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Alpha-synuclein at the interface between depression and neurodegeneration: Evidence from epidemiological and genetic data

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Abstract

Parkinson's disease (PD) and Alzheimer's disease (AlzD) are the two most common neurodegenerative disorders. Although these two disorders differ in terms of their underlying pathophysiology, clinical features, and course, there is a certain degree of overlap between them. This overlap may be partly related to alpha-synuclein (α-synuclein)-mediated neuropathological changes. Recent evidence has found that depression is associated with increased subsequent risk of both these neurological disorders and α-synuclein may also play a pathogenic role in depression. In the current study, epidemiological, population genetic, and environmental exposure data were examined in relation to the estimated prevalence of depressive disorders, PD, and AlzD using a cross-sectional, country-level analysis. The results showed a significant relationship between depressive disorders and neurodegenerative disorders, a possible shared genetic vulnerability related to the functional polymorphisms of *SNCA* gene, and potential gene-environment interactions involving fine particulate matter pollution. The significance of these results is discussed in light of existing translational, clinical, and epidemiological research on the links between these disorders.

Keywords: Alpha-synuclein; *SNCA*; Major depression; Dysthymia; Parkinson's disease; Epidemiology

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1. Introduction

Alzheimer's disease (AlzD) and Parkinson's disease (PD) are the most prevalent neurodegenerative disorders globally[1,2]. The burden associated with these disorders is expected to increase substantially over the next three decades, particularly in low- and middle-income countries, largely due to demographic shifts[3,4]. Both these disorders are chronic and progressive in nature, and they are associated with substantial disability, caregiver burden, and financial loss[5-8]. AlzD is mainly characterized by progressive memory impairment and loss of other cognitive functions[9], while PD is characterized by progressive motor symptoms and disability[10]. Despite their clinical and pathophysiological distinctiveness, there are significant clinical and neuropathological overlaps between them. Clinically, PD is associated with high rates of cognitive impairment, including dementia[11]; likewise, a subset of patients with AlzD tend to show signs of parkinsonism[12]. Pathologically, beta-amyloid (β-amyloid) deposition, which

is typical of AlzD, has been reported in patients with PD and related syndromes, in which it appears to correlate with cognitive impairment[13,14]. Similarly, alpha-synuclein (α-synuclein), which is specifically associated with PD, has been found to be elevated in the cerebrospinal fluid of patients with AlzD and may be linked to the severity of cognitive deterioration[15]. At a molecular level, α-synuclein appears to increase the production of β-amyloid from amyloid precursor protein (APP), and this effect may be mediated through the induction of beta-secretase, an enzyme that converts APP into β-amyloid[16].

Both PD and AlzD are associated with neuropsychiatric manifestations, particularly symptoms of depression and anxiety[17-19]. In PD, depressive symptoms are associated with more severe cognitive and motor coordination deficits[20,21], and fluctuations in mood and anxiety are associated with motor fluctuations[22], thus suggesting a shared pathophysiological link between these symptoms. Symptoms of anxiety and depression are also common in patients with AlzD and may reflect neurodegenerative changes in their cortical and limbic brain regions; however, such symptoms tend to be more severe in the early stages of the disease but decrease in severity as cognitive deficits worsen[23].

The chronic and progressive nature of both these disorders and the lack of effective disease-modifying treatment in patients with well-established motor or cognitive symptoms of either disorder have led researchers and clinicians to consider the possibility of early intervention in both PD and AlzD[24,25]. For such an approach to be effective, it would require early identification of specific biomarkers of disease risk and progression[26,27], early or "prodromal" symptoms that are associated with progression to marked neurodegeneration, and overt cognitive or motor symptoms[25,28], or both.

Recent research has drawn attention to a link between certain psychiatric disorders, particularly depression, anxiety disorders, and post-traumatic stress disorder, and the subsequent emergence of either PD or various subtypes of dementia, including AlzD[29,30]. Among these psychiatric disorders, the most consistent and significant associations have been reported for depression[31]. In a study of patients with severe depression without signs of parkinsonism, 6.5% of them developed PD over a nine-year follow-up[32]. A meta-analysis of eleven studies has found that depression is associated with at least a two-fold increase in risk of subsequent Parkinsonism regardless of age; the results remained significant even after adjusting for potential confounders[33]. Likewise, a meta-analysis of longitudinal studies has found a significant association between depression and the subsequent risk of AlzD, with stronger effects observed in severe- or late-life depression[34]; according to a review of six meta-analyses, syndromal depression is associated with a 1.5-fold increase in rates of subsequent AlzD[35]. The exact mechanism underlying these associations is unknown, but various mechanisms have been suggested to account for these links. These include immune-inflammatory dysfunction, dysfunction related to monoaminergic pathways, altered microglial or astrocytic functioning, and shared risk factors, such as stress or environmental toxins. There is a significant degree of overlap between these proposals; for instance, air pollution or stress can cause altered immune-inflammatory activity, which can lead to alteration in microglial activity, in turn causing neural inflammation and cell damage[36-40]. At a molecular level, there is now significant translational and clinical evidence suggesting that α-synuclein may also play a role in this association. In animal models, increased expression of α-synuclein is associated with depressive- and anxiety-like behaviors, and treatments that reverse depression are associated with reduced α-synuclein aggregation[41-43]. Similarly, chronic exposure to corticosterone, mimicking the biochemical effects of chronic stress, worsened the neural and behavioral changes in a mouse model of α-synucleinopathy[44]. Studies in human patients with depression without features of PD or AlzD have shown increased serum α-synuclein and α-synuclein expression, as indicated by increased messenger RNA (mRNA) levels[45-47]. In addition, a study has found an indirect association between the cerebrospinal fluid levels of α-synuclein and cognitive impairment in patients with depression[48]. Variations in the expression of *SNCA* gene, which encodes α-synuclein, have also been associated with the response to antidepressants in elderly individuals with depression[49]. It is therefore plausible that alterations in the expression of α-synuclein may represent a common pathway linking depression with the subsequent risk of PD or AlzD. The aim of the current study was to examine the plausibility of this association through the analysis of epidemiological, population genetic, and environmental risk factor data.

The objectives of this study were as follows:

(i) To examine the cross-sectional and longitudinal associations between the prevalence of depression, AlzD and PD over a certain period (1990 – 2019) using data from the global burden of disease study;
(ii) To examine the relationship between population-level variations in specific polymorphisms of *SNCA* gene and the prevalence of these disorders, both cross-sectionally and longitudinally;
(iii) To examine whether these associations remain significant after correction for two established environmental risk factors for AlzD and PD: air pollution and pesticide exposure.

2. Materials and methods

2.1. Materials

The Global Burden of Disease Study, which began in the year 1990 and was most recently updated in 2019, represents a systematic attempt to estimate the prevalence, burden, and outcome associated with diseases and their risk factors at a global level[50]. Data on the estimated prevalence of depressive disorders (major depressive disorder [MDD] and dysthymia), PD, and AlzD and related dementias were retrieved for the years 1990 and 2019 through database queries from the Global Health Data Exchange, which provides access to the entire data set of the Global Burden of Disease Study[51]. MDD, which is characterized by distinct episodes of depression with total or partial inter-episode recovery, has been consistently associated with both PD and AlzD[32-34]. Since older research has suggested that dysthymia may be associated with PD[52], it was also included in the analyses.

Several polymorphisms of *SNCA* gene have been associated with the risk or symptomatology of PD[53,54]. Although the association between this gene and AlzD has not been subjected to a comparable level of study, there is both direct and indirect evidence that variants in *SNCA* are correlated with the risk of AlzD and its underlying pathophysiology[55-58]. Recent research has suggested that *SNCA* may also be a candidate gene for major depression[59]. In light of these findings, the relationship between selected functional polymorphisms of the *SNCA* gene and the prevalence of major depression, PD, and AlzD was examined at a population level.

For the purpose of this analysis, data on allele frequencies for these polymorphisms were obtained from the Allele Frequency Database, a public-domain repository that contains data on over 660,000 genetic polymorphisms in 762 distinct populations[60,61]. Although this database contains data on several polymorphisms of *SNCA*, most of them are of unknown functional significance. Only polymorphisms that fulfilled the following criteria were selected for analysis:

(i) Evidence of an association of the specific polymorphism with either the disorders being studied or with their clinical manifestations based on human genetic studies;
(ii) Availability of data for diverse populations across 15 or more countries.

On the basis of these criteria, the following functional single-nucleotide polymorphisms (SNPs) of *SNCA* were selected for analysis: *rs356220*, *rs2736990*, and *rs3775439*. Details of the functional significance of these polymorphisms and the availability of allele frequency data for each of them are shown in Table 1[62-66].

Table 1. Functional polymorphisms of the alpha-synuclein gene *SNCA* analyzed in the current study and their significance

Polymorphism	Functional significance	Data availability
rs356220 (C/T)	Known to be associated with an increased risk of Parkinson's disease in both European and Asian populations[67] and more severe cognitive decline in Parkinson's disease[68]	18 countries
rs2736990 (T/C)	Known to be associated with an increased risk of Parkinson's disease, especially in East Asian populations[69], and altered levels of specific *SNCA* transcripts[68]	32 countries
rs3775439 (G/A)	The minor allele (*A*) is known to be associated with an increased risk of Parkinson's disease in the elderly[70] and may interact with other genes to influence the risk of developing Parkinson's disease[71]	32 countries

Among the environmental risk factors linked to both PD and AlzD, air pollution and pesticide exposure have shown to be the most consistently replicated associations[67-69]. Environmental air pollution, particularly exposure to particulate matter with a diameter of ≤2.5 microns (PM2.5), has been associated with significantly increased risk for both PD and AlzD in studies across 26 countries[70] and increased rates of depression[71]. Cumulative exposure to pesticides is associated with an approximately 50% relative risk increase for both PD and AlzD[72]; there is also evidence of a link between pesticide exposure and depression[73]. Genetic factors may partially mediate the association between pesticide exposure and PD[74]. Therefore, the effect of these two environmental factors on the possible associations between depression, PD, and AlzD was also examined in the current study through epidemiological and population genetic analyses. Information on the PM2.5 levels of each of the 193 countries and regions under the WHO's Global Health Observatory[75] and data on the levels of pesticide exposure, measured in terms of average pesticide application (in kilograms) per unit of cropland (in hectares), were obtained from the Food and Agriculture Organization's FAOSTAT database[76].

2.2. Methods

The identification of a positive correlation between the prevalence of distinct disorders across populations is suggestive, but not confirmatory, of a significant association between them. Such an association may also arise by chance or may be related to confounding factors[77]. Similar concerns arise when attempting to correlate putative risk factors, either genetic or environmental, with the

prevalence of specific disorders. In the current study, it is possible that depression, PD, and AlzD share common risk factors and depression may predict the subsequent risk of developing PD or AlzD. To test these hypotheses and minimize the risk of false-positive findings, the analysis of the aforementioned data was carried out according to the following steps:

(i) Direct bivariate correlations were computed between the prevalence of depression, PD, and AlzD at both time points (1990 and 2019);
(ii) A cross-lagged regression analysis was carried out between the two time points (1990 and 2019); in this model, a significantly greater "cross-correlation" between depression in 1990 and PD/AlzD in 2019 than that between PD/AlzD in 1990 and depression in 2019 would strengthen the possibility of a causal relationship[78];
(iii) Bivariate correlations were computed to examine the association between the prevalence of depression in 1990 and the percentage of change in the prevalence of PD and AlzD between 1990 and 2019; a positive correlation between these variables would also suggest a causal relationship;
(iv) For population genetic data, estimated allele frequency distributions were correlated with both the prevalence of each disorder at each time point and the percentage of change in the prevalence of each disorder over time;
(v) A general linear model was used to examine the influence of *SNCA* gene polymorphisms and baseline prevalence of depression on changes in the prevalence of PD and AlzD over the study period (1990–2019);
(vi) All the aforementioned analyses were adjusted for PM2.5 levels and pesticide exposure.

2.3. Data analysis

All study variables were tested for normality prior to further analysis using the Shapiro-Wilk test. Paired-samples *t*-test was performed to determine if the changes in the prevalence of depression, PD, and AlzD over the study period (1990 – 2019) were statistically significant.

Bivariate correlations were computed using Pearson's coefficient (*r*) and Pearson's partial coefficient (partial *r*). Analyses of epidemiological data were corrected for multiple comparisons using Bonferroni's method. Analyses of genetic data were not subjected to this correction due to the small number of cases available for study. Adopting such a method would raise the possibility of a false-negative finding. The strength of bivariate correlations was quantified using standard guideline values for biomedical research[79].

Repeated measures analysis of variance was used to examine the influence of *SNCA* polymorphisms and the baseline levels of depression on changes in the prevalence of PD and AlzD across countries.

All analyses were carried out using Statistical Package for the Social Sciences, version 26.0 (SPSS 26.0). All tests were two-tailed, and a significance level of $P < 0.05$ was used for all analyses in this study.

3. Results

Epidemiological and genetic data analyses were carried out for 204 countries and 32 countries, respectively, while environmental data analyses in relevance to PM2.5 and pesticide were carried out for 193 countries and 155 countries, respectively. The estimated prevalence of depression, PD, and AlzD in 1990 was 3.46%, 0.07%, and 0.40%, respectively, while that in 2019 was 3.95%, 0.11%, and 0.69%, respectively. The mean increases in the prevalence of each disorder over this 30-year period were 15.95% for depression, 11.30% for PD, and 66.67% for AlzD. All these changes were statistically significant (depression: $t = 14.93$, $P < 0.001$; PD: $t = 14.06$, $P < 0.001$; AlzD: $t = 12.13$, $P < 0.001$), indicating substantial increases in the prevalence of all three disorders over this period.

3.1. Bivariate correlations between the prevalence of depression and both PD and AlzD

The results of direct correlations between the estimated prevalence of depression and both PD and AlzD in the years 1990 and 2019 are presented in Table 2. From these results, it can be seen that the prevalence of all forms of depression (major depression, dysthymia, and depressive

Table 2. Correlations between the prevalence of depression and both Parkinson's disease and Alzheimer's disease in 1990 and 2019

Year	Variable	Parkinson's disease	Alzheimer's disease
1990	Depression	0.49 (<0.001)[a]	0.53 (<0.001)[a]
	MDD	0.38 (<0.001)[a]	0.43 (<0.001)[a]
	Dysthymia	0.62 (<0.001)[a]	0.61 (<0.001)[a]
	Depression*	0.45 (<0.001)[a]	0.51 (<0.001)[a]
	MDD*	0.35 (<0.001)[a]	0.41 (<0.001)[a]
	Dysthymia*	0.59 (<0.001)[a]	0.56 (<0.001)[a]
2019	Depression	0.31 (<0.001)[a]	0.34 (<0.001)[a]
	MDD	0.19 (0.004)[b]	0.25 (<0.001)[a]
	Dysthymia	0.47 (<0.001)[a]	0.35 (<0.001)[a]
	Depression**	0.24 (0.004)[b]	0.22 (0.006)[b]
	MDD**	0.16 (0.054)	0.19 (0.022)[b]
	Dysthymia**	0.34 (<0.001)[a]	0.17 (0.037)[b]

MDD: Major depressive disorder. [a]Significant at $P < 0.05$ after applying Bonferroni's correction. [b]Significant at $P < 0.05$, uncorrected. *Adjusted for life expectancy. **Adjusted for life expectancy, particulate matter (PM2.5) pollution, and pesticide exposure

disorders as a whole) was significantly and positively correlated with the prevalence of both PD and AlzD at both time points, even after correction for multiple comparisons. The magnitude of these correlations was somewhat greater in 1990 (r = 0.38 – 0.61) than in 2019 (r = 0.19 – 0.47) and appeared to be slightly greater for dysthymia (r = 0.35 – 0.62) than for major depression (r = 0.19 – 0.38). When these associations were adjusted for life expectancy (in 1990 and 2019) and environmental risk factors (in 2019), their strength was somewhat attenuated (r = 0.16 – 0.59), but they remained statistically significant. This suggests that the link between these disorders cannot be entirely ascribed to shared environmental risk factors.

3.2. Cross-lagged regression analysis of depression, PD, and AlzD

The results of cross-lagged regression analysis are presented in Table 3. From these results, it can be seen that the cross-correlations between depressive disorders in 1990 and PD/AlzD in 2019 were greater (r = 0.34 – 0.60) than those between PD/AlzD in 1990 and depressive disorders in 2019 (r = 0.22 – 0.41). For depressive disorders as a whole and for major depression, this difference was not statistically significant (regression coefficient: 0.09 – 0.14, $P > 0.05$). However, for dysthymia, this difference was statistically significant (dysthymia/PD: 0.19, $P = 0.005$; and dysthymia/AlzD: 0.21, $P = 0.004$). These results support the possibility of a causal relationship; in other words, dysthymia appears to be prospectively associated with the subsequent risk of PD and AlzD.

3.3. Bivariate correlations between *SNCA* allele frequencies, depression, PD, and AlzD

The associations between population genetic data and the prevalence of each specific disorder are presented in Table 4. In these analyses, the frequencies of all three alleles included in this study (*rs356220*, *rs2736990*, and *rs3775439*) showed significant correlations with the estimated prevalence of depressive disorders at both time points. The *rs2736990* and *rs3775439* allele frequencies were significantly correlated with the prevalence of both PD and AlzD. After correcting for possible confounding factors (life expectancy, air pollution, and pesticide exposure), only the *rs3775439* allele frequency distribution remained significantly and negatively correlated with the prevalence of depression and PD (at both time points) as well as AlzD (in 1990). This suggests that the distribution of the *rs3775439 (A)* allele across populations may be associated with a lower prevalence of the aforementioned disorders.

To examine the possibility that the above association might be mediated by depression, partial correlation analyses of the associations between each allele frequency and both PD and AlzD were carried out, while adjusting for the prevalence of depression (Table 5). In these analyses, the association between *SNCA* variants and both PD and AlzD was not significant after adjusting for MDD but remained significant when adjusting for dysthymia. This suggests that while *SNCA* gene variants may influence the development of both MDD and neurological disorders, these variants may interact with dysthymia to influence the risk of subsequent PD or AlzD.

3.4. Bivariate correlations between depression, *SNCA* allele frequencies, and changes in PD and AlzD over time

The results of these analyses are presented in Tables 6 and 7. In both the unadjusted and unadjusted analyses, neither the baseline prevalence of depression nor the frequencies of specific *SNCA* alleles were significantly correlated with subsequent increases in the prevalence of PD or AlzD. There was a positive correlation between changes in the prevalence of depression and changes in the prevalence of PD or AlzD over the study period, but only the correlation with PD remained significant after adjusting for life

Table 3. Cross-lagged regression analyses of the associations between depression, Parkinson's disease, and Alzheimer's disease

Association	Cross-correlation (depression in 1990 to neurological disorder in 2019)	Cross-correlation (neurological disorder in 1990 to depression in 2019)	Regression coefficient	Interpretation
Depression and Parkinson's disease	0.46	0.32	0.14	Causal relationship not supported
Major depression and Parkinson's disease	0.34	0.22	0.12	Causal relationship not supported
Dysthymia and Parkinson's disease	0.60	0.41	0.19[a]	Causal relationship supported
Depression and Alzheimer's disease	0.47	0.37	0.10	Causal relationship not supported
Major depression and Alzheimer's disease	0.38	0.29	0.09	Causal relationship not supported
Dysthymia and Alzheimer's disease	0.54	0.33	0.21[a]	Causal relationship supported

[a]Significant at $P<0.05$

Table 4. Correlations between frequencies of *SNCA* gene polymorphisms and depression, Parkinson's disease, and Alzheimer's disease

SNCA variant	Major depression	Dysthymia	Depression	Parkinson's disease	Alzheimer's disease
			1990		
rs356220 (A)					
Unadjusted	0.58[a]	0.48[a]	0.62[a]	0.43	0.59[a]
Adjusted*	0.47	0.35	0.50[a]	0.11	0.35
rs2736990 (C)					
Unadjusted	−0.47[a]	−0.36[a]	−0.48[a]	−0.47[a]	−0.55[a]
Adjusted*	−0.31	−0.19	−0.31	−0.17	−0.28
rs3775439 (A)					
Unadjusted	−0.75[a]	−0.57[a]	−0.76[a]	−0.65[a]	−0.72[a]
Adjusted*	−0.69[a]	−0.48[a]	−0.70[a]	−0.52[a]	−0.64[a]
			2019		
rs356220 (A)					
Unadjusted	0.58[a]	0.21	0.62[a]	0.50[a]	0.46
Adjusted**	0.48	0.74[a]	0.63[a]	0.37	−0.11
rs2736990 (C)					
Unadjusted	−0.50[a]	−0.26	−0.53[a]	−0.49[a]	−0.45[a]
Adjusted**	−0.38	−0.32	−0.41	−0.07	−0.01
rs3775439 (A)					
Unadjusted	−0.71[a]	−0.24[a]	−0.72[a]	−0.51[a]	−0.45[a]
Adjusted**	−0.62[a]	−0.52[a]	−0.68[a]	−0.47[a]	−0.04

SNCA: Alpha-synuclein gene. *Adjusted for life expectancy. **Adjusted for life expectancy, particulate matter (PM2.5) pollution, and pesticide exposure. [a]Significant at $P < 0.05$

Table 5. Correlations between frequencies of *SNCA* gene polymorphisms and both Parkinson's disease and Alzheimer's disease, corrected for the prevalence of depressive disorders

SNCA variant	Parkinson's disease (1990)	Parkinson's disease (2019)	Alzheimer's disease (1990)	Alzheimer's disease (2019)
rs356220 (A)				
Adjusted for MDD	0.12	0.39	0.34	0.42
Adjusted for Dys	0.18	0.46	0.42	0.49[a]
Adjusted for Dep	0.01	0.34	0.26	0.45
rs2736990 (C)				
Adjusted for MDD	−0.23	−0.33	−0.34	−0.33
Adjusted for Dys	−0.34	−0.43[a]	−0.46[a]	−0.44[a]
Adjusted for Dep	−0.20	−0.29	−0.32	−0.32
rs3775439 (A)				
Adjusted for MDD	−0.25	−0.28	−0.37[a]	−0.27
Adjusted for Dys	−0.42[a]	−0.47[a]	−0.55[a]	−0.44[a]
Adjusted for Dep	−0.17	−0.22	−0.29	−0.27

All statistics are given as Pearson's partial *r*. Dep: Depression; Dys: Dysthymia; MDD: Major depressive disorder; SNCA, Alpha-synuclein gene. [a]Significant at $P < 0.05$

expectancy. These results do not support a prospective longitudinal association between depression, PD, and AlzD; instead, they are more suggestive of possible shared risk factors for all three conditions.

Table 6. Bivariate correlations between depression, *SNCA* allele frequencies, and changes in Parkinson's disease and Alzheimer's disease in the period 1990 – 2019

Variable	MDD, baseline prevalence	Dysthymia, baseline prevalence	Depression, baseline prevalence	*rs356220*	*rs2736990*	*rs3775439*
Parkinson's disease, change (%)						
Unadjusted	−0.13	0.07	−0.10	−0.01	−0.09	0.35
Adjusted*	−0.13	0.03	−0.11	0.01	−0.11	0.33
Alzheimer's disease, change (%)						
Unadjusted	−0.03	0.07	−0.01	0.09	−0.20	0.18
Adjusted*	−0.03	0.04	−0.02	0.09	−0.21	0.17

MDD: Major depressive disorder. *Adjusted for changes in life expectancy over the period 1990–2019

Table 7. Bivariate correlations between changes in the prevalence of depression and both Parkinson's disease and Alzheimer's disease in the period 1990 – 2019

Variable	MDD, change (%)	Dysthymia, change (%)	Depression, change (%)
Parkinson's disease, change (%)			
Unadjusted	0.12	0.11	0.26[a]
Adjusted*	0.08	0.10	0.23[a]
Alzheimer's disease, change (%)			
Unadjusted	0.09	0.06	0.17[a]
Adjusted*	0.05	0.05	0.13

MDD: Major depressive disorder. *Adjusted for changes in life expectancy over the period 1990–2019. [a]Significant at $P < 0.05$

3.5. General linear model analyses of changes in PD and AlzD over time

The results of repeated measures analyses of variance are presented in Table 8. As observed in the independent sample *t*-tests, there was a significant increase in the prevalence of both disorders (PD: $F = 197.78$, $P < 0.001$; AlzD: $F = 147.24$, $P < 0.001$) over time. There was a significant effect of the baseline prevalence of all forms of depression on this increase for both PD and AlzD over time. In contrast, no such effect was observed for the frequencies of *SNCA* polymorphisms included in this study. These results are suggestive of a prospective relationship between the baseline levels of depression in a population and the subsequent risk of both PD and AlzD.

4. Discussion

The current study was conducted to strengthen the evidence supporting the association between depressive disorders, AlzD, and PD as well as to investigate the potential effect of functional polymorphisms of the *SNCA* gene on these associations, while adjusting for confounding factors. Significant associations were found between the prevalence of depressive disorders and that of both PD and AlzD at a cross-national level. When longitudinal methods of analysis were adopted, two out of the three analyses (cross-lagged regression and general linear models) were suggestive of a prospective association between depression and the subsequent risk of both neurological disorders (Table 3 and Table 8). These results are consistent with existing evidence on the shared pathogenic mechanisms for these disorders[80-83] and the results of longitudinal research in community samples demonstrating a prospective link between depressive disorders and neurodegenerative disorders[84-87]. Prior evidence has suggested that the links between depression and both PD and AlzD are mediated by genetic vulnerability[88-90] and exposure to environmental risk factors, such as stress and environmental toxins[91-93]. These two sets of risk factors do not operate in isolation. There is preliminary evidence that the development of subsequent PD is influenced by gene-environment interactions between genetic risk and diabetes mellitus as well as between genetic variants and pesticide exposure[74,94].

In this study, the cross-sectional association between dysthymia and each neurological disorder was stronger than that observed for MDD (Table 2), and dysthymia was the only form of depression that showed evidence of a prospective link with both PD and AlzD in the cross-lagged analyses (Table 3). Dysthymia is defined as a chronic form of depression, characterized by mild but persistent depressive symptoms that remain below the diagnostic threshold for MDD[95]. Many patients with dysthymia have superimposed episodes of MDD, in which this is referred to as "double depression"[96]. Dysthymia has not been studied as extensively as MDD in relation to PD or AlzD. According to available data, at least 13% patients with established PD fulfill the diagnostic criteria for dysthymia[97]. Furthermore, a study has found that 28% of AlzD patients qualify for a diagnosis of dysthymia[98]. The presence of dysthymia has also been found to be associated with the occurrence of extrapyramidal features

Table 8. General linear model analyses of changes in Parkinson's disease and Alzheimer's disease over the period 1990 – 2019

Variable	Time (1990 – 2019)	MDD	Dysthymia	Depression	*rs356220*	*rs2736990*	*rs3775439*
Parkinson's disease, change over time	197.78[a]	10.05[a]	47.30[a]	21.28[a]	3.89	3.69	0.66
Alzheimer's disease, change over time	147.24[a]	13.02[a]	30.98[a]	22.48[a]	1.21	2.47	0.68

MDD: Major depressive disorder. All test statistics were given as repeated measures analysis of variance (RMANOVA) or repeated measures analysis of covariance (RMANCOVA) test statistic (F). [a]Significant at $P<0.05$

in patients with AlzD[12]. Although no studies linking dysthymia to the levels of α-synuclein or *SNCA* gene have been done, a study of older adults with either depression or dysthymia has found evidence of abnormal dopamine transporter binding on single-photon emission computed tomography (SPECT), and these alterations are associated with prodromal features of PD[99]. In a similar imaging study comparing patients with MDD alone and those with MDD superimposed on dysthymia (double depression), ligand binding to striatal dopamine transporters was found to be inversely correlated with illness duration only in the double depression group[100]. These findings, although few in number, are consistent with the possibility of a shared "hypodopaminergic" phenotype, characterized by specific neuropsychological deficits, that can be identified in patients with depressive disorders, AlzD, and PD[80]. It is possible that some cases of dysthymia may reflect an early or prodromal stage of neurodegenerative disorders linked to dopaminergic deficit. This possibility is also supported by the overlap between some of the core symptoms of dysthymia, such as fatigue and apathy, and the non-motor symptoms of PD[101]. When adjusting for PM2.5 levels and pesticide exposure in the present study, the relationship between dysthymia and both PD and AlzD remained significant. This suggests that depressive disorders and environmental toxins may independently influence the risk of neurodegenerative disorders, similar to what earlier studies have discovered[102].

When examining the relationship between the allele frequencies of specific *SNCA* SNPs in the current study, it was found that the distributions of all three SNPs (*rs356220*, *rs2736990*, and *rs3775439*) were significantly correlated with the prevalence of depression, PD, and AlzD at both time points (Table 4). With the exception of dysthymia in 2019, the strengths of the observed correlations were almost identical in 1990 and 2019, which is consistent with the relatively "fixed" effect that would be expected from specific vulnerability loci. After adjustment for confounding factors, the *rs3775439 A→G* polymorphism remained significantly associated with depression, PD, and AlzD. These results should be interpreted with caution in view of the minimal number of countries for which data were available (n = 18–32). However, they are consistent with the hypothesis of a shared genetic vulnerability for these disorders. A large-scale analysis of genome-wide association data has found plausible evidence that the *SNCA* gene is involved in the shared genetic vulnerability for PD and AlzD[103], and recent evidence has implicated the *SNCA* gene in the pathogenesis of depressive disorders[59]. Although a definitive causal association cannot be established through the current results, they do provide some support to the growing body of evidence implicating α-synuclein in the pathophysiology of depression[47-49] and AlzD[16,104,105]. The links between *SNCA* and both PD and AlzD were not significant after correcting for the prevalence of MDD; however, they remained significant after adjusting for dysthymia. When taken in conjunction with the results of direct bivariate correlations between *SNCA* distributions and depression, the following tentative interpretation can be advanced: certain functional polymorphisms of *SNCA* may be a shared risk factor for MDD, PD, and AlzD, and they may interact with dysthymia to influence the subsequent risk of both neurological disorders. Although it is intriguing and consistent with recent clinical evidence[17], this association is purely ecological in nature and requires careful evaluation in clinical and community samples.

The analysis of gene-environment interactions based on ecological data has certain shortcomings, and such results should be interpreted with caution[106]. Therefore, these analyses were considered a secondary objective in the current study. After taking air pollution and pesticide exposure into account, two of the studied polymorphisms (*rs356220* and *rs2736990*) were no longer associated with either PD or AlzD, suggesting that if these genes do truly represent vulnerability factors for either disorder, they do so only in association with exposure to environmental toxins. However, this was not observed in the case of *rs3775439*, thus suggesting the absence of such an interaction (Table 4). An earlier case-control study of patients with PD has found that the gene-environment interaction between exposure to ambient nitrogen dioxide (NO_2) and the functional polymorphism of *IL1β* gene is significant associated with the risk of PD[107]. It is possible that similar effects may occur in the case of *SNCA* gene variations, but this cannot be conclusively deduced from the current results.

Certain key limitations of the current study should be borne in mind. First, as the study was based on cross-national estimates, there may be a certain level of

uncertainty or error in each parameter that could affect the certainty of any conclusions drawn from these results. Second, any conclusions regarding causation should be considered provisional: evidence of significant cross-sectional or cross-lagged correlations does not necessarily imply a causal chain linking genetic variations, depressive disorders, and neurodegenerative disorders. Third, as the estimates used in this study covered countries in whole, they cannot account for variations within a country, such as urban/rural differences in particulate matter pollution or pesticide exposure. Fourth, the number of cases available for population genetic analysis was relatively low, and it was based on a relatively small number of volunteers who were willing to participate in research on allele frequencies. Fifth, the results obtained at the national level cannot be extrapolated directly to individuals. Sixth, since the research focus was on α-synuclein, other genes that may be involved in mediating the link between depression, environmental toxins, and neurodegenerative disorders, such as those involved in dopaminergic transmission or inflammation, were not analyzed. Finally, the effects of other environmental factors that may be associated with both AlzD and PD, such as diet, smoking, and other occupational exposures, could not be assessed in a study of this sort due to a lack of large-scale, cross-national data.

It should also be noted that epidemiological findings, even if replicated, represent a starting point for further research and not an end in themselves. To translate these findings into improved diagnostic and early intervention strategies, a deeper understanding of the molecular links between depression and neurodegeneration as well as the gene-environment interactions mediating these links is required. Innovative approaches aimed at elucidating this association include studies of epigenome or transcriptome[108,109] and genome-wide association studies that identify shared genetic components across these disorders[110]. The associations between the normal processes involved in brain aging and those implicated in neurodegeneration also represent a fruitful line of inquiry, given that depression may be associated with both these phenomena[111]. Such research would build on the foundations laid by epidemiological and genetic association studies and lead to a precision medicine-based approach to early intervention in PD and AlzD.

5. Conclusion

Despite certain inherent methodological limitations, the current study provides some evidence of a significant association between depressive disorders, particularly dysthymia, and the subsequent risk of PD and AlzD. This relationship may be partly related to the functional variants of the α-synuclein gene *SNCA*, either alone or in combination with exposure to environmental toxins. Although these results cannot be taken as definitive, they highlight the need for further investigations into the molecular mechanisms underlying this relationship. These results may be of value to those examining the shared pathophysiological basis of these conditions and pave the way for early intervention or preventive strategies for both PD and AlzD.

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Conflict of interest

The author declares that he has no competing interests.

Author contributions

This is a single-authored manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All the data used in this study were obtained from public domain databases that have been cited in the paper. A complete data sheet is available from the author, without undue reservation, on request.

Further disclosure

This paper has been uploaded to or deposited in a preprint server at *Preprints* (doi: 10.20944/preprints202209.0197.v1). However, the current paper is a substantial revision of the preprint and contains new results (longitudinal analyses) that were not included in the original preprint.

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