported. Given that PD cannot influence climate warming, these results indicate that in warm countries, climate change has an impact on PD that depends on the intensity of the warming, and thus should be considered as one of the 'environmental factors' that can impact Parkinson's Disease.

Supplementary Material

Appendix A: climate change and PD data

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.joclim.2022.100130.

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