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ORIGINAL ARTICLE

Season of birth and Parkinson's disease: possible relationship?

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Abstract The amount of sun exposure in early life and consequent vitamin D3 level may influence the risk of developing Parkinson's disease (PD). Yet few studies have previously investigated birth trends in PD related to a possible seasonality and sun exposure. The aim of this study was to investigate a possible relationship between PD risk and sun exposure looking at seasonal birth variation of PD subjects in the homogenous geographic area of Naples, Italy. We selected 898 PD subjects and matched with 1796 controls. McNemar's test with Bonferroni correction and autocorrelation were used to test seasonality in birth trends. No difference was found for the month and season of birth between PD subjects and controls. We found a 3.3 % increase of PD female subjects born in September (3.3 %) and 4.1 % increase of PD male subjects born in spring comparing to controls but were not significant after Bonferroni correction. This study evaluated for the first time the seasonal birth trends in relation to PD risk in a Southern European population. We found no association between seasonal birth variations and risk of PD.

Keywords Birth · Parkinson · Season · Sun · Trend · Vitamin D

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Introduction

Sun exposure is the main activating factor of vitamin D3, and can have a lifelong effect on its levels since early life [1]. Vitamin D3 inhibits the production of reactive oxygen species, preventing neuronal damage occurring, for instance, in Parkinson's disease (PD) [2]. In addition, the vitamin D3 receptor and the 1α-hydroxylase, the enzyme activating the vitamin D3, are highly expressed in neurons within the substantia nigra, which is severely affected by neuropathological changes of PD [3]. Therefore, it has been hypothesized a relationship between vitamin D3 levels and PD [2, 4].

Interestingly, there are seasonal variations in vitamin D levels due to different sun exposure and subsequent vitamin D activation. In this view, low sun exposure in childhood with subsequent low levels of vitamin D3 have already been related to the risk of developing different neurological disorders, such as multiple sclerosis (MS) [5]. In particular, longitudinal studies showed a relationship among sunlight exposure in childhood [6], serum concentration of vitamin D3, and the risk of MS [7]. In the Northern hemisphere there is a seasonal variation in risk of MS with higher frequency among people born in the spring [8]. Therefore, the amount of sun exposure in early phases of life can possibly affect different conditions related to vitamin D levels, and this effect cannot be excluded for the risk of developing PD [1]. However, birth trends in PD

have been investigated only in few studies [9, 10], with discordant results. Therefore, the aim of the present study is to explore possible relationships between PD risk and sun exposure in early phases of the life with subsequent variations in vitamin D3 levels, by investigating seasonal birth variations in relation to the risk of PD in the homogenous geographic area of Naples, Italy.

Materials and methods

Study design

We performed a cross-sectional case–control analysis to evaluate differences in month and season of birth between PD subjects and healthy controls. Due to the type of study carried out in a university setting, specific ethical approval was not required. All subjects signed the general informed consent form, authorizing the use of observational clinical data for research purposes. The study was performed in accordance with good clinical practices and Declaration of Helsinki.

PD subjects

We selected subjects who had been admitted to the University Hospital "Federico II" of Naples (Italy) between January 1, 2008 and August 31, 2014. We included subjects with a diagnosis of PD reported in the medical records, with admission or discharge from the Neurology Clinic, or with a medical consultation by a neurologist during their stay at the hospital. We only included subjects who were born in the area of Naples (Italy) and still resident in the same area, to avoid migration bias with possible different exposure to environmental factors (i.e. sun exposure). We excluded subjects younger than 50 years old at the time of the hospitalization to avoid bias from genetic forms of PD, and subjects with a concomitant diagnosis of dementia or of chronic cerebral vascular disease to exclude causes of parkinsonism different from PD (i.e. Dementia with Lewy Bodies, or vascular parkinsonism). 898 PD subjects admitted during the selected period met the inclusion criteria.

Controls

We selected 50 years old and older control subjects from the database of the outpatient clinic of Preventive Medicine Unit of the same hospital who underwent targeted scheduled medical examination for health surveillance. Visits were not related to current health problems but were performed in accordance to Italian occupational medicine regulations for preventive purposes. We selected subjects who were examined within the same period and who were born and still resident in the area of Naples. We excluded subjects with a diagnosis of PD, dementia and chronic cerebral vascular disease.

Sample size

Considering the study design, the number of 900 PD subjects (case control ratio 1:2) was considered acceptable to detect any association between the seasonality and risk of PD (McNemar's test, $\alpha = 0.05$, power $= 0.8$, $\Delta = 0.08$).

Statistical analysis

PD subjects were individually matched to healthy controls according to age (within 1 year) and gender, with a case:control ratio of 1:2. Demographic differences between groups were evaluated by χ^2 or paired t test, as appropriate. Data sets were tested for evidence of seasonality by comparison with the distribution of births in each month and season under the assumption of a uniform birth rate using a χ^2 test (11 and 3 degrees of freedom, respectively). Furthermore we built for each month and season a 2×2 contingency table, each comparing the number of cases and controls birth in each month/season with the number in all the other months/seasons, and used a McNemar's test to assess possible differences in the frequency of birth between PD subjects and controls. The results were considered significant after Bonferroni correction ($p < 0.05/12 = 0.0042$ for month of birth and $p < 0.05/4 = 0.0125$ for season of birth). In the second part of the analysis, to better explore a possible seasonality, we tested our data for time-series autocorrelation under the assumption that the frequency of a specific month could predict not only the frequency of the following month but also the frequency of that specific month in the following year. We examined specifically for seasonality by performing regression of the monthly count of births of PD subjects and including in the regression model a variable that reflects a periodicity of 12 (to test whether the counts for a given month can be predicted using the counts of that specific month over the years). This was compared with a meaningless periodicity (i.e. 13) and the amplitude of the increase in R^2 correlation coefficient served as an indicator of the strength of seasonality. Specifically we decided to analyze the whole range of years of births and, to minimize possible bias, we performed a sensitivity analysis considering only the last 12 years of birth (1950–1962). STATA 12.0 and Microsoft Excel 2011 software were used for data processing and statistical analysis.

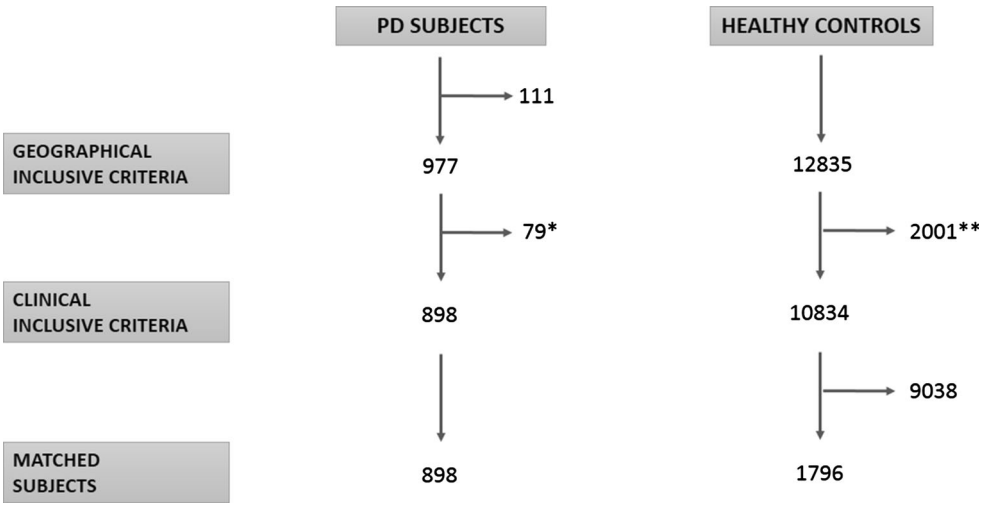

Fig. 1 Study tree displaying the number of included/excluded PD subjects and healthy controls at every stage of the study selection (PD = Parkinson's Disease; *asterisk* reasons for exclusion for PD subjects were: 19 subjects age <50 years old, 23 concomitant dementia, 37 concomitant cerebral vascular disease; *double asterisks* reasons for exclusion for healthy controls were: *2001* age <50 years old)

Table 1 Demographic characteristics of PD subjects and controls

	PD subjects ($n = 898$)	Controls ($n = 1796$)	p values
Age			
Mean ± SD	66.7 ± 7.7	66.7 ± 7.7	1.000
Range	50–83	50–83	
Gender			
Males/females	534/364	1068/728	1.000
Percentage	59.5/40.5	59.5/40.5	

PD Parkinson's Disease

Results

898 PD subjects admitted during the selected period met the inclusion criteria. After performing the matching we included 1796 healthy controls (Fig. 1). Demographic characteristics of the two groups are shown in Table 1. No significant difference was found in sex ($p = 1.000$) and age ($p = 1.000$, Table 1).

No difference was found between PD subjects and controls for the month of birth analysing all the months together, as well as when analysing each month separately, although we found a 1.9 % increase of PD subjects born in September comparing to controls that was not significant after Bonferroni correction ($p = 0.031$, Fig. 2). The analysis was repeated stratifying for gender and we found no significant difference for male subjects with PD comparing to controls. We found that 3.3 % more of female subjects with PD were born in September comparing to controls ($p = 0.018$) but it was not significant after Bonferroni correction. Table 2 shows frequencies of birth in each month of the year for both groups. We also considered the season of birth and we also found no statistically significant difference at this level, although male subjects with PD born in spring were 4.1 % higher than controls ($p = 0.031$, Fig. 3), but the result was not significant after Bonferroni correction.

In the second part of our study we evaluated a possible seasonality of the month of birth using a time series analysis looking at possible autocorrelation. When fitting a model with the variable reflecting the annual periodicity (flagging data every 12 months) the R^2 was 0.16; for the equation with a variable reflecting a meaningless periodicity of 13 the R^2 was also 0.16. Moreover, we performed a sensitivity analysis considering only the last period, starting from 1950, and also in this case there was no substantial difference in the R^2 values (R^2 0.35 and R^2 0.34, respectively).

Discussion

This study evaluated for the first time the seasonal birth trends in relation to PD in a southern European population, considering the hypothesis that sun exposure in pre-natal and early life might act on vitamin D3 levels and, subsequently, on the risk of developing PD. According to our findings we did not find any seasonality for the risk of PD.

Two previous studies explored risk of PD in relation to intrauterine influenza, and described absence of seasonal effect in PD birth variations [10, 11]. More in detail, Mattock et al. [11] found an excess of PD subjects born in May, although the study was conducted with a relatively small sample size. In a more recent study Postuma et al. [10] tested the same hypothesis on a much larger nationwide sample applying a highly appropriate methodology, and found no evidence of PD seasonality, with no month presenting more than 10 % excess in birth counts, as compared to expected values. By contrast, previous larger American studies showed a marginal not statistically significant increased risk for subjects born in spring [9] with a

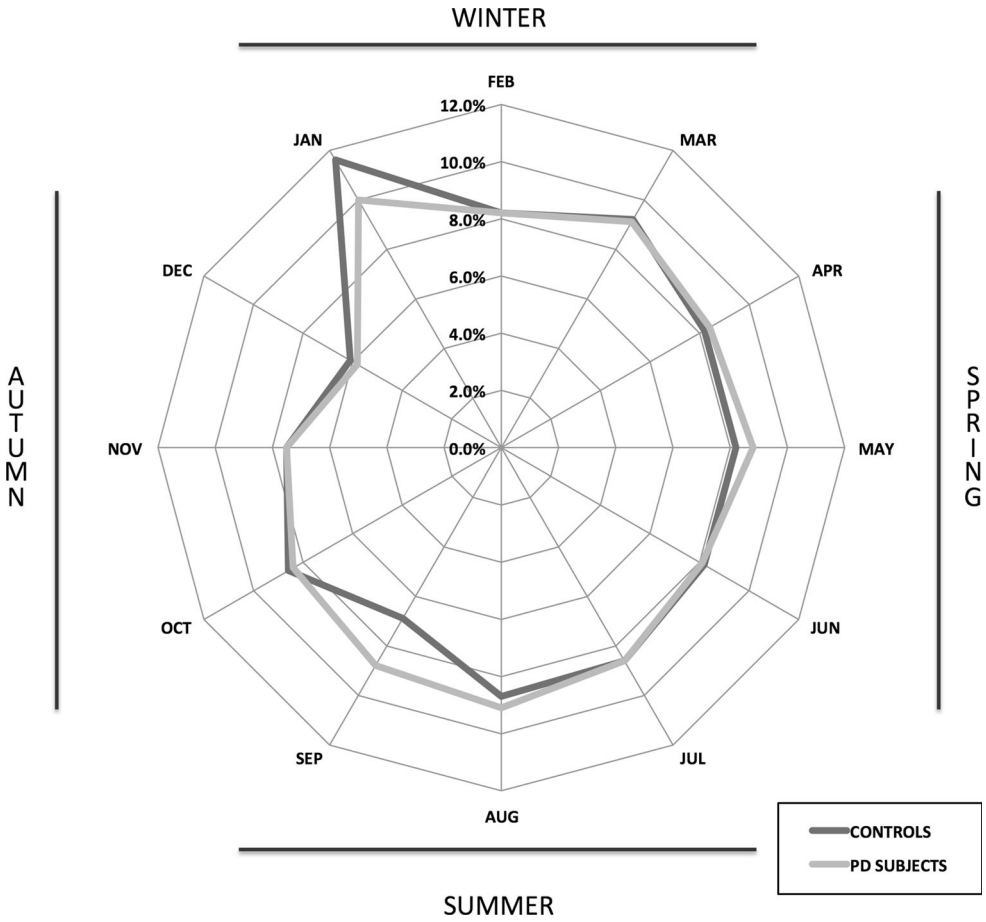

Fig. 2 Spider web plot of the distribution of monthly total of births for PD subjects and controls. *PD* Parkinson's Disease

Table 2 Distribution of months of birth of PD subjects and controls

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Pooled data													
Controls	209	148	165	147	147	147	155	157	123	154	134	110	1796
%	11.6	8.2	9.2	8.2	8.2	8.2	8.6	8.7	6.9	8.6	7.5	6.1	100.0
PD subjects	90	74	82	75	79	73	70	82	79	75	67	52	898
%	10.0	8.2	9.1	8.4	8.8	8.1	7.8	9.1	8.8	8.4	7.5	5.8	100.0
Male													
Controls	131	87	94	75	83	91	88	97	83	105	72	62	1068
%	12.3	8.2	8.8	7.0	7.8	8.5	8.2	9.1	7.8	9.8	6.7	5.8	100.0
PD subjects	58	40	48	44	54	44	43	45	47	49	35	27	534
%	10.9	7.5	9.0	8.2	10.1	8.2	8.1	8.4	8.8	9.2	6.6	5.1	100.0
Female													
Controls	78	61	71	72	64	56	67	60	40	49	62	48	728
%	10.7	8.4	9.8	9.9	8.8	7.7	9.2	8.2	5.5	6.7	8.5	6.6	100.0
PD subjects	32	34	34	31	25	29	27	37	32	26	32	25	364
%	8.8	9.3	9.3	8.5	6.9	8.0	7.4	10.2	8.8	7.1	8.8	6.9	100.0

PD Parkinson's disease

peak of births in May [12]. This hypothesis is corroborated by findings in MS [13] as an excess of birth during spring in different North European countries is well related to concomitant reduced vitamin D3 levels [14, 15]. However, most of these studies have been conducted at higher latitudes comparing to Naples area. Moreover, a recent study

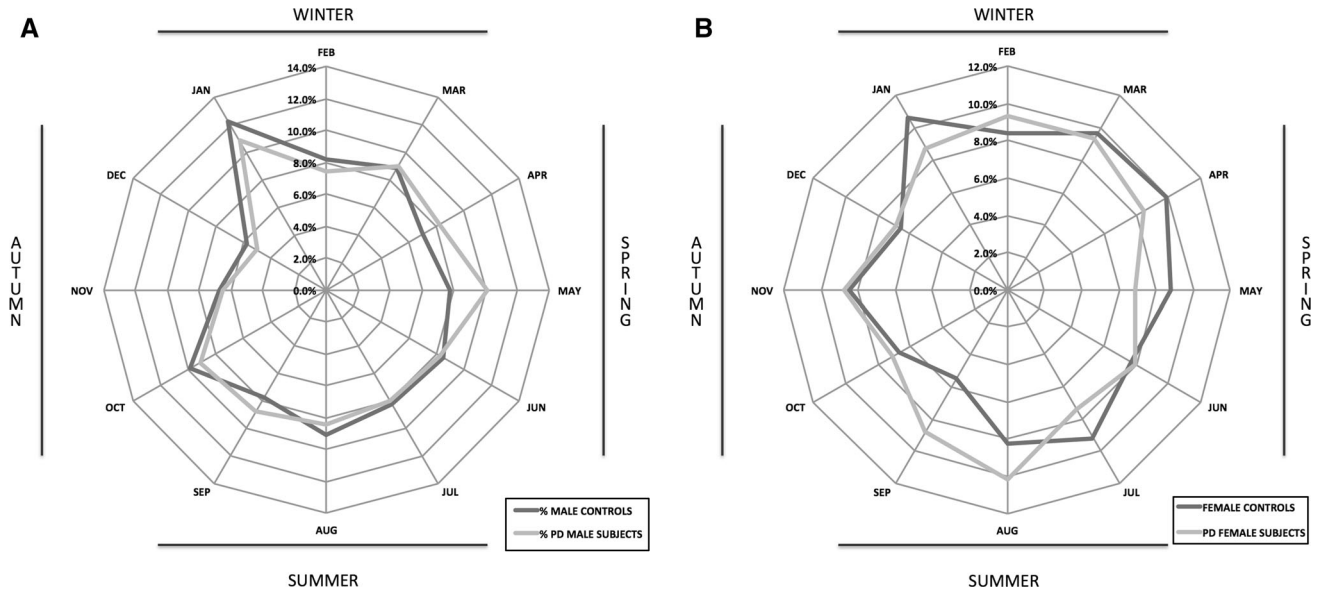

Fig. 3 Spider web plot of the distribution of monthly total of births for PD subjects and controls stratified by gender. *PD* Parkinson's Disease

showed that effect of sun exposure on MS can be different in relation to the latitude [16]. Therefore, a possible explanation of our findings is that the typical weather of the Naples area, that is located in the lower part of the temperate zone that features a constant sun exposure along the year [17], reduces the seasonal variations in vitamin D3 levels.

Although our sample is from a homogeneous area, we must acknowledge that is relatively small, however, it is considered sufficient by our power analysis estimation to detect a possible effect. Moreover, we did not consider clinical data and, subsequently, scales such as the Unified Parkinson's Disease Rating Scale or the Hoehn and Yahr, were not available. Furthermore, we did not assess vitamin D levels and, thus, our conclusions are only supported by previous studies showing variability of vitamin D in relation to the season of birth [14, 15]. Finally, we performed a cross-sectional study that is not the best design to investigate a causal effect. However, matching PD subjects with healthy controls for sex and age, and the exclusion of subjects born or living outside the area, reduced possible bias from different environmental and time conditions, as it can happen when matching PD subjects to unweighted national population [14].

In conclusion, in spite of previous significant evidence supporting the importance of vitamin D in PD risk and progression, we did not find a trend of increased risk of PD for subjects born during spring in the area of Naples. Therefore, it is possible that the low seasonal variability of sun exposure levels in geographical areas like the lower part of the temperate zone might be responsible for such results. Future studies should be conducted in different geographic areas to minimize possible differences in environmental factors, and should integrate weather information together with laboratory findings to further investigate the importance of vitamin D levels and of sun exposure in PD.

Conflict of interest The authors have neither financial disclosures nor conflict of interests to declare in relation to the content of this paper.

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