 doi:10.20944/preprints202209.0197.v1

Article

Alpha-Synuclein at the Interface between Depression, Parkinson's Disease and Dementia: Evidence from Epidemiology, Population Genetics and Gene-Environment Interactions

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

Keywords: alpha-synuclein; *SNCA*; major depression; dysthymia; Parkinson's disease; dementia; neurodegeneration; gene-environment interaction; $PM_{2.5;}$ pesticides

1. Introduction

Alzheimer's disease and Parkinson's disease are the most prevalent neurodegenerative disorders at a global level [1, 2]. The burden associated with both 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 diseases are chronic and progressive in nature, and are associated with substantial disability, caregiver burden, and economic costs [5-8]. Alzheimer's disease is characterized primarily by progressive impairment of memory and other cognitive functions [9], while Parkinson's disease is chiefly characterized by progressive motor symptoms and disability [10]. Despite their clinical and pathophysiological distinctiveness, there are certain significant overlaps between these conditions, both clinically and in terms of underlying neuropathological changes. Clinically, Parkinson's disease is associated with high rates of cognitive impairment, including dementia [11]; likewise, a subset of patients with Alzheimer's disease show signs of parkinsonism [12]. Pathologically, beta-amyloid deposition, though typical of Alzheimer's disease, has been documented in patients with Parkinson's disease and related syndromes, in which it appears to correlate with cognitive impairment [13, 14]; similarly, alpha-synuclein (α-synuclein), which is specifically associated with Parkinson's disease, is elevated in the cerebrospinal fluid of patients with Alzheimer's disease and may be linked to the severity of cognitive deterioration [15]. At a molecular level, α-synuclein appears to increase the production of beta-amyloid from amyloid precursor protein

 doi:10.20944/preprints202209.0197.v1

(APP), and this effect may be mediated through induction of the enzyme beta-secretase, which converts APP into beta-amyloid [16].

Both Parkinson's disease and Alzheimer's disease are associated with neuropsychiatric manifestations, particularly symptoms of depression and anxiety [17-19]. Depressive symptoms in Parkinson's disease are associated with more severe deficits in motor coordination [20] and cognition [21], and fluctuations in mood and anxiety are associated with motor fluctuations [22], suggesting a shared pathophysiological link between these domains of the disease. Symptoms of anxiety and depression are also prominent in patients with Alzheimer's disease and may reflect neurodegenerative changes in cortical and limbic brain regions; however, such symptoms tend to be more severe in the early stages of this disease and to decrease in severity as cognitive deficits progress [23].

The chronic and progressive nature of both these diseases, and the lack of effective disease-modifying treatments in patients with well-established motor or cognitive symptoms of either disorder, has led researchers and clinicians to consider the possibility of early intervention in both Alzheimer's disease and Parkinson's disease [24, 25]. To be effective, such an approach would require that patients are identified either through specific biomarkers of disease risk and progression [26, 27], through early or "prodromal" symptoms that are associated with progression to marked neurodegeneration and overt cognitive or motor symptoms [25, 28], or through a combination of both approaches. For example, it is now fairly well-established that idiopathic REM sleep behavior disorder (RBD), a parasomnia characterized by REM sleep without atonia and the "acting out" of dreams, often precedes the onset of neurodegeneration, particularly in Parkinson's disease and related synucleinopathies [29]. Low levels of cerebrospinal fluid α-synuclein have been associated with more severe symptoms of RBD in patients with early Parkinson's disease [30], while cutaneous levels of α-synuclein were associated with autonomic dysfunction – a non-motor symptom of Parkinsonism [31] – in patients with RBD but without any features of Parkinson's disease [32]. Thus, it is possible that the combination of RBD symptomatology and altered α-synuclein levels could identify a subset of patients at risk of progression to Parkinson's disease, and therefore suitable for trials of early interventions [25, 33].

More recently, attention has been focused on evidence suggesting a link between certain psychiatric syndromes – particularly depression, anxiety disorders, and post-traumatic stress disorder (PTSD) – and the subsequent emergence of either Parkinson's disease or various subtypes of dementia, including Alzheimer's disease [34, 35]. Among these psychiatric disorders, the most consistent and significant associations have been reported for depression [36]. In a study of patients with severe depression and no signs of parkinsonism, 6.5% of patients developed Parkinson's disease when followed up over 9 years [37], and a meta-analysis of eleven studies found that, regardless of age, a diagnosis of depression was associated with at least a two-fold increase in the risk of subsequent Parkinsonism; these results remained significant even after adjusting for potential confounders [38]. Likewise, a meta-analysis of longitudinal studies found a significant association between depression and the subsequent risk of Alzheimer's disease, with stronger effects noted for severe- or late-life depression [39], and a review of six meta-analyses found that syndromal depression was associated with a 1.5-fold increase in rates of subsequent Alzheimer's disease [40]. The exact mechanism underlying these associations is unknown, but various mechanisms have been suggested to account for this link. 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, and there is a significant degree of overlap between these proposals – for example, air pollution or stress can cause altered immune-inflammatory activity, which can lead to alteration in microglial activity, in turn causing neural inflammation

 doi:10.20944/preprints202209.0197.v1

and cell damage [41-45]. Apart from these mechanisms, there is now a significant amount of 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 behaviours, and treatments that reverse depression are associated with reduced α-synuclein aggregation [46-48]; similarly, chronic exposure to corticosterone, mimicking the biochemical effects of chronic stress, worsened the neural and behavioural changes associated with a mouse model of α-synucleinopathy [49]. Studies in human patients with depression and no features of Parkinson's or Alzheimer's disease have revealed increased serum α-synuclein [50] and increased α-synuclein expression as indicated by increased mRNA levels [51, 52], and cerebrospinal fluid levels of α-synuclein have been indirectly associated with cognitive impairment in patients with depression [53]. Variations in the expression of the *SNCA* gene, which encodes α-synuclein, have also been associated with the response to antidepressants in elderly individuals with depression [54]. It is therefore plausible that alterations in the expression of α-synuclein may represent a common pathway linking depression with the subsequent risk of Parkinson's disease or Alzheimer's disease. The current study aims to examine the plausibility of this association through the analysis of epidemiological, population genetic and environmental risk factor data.

2. Results

a. Epidemiological analysis

Data on the estimated prevalence of major depression (MDD), dysthymia (Dys), Parkinson's Disease (Park) and Alzheimer's disease (Alz) was available from the Global Burden of Disease Study (2019) for 204 countries and regions. Correlations between the prevalences of these four disorders – both uncorrected and adjusted for life expectancy – are presented in **Table 1**.

Table 1: Correlations between the estimated prevalence of depressive disorders, Parkinson's disease and Alzheimer's disease.

Disorder	**MDD-Prev**	**Dys-Prev**	**Park-Prev**	**Alz-Prev**
MDD-Prev	-	.01 (.867) .01 (.955)	.12 (.078) -.11 (.126)	.24 (<.01)* .07 (.350)
Dys-Prev		-	.52 (<.01)* .41 (<.01)*	.47 (<.01)* .36 (<.01)*
Park-Prev			-	.95 (<.01)* .85 (<.01)*

Abbreviations: MDD, major depressive disorder; Dys, dysthymia; Park, Parkinson's disease; Alz, Alzheimer's disease; Prev, estimated prevalence. All correlations are presented as: unadjusted Spearman's ϱ (significance level), adjusted Spearman's ϱ (significance level). All significance levels are corrected for a 4 x 4 correlation matrix. * denotes statistical significance at $p < .05$ after Bonferroni's correction.

In these analyses, it was observed that the prevalence of MDD was not significantly correlated with the prevalence of Parkinson's disease. A weak positive correlation was observed between the prevalences of MDD and of Alzheimer's disease was found, but this was not significant after adjusting for life expectancy. On the other hand, the estimated prevalence of dysthymia was significantly and positively correlated with the prevalence of both Parkinson's disease and Alzheimer's disease, and this remained significant at a fair level of magnitude even when considering life expectancy as a

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covariate. The prevalences of Parkinson's disease and of Alzheimer's disease were strongly correlated with each other at a cross-national level.

b. Population genetic analysis

Analyses of the correlations between variations in allele frequencies for the three relevant polymorphisms of the *SNCA* gene and the prevalence of MDD, Dys, Park and Alz are presented in **Table 2**. In these analyses, it can be observed that the distribution of the *A* allele of *SNCA rs356220* is positively correlated with the prevalence of depressive disorders as well as of Parkinson's disease and Alzheimer's disease, even after adjusting for life expectancy. On the other hand, both the *C* allele of *SNCA rs2736990* and the *A* allele of *SNCA rs3775439* were negatively correlated with the estimated prevalence of all four disorders, even after adjustment. The strength of these correlations ranged from fair to moderate.

Table 2: Associations between variations in allele frequencies for *SNCA* polymorphisms, prevalence of depressive disorders, and prevalence of Parkinson's and Alzheimer's disease

Variable	***rs356220 (A)***	***rs2736990 (C)***	***rs3775439 (A)***
MDD-Prev	.78 (<.001)*	-.62 (<.001)*	-.72 (<.001)*
	.73 (<.001)*	-.60 (<.001)*	-.73 (<.001)*
Dys-Prev	.40 (.098)	-.38 (.029)*	-.42 (.016)*
	.54 (.031)*	-.43 (.019)*	-.44 (.017)*
Park-Prev	.50 (.033)*	-.56 (<.001)*	-.49 (.004)*
	.55 (.028)*	-.40 (.028)*	-.47 (.010)*
Alz-Prev	.50 (.034)*	-.59 (<.001)*	-.57 (<.001)*
	.46 (.070)	-.46 (.012)*	-.56 (<.001)*

Abbreviations: MDD, major depressive disorder; Dys, dysthymia; Park, Parkinson's disease; Alz, Alzheimer's disease; Prev, estimated prevalence. All correlations are presented as: unadjusted Spearman's ϱ (significance level), Spearman's ϱ adjusted for life expectancy (significance level).

* denotes statistical significance at $p < .05$.

Table 3 presents the results of partial correlation analyses examining the following possibilities: (a) is the observed association between depressive disorders, Parkinson's disease and Alzheimer's disease partially mediated by these polymorphisms? and (b) is the observed association between these genotypes and Parkinson's disease or Alzheimer's disease partially mediated by depression? The first three columns of **Table 3** present the results of partial correlations between each allele frequency and the prevalence of Parkinson's disease and Alzheimer's disease, taking the prevalences of MDD and dysthymia as covariates. In this analysis, only the association between *SNCA rs2736990* and the prevalence of Alzheimer's disease remained significant, though this was not maintained after adjustment for life expectancy. The next three columns present partial correlations between the prevalence of depressive disorders and the prevalence of Parkinson's disease and Alzheimer's disease, with all three allele frequencies taken as covariates. None of these associations remained significant. In view of the smaller number of allele frequencies available for *SNCA rs356220*, this analysis was repeated using only *SNCA rs2736990* and *SNCA rs3775439* allele frequencies as covariates. In this analysis, associations with depression were not significant (ϱ = .27, $p = .176$ for MDD x

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Park; ϱ = .16, p = .419 for MDD x Alz); however, the associations between dysthymia and both Parkinson's disease and Alzheimer's disease remained significant, even when further adjusted for life expectancy (ϱ = .75, p < .001 for Dys x Park; ϱ = .43, p = .029 for Dys x Alz).

Table 3: Partial correlation analyses of the interaction between *SNCA* polymorphisms, depressive disorders, and the prevalence of Parkinson's and Alzheimer's disease

Variable	**Park-Prev (adjusted for depressive disorders)**	**Alz-Prev (adjusted for depressive disorders)**	Variable	**Park-Prev (adjusted for allele frequencies)**	**Alz-Prev (adjusted for allele frequencies)**
rs356220 (A)	.08 (.753) .03 (.907)	.21 (.447) .28 (.324)	**MDD-Prev**	-.13 (.638) -.03 (.936)	-.14 (.626) -.28 (.357)
rs2736990 (C)	-.32 (.085) .12 (.568)	-.37 (.043)* -.10 (.609)	**Dys-Prev**	.17 (.547) .41 (.161)	-.08 (.766) .08 (.798)
rs3775439 (A)	-.15 (.443) .07 (.746)	-.28 (.129) -.23 (.244)			

Abbreviations: MDD, major depressive disorder; Dys, dysthymia; Park, Parkinson's disease; Alz, Alzheimer's disease; Prev, estimated prevalence; *SNCA*, alpha-synuclein gene. All correlations are presented as: unadjusted Spearman's ϱ (significance level), Spearman's ϱ adjusted for life expectancy (significance level).

* denotes statistical significance at p < .05

c. Gene-environment analysis: The results of a re-analysis of the data presented in **Table 2,** adjusted for both the level of fine particulate matter pollution (PM2.5) and pesticide consumption per hectare, are presented in **Table 4**. In these analyses, the prevalence of major depression was significantly associated with the prevalence of Alzheimer's disease after adjusting for these environmental risk factors, while the prevalence of dysthymia was significantly associated with the prevalences of both Parkinson's disease and Alzheimer's disease, even after adjustment for life expectancy.

Table 4: Correlations between the estimated prevalence of depressive disorders, Parkinson's disease and Alzheimer's disease, adjusted for fine particulate matter ($PM_{2.5}$) pollution and pesticide consumption

Disorder	**MDD-Prev**	**Dys-Prev**	**Park-Prev**	**Alz-Prev**
MDD-Prev	-	.13 (.128) .09 (.299)	.19 (.019)* .02 (.790)	.29 (<.001)* .18 (.027)*
Dys-Prev		-	.48 (<.001)* .44 (<.001)*	.43 (<.001)* .37 (<.001)*
Park-Prev			-	.90 (<.001)* .78 (<.001)*

Abbreviations: MDD, major depressive disorder; Dys, dysthymia; Park, Parkinson's disease; Alz, Alzheimer's disease; Prev, estimated prevalence; $PM_{2.5}$, fine particulate matter of diameter ≤ 2.5 microns. All correlations are presented as: Spearman's partial ϱ (significance level), Spearman's partial ϱ adjusted for life expectancy (significance level). * denotes statistical significance at p < .05.

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Likewise, a re-analysis of the genetic data examined in **Table 2**, corrected for the effects of both $PM_{2.5}$ and pesticide consumption, is presented in **Table 5**. In these analyses, the observed correlations between *SNCA* gene polymorphisms and the prevalence of each disorder of interest remained significant, particularly for the *rs2736990* and *rs3775349* SNPs, even after correction for pesticide exposure. However, after correction for PM2.5 exposure, these associations were no longer statistically significant. When considering neurodegenerative disorders alone, the association between *rs3775439* allele frequencies and the prevalence of Alzheimer's disease remained significant after correcting for both environmental risk factors; a correlation of similar magnitude was observed for Parkinson's disease at a trend level ($p = .056$).

Table 5: Associations between variations in allele frequencies for *SNCA* polymorphisms, prevalence of depressive disorders, and prevalence of Parkinson's and Alzheimer's disease, adjusted for environmental risk factors

Variable	***rs356220 (A)***	***rs2736990 (C)***	***rs3775439 (A)***
MDD-Prev			
Adjusted (PM2.5)	.60 (.018)*	-.52 (.004)*	-.64 (<.001)*
Adjusted (Pesticide)	.62 (.041)*	-.67 (<.001)*	-.72 (<.001)*
Adjusted (Both)	.34 (.343)	-.56 (.007)*	-.58 (<.001)*
Dys-Prev			
Adjusted (PM2.5)	.54 (.038)*	-.36 (.059)	-.35 (.071)
Adjusted (Pesticide)	.71 (.014)*	-.43 (.043)*	-.45 (.029)*
Adjusted (Both)	.69 (.026)*	-.30 (.177)	-.30 (.176)
Park-Prev			
Adjusted (PM2.5)	.38 (.165)	-.27 (.163)	-.28 (.150)
Adjusted (Pesticide)	.57 (.068)	-.50 (.014)*	-.63 (.001)*
Adjusted (Both)	.57 (.083)	-.31 (.158)	-.41 (.056)
Alz-Prev			
Adjusted (PM2.5)	.40 (.139)	-.35 (.071)	-.42 (.025)*
Adjusted (Pesticide)	.35 (.287)	-.47 (.026)*	-.63 (.001)*
Adjusted (Both)	.53 (.119)	-.30 (.182)	-.46 (.030)*

Abbreviations: MDD, major depressive disorder; Dys, dysthymia; Park, Parkinson's disease; Alz, Alzheimer's disease; Prev, estimated prevalence; $PM_{2.5}$, fine particulate matter of diameter ≤ 2.5 microns. All correlations are presented as: Spearman's ϱ (significance level) and are adjusted for life expectancy. * denotes statistical significance at $p < .05$.

In view of the non-Gaussian distribution of the study variables, and the limited number of cases available for population genetic data, multivariate analysis was not attempted.

3. Discussion

The current study found evidence of significant associations between the prevalence of depressive disorders – major depressive disorder (MDD) and dysthymia – and the prevalence of both Alzheimer's disease and Parkinson's disease at a cross-national level. These results are consistent with existing research on the shared pathogenic mechanisms for these disorders [55-58], as well as with the results of longitudinal research in individual countries demonstrating a prospective link between depressive disorders and neuro-

 doi:10.20944/preprints202209.0197.v1

degenerative disorders [59-62]. Prior evidence suggests that the links between depression, Parkinson's disease and Alzheimer's disease are mediated by both genetic vulnerability [63-65] and exposure to environmental risk factors, such as stress and environmental toxins [66-68]. These two sets of risk factors should not be seen in isolation; there is already preliminary evidence of gene-environment interactions between genetic risk and diabetes mellitus [69] and between genetic variants and pesticide exposure [70] in influencing the development of subsequent Parkinson's disease. The current research was conducted to strengthen the evidence for the association between depressive disorders, Alzheimer's disease and Parkinson's disease, and to examine the potential effect of functional polymorphisms of the *SNCA* gene on these associations, while taking into account the confounding effects of population demographics and environmental risk factors.

In this study, the association between major depressive disorder (MDD) and each neurological disorder was weak, and was not statistically significant after correction for life expectancy. However, dysthymia remained associated with both Parkinson's disease and Alzheimer's disease even after adjusting for this variable. Dysthymia is defined as a chronic, "low-grade" form of depression, characterized by mild but persistent depressive symptoms that remain below the diagnostic threshold for MDD [71]. Many patients with dysthymia have superimposed episodes of MDD (referred to as "double depression"), and this disorder shows strong genetic and pathophysiological links with MDD [72]. Dysthymia has not been studied as extensively as MDD in relation to Parkinson's disease or Alzheimer's disease. The available data suggests that at least 13% patients with established Parkinson's disease fulfill the diagnostic criteria for dysthymia [73], and a study of patients with Alzheimer's disease found that 28% qualified for a diagnosis of dysthymia [74]. The presence of dysthymia is also associated with the occurrence of extrapyramidal features in patients with Alzheimer's disease [12]. Though no studies exist linking dysthymia to levels of α-synuclein, or to the *SNCA* gene, a study of older adults with either depression or dysthymia found evidence of abnormal dopamine transporter binding on single photon emission computed tomography (SPECT), and these alterations were associated with prodromal features of Parkinson's disease [75]. A similar imaging study comparing patients with MDD alone and those with MDD superimposed on dysthymia found that ligand binding to striatal dopamine transporters was inversely correlated with illness duration only in the dysthymia group [76]. These results, though 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, Alzheimer's disease, and Parkinson's disease [55]. It is possible that at least some cases of dysthymia may represent an early or prodromal stage of neurodegenerative disorders linked to a dopaminergic deficit; this possibility is also supported by the overlap between some of the clinical features of dysthymia, such as fatigue and apathy, and the non-motor symptoms of Parkinson's disease [77].

Studies of variations in the allele frequencies for specific SNPs of the *SNCA* gene were associated with the prevalence of depressive disorders, as well as with the prevalence of Alzheimer's disease. These correlations remained significant after adjusting for age, and were stronger for major depression and Alzheimer's disease than for dysthymia and Parkinson's disease. These results should be interpreted with caution due to the low number of populations for which data was available (n = 18 to 32); however, they are consistent with the hypothesis of a shared genetic vulnerability between these disorders. A large-scale analysis of genome-wide association data found plausible evidence that the *SNCA* gene was involved in the shared genetic liability for Parkinson's disease and Alzheimer's disease [78], and recent evidence has implicated the *SNCA* gene in the pathogenesis of depressive disorders [79]. Though the current results cannot establish a definitive causal association, they do provide some support to the growing body of evidence implicating

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α-synuclein pathology in the pathophysiology of depression [52-54] and Alzheimer's disease [16, 80, 81]. In the partial correlation analyses, allele frequencies were not significant associated with Alzheimer's or Parkinson's disease after correcting for the prevalence of depressive disorders; on the other hand, dysthymia remained significantly associated with both these disorders after adjusting for allele frequencies. This suggests that depressive disorders, and more specifically dysthymia, may mediate the potential association between *SNCA* functional polymorphisms and neurological outcomes, but this result requires replication in more rigorous, individual-subject studies.

In the final set of analyses, examining the possibility of gene-environment interactions, it was found that correction for particulate matter pollution – but not pesticide exposure – attenuated the associations between genotype on the one hand, and depressive disorders, Alzheimer's disease and Parkinson's disease on the other. This suggests that the deleterious effects of pesticide exposure on psychiatric and neurological outcomes may not be associated with the *SNCA* genotype, while there may be a gene-environment interaction in the case of air pollution. An earlier case-control study of patients with Parkinson's disease found that a gene-environment interaction between exposure to ambient nitrogen dioxide (NO_2) and a functional polymorphism of the interleukin-1 beta (IL-1β) gene was significant associated with the risk of Parkinson's disease [82]. It is possible that similar interactions between genetic vulnerability and toxins may explain the results obtained in this study. On the other hand, when correcting for $PM_{2.5}$ levels and pesticide consumption, the relationship between dysthymia and both Parkinson's disease and Alzheimer's disease remained significant, while the association between MDD and Alzheimer's disease was strengthened. This suggests that depressive disorders and environmental toxins may each independently influence the risk of neurodegenerative disorders. This is consistent with the results of an earlier study which found that depression and prolonged exposure to air pollution were both independently associated with Parkinson's disease [83].

Certain key limitations of the current study should be borne in mind. First, as they are 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, due to the cross-sectional nature of this study, no clear conclusions can be drawn regarding causation: even if significant correlations are demonstrated, this does not necessarily imply a causal chain linking genetic variations, depressive disorders and neurodegenerative disorders. Third, as the estimates used in this analysis cover entire countries, 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 the analysis of population genetics was relatively low, and was based on relatively small numbers of volunteers willing to participate in research on allele frequencies. Fifth, results obtained at a national level cannot be extrapolated directly to individuals. Sixth, 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 due to the focus of this study on α-synuclein. Finally, the effects of other environmental factors that could be associated with both Alzheimer's disease and Parkinson's disease, such as diet, smoking and other occupational exposures, could not be assessed in a study of this sort.

4. Materials and Methods

The current study is a cross-national, cross-sectional analysis of the associations between depressive disorders (major depression and dysthymia) and both Parkinson's disease and Alzheimer's and related dementias. Three sources of data were analyzed for this purpose:

a) Epidemiological data on the prevalence of these conditions across 204 countries and regions, based on the 2019 Global Burden of Disease (GBD 2019) study

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b) Population genetic data on the allele frequencies of specific polymorphisms of the α-synuclein gene *SNCA* across 32 countries, using data available in the public domain from the Allele Frequency Database (ALFRED)
c) Analyses of the interactions of the above two data sets in relation to two well-established risk factors for both Parkinson's disease and Alzheimer's disease, namely exposure to particulate matter air pollution (PM2.5) and pesticides

a. Epidemiological analysis: To establish the possibility of a significant relationship between seemingly unrelated disorders, it is important to examine if their prevalence is significantly correlated across diverse populations and settings. However, such an association may also be due to the confounding effects of demographic factors, particularly in the case of disorders that are diagnosed late in life [84].

In the current study, data on the estimated prevalence of two types of depressive disorder – major depressive disorder (MDD) and dysthymia – was obtained via a database query from the Global Health Data Exchange, which provides access to data from the Global Burden of Disease studies from 1990-2019 [85]. The most recent data (2019) was used for the current study. Though there is significant evidence for an association between MDD and both Parkinson's and Alzheimer's disease [37-39], dysthymia was also included in the analysis in view of older data suggesting that it may be associated with both these disorders [86]. Data on the estimated prevalence of Parkinson's disease, and of Alzheimer's and related dementias, was obtained from the same source. To ensure that any observed associations were not due to demographic variations across countries, all analyses were adjusted for life expectancy. Data on life expectancy for each country for the year 2019 was obtained from the World Health Organization's Global Health Observatory [87].

b. Population genetic analysis: Examining the relationships between variations in specific genetic polymorphisms and the frequency of specific disorders across diverse populations is a valuable, though indirect, method of identifying potential causal associations; such an approach has been used both for disorders such as major depression [88, 89] and for broader phenotypes such as cognitive impairment related to central nervous system inflammation [90]. Though the results of such analyses should be interpreted with caution, and require replication in individual subjects, they may represent a valuable "first step" in identifying candidate genes for more rigorous methods of study.

Several polymorphisms of the *SNCA* gene, which encodes α-synuclein, have been associated with either the risk of developing Parkinson's disease or with specific aspects of this disorder [91, 92]. Though the association between this gene and Alzheimer's disease 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 Alzheimer's disease and its underlying pathophysiology [93-96]. Recent research suggests that *SNCA* may also be a candidate gene for major depression [79]. Given these findings, as well as the documented associations between α-synuclein and these disorders discussed earlier, the relationship between selected functional polymorphisms of *SNCA* and the prevalence of major depression, Parkinson's disease and Alzheimer's disease was examined at a population level. For the purpose of this analysis, data on allele frequencies for these polymorphisms was obtained from the Allele Frequency Database (ALFRED), a public-domain repository that contains data on over 660,000 genetic polymorphisms in 762 genetically diverse population samples [97, 98]. Though this database contains data on several polymorphisms of *SNCA*, most of them are of unknown functional significance. Polymorphisms were selected for analysis in this study only if they fulfilled the following criteria: (a) evidence of an association of the specific polymorphism with either the diseases being studied, or with their clinical manifestations, based on human genetic studies; (b) availability of data for

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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 in this study: *rs*356220, *rs2736990* and *rs3775439*. Details of the functional significance of these polymorphisms, and the availability of allele frequency data for each of them, are summarized in **Table 1** below.

Table 6: 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 susceptibility to Parkinson's disease in both European and Asian populations [99]; associated with more severe cognitive decline in Parkinson's disease [100]	18 countries
rs2736990 (T/C)	Associated with an increased risk of Parkinson's disease, most significantly in East Asian populations [101]; associated with altered levels of specific SNCA transcripts [100]	32 countries
rs3775439 (G/A)	Minor allele (A) associated with an increased risk of Parkinson's disease in the elderly [102]; may interact with other genes to influence Parkinson's disease risk [103]	32 countries

The relationship between variations in the distributions of these polymorphisms and the estimated prevalence of major depression, dysthymia, Parkinson's disease and Alzheimer's disease was examined for all available populations. Analyses were adjusted for life expectancy to rule out the confounding effect of variations in population demographics. If significant correlations were observed, partial correlation analyses were carried out to assess a possible mediating effect of depressive disorders.

c. Possible gene-environment interactions: Even if meaningful associations are observed between the frequencies of specific disorders, such associations may reflect the effects of shared environmental risks rather than genetic factors. A variety of environmental risk factors have been identified for both Parkinson's disease [104] and Alzheimer's disease [105]. Among these risk factors, the two that have been consistently associated with both disorders, and which are likely to affect a substantial proportion of the general population, are air pollution [106] and pesticide exposure [107, 108]. Environmental air pollution, particularly exposure to inhaled particulate matter with a diameter of ≤ 2.5 microns ($PM_{2.5}$), has been associated with a significant increase in the risk of both Parkinson's disease and

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Alzheimer's disease in studies conducted across 26 countries [109]. $PM_{2.5}$ exposure has also been associated with increased rates of depression [110]. Likewise, cumulative exposure to pesticides is associated with an approximately 50% relative risk increase for both Parkinson's disease and Alzheimer's disease [111]; there is also some evidence of a link between pesticide exposure and depression, though this association has been relatively less studied [112]. Genetic factors may partially mediate association between pesticide exposure and Parkinson's disease [70]. In the light of this evidence base, the current study also examined the effect of these two environmental factors on the possible associations between depression, Parkinson's disease and Alzheimer's disease in the epidemiological and population genetic analyses described above. Information on levels of PM2.5 for each country were obtained for 193 countries and regions from the WHO's Global Health Observatory [87], and data on levels of pesticide exposure, measured in terms of average pesticide application (in kilograms) per unit of cropland (in hectares), was obtained from the Food and Agricultural Organization's FAOSTAT database [113].

d. Data analysis: All study variables were tested for normality prior to further analysis. As none of the variables followed a normal distribution ($p \leq .01$, Shapiro-Wilk test), Spearman's rank correlation and partial correlation coefficients (ϱ and partial ϱ) were used for all three analyses. All tests were two-tailed, and the significance level for this study was set at $p < .05$.

For the analysis of epidemiological data, correlation coefficients (ϱ) were computed to test for a monotonic association between the estimated prevalence of depressive disorders (MDD and dysthymia) and the estimated prevalence of Parkinson's disease and Alzheimer's disease. All correlations were subjected to Bonferroni's correction for a 4 x 4 correlation matrix. Partial correlation analyses (partial ϱ, with life expectancy as the covariate) were then carried out to examine a possible confounding effect caused by differences in population demographics.

For the analysis of genetic data, correlation coefficients (ϱ) were computed to test for a monotonic association between allele frequencies for the three polymorphisms of interest (*rs356220, rs2736990* and *rs3775439*) and the prevalence of all the above disorders, adjusted for life expectancy. Subsequently, analyses of the partial correlations between depressive disorders and both Parkinson's and Alzheimer's disease, adjusted for variations in the frequencies of each polymorphism of interest, were also examined. Due to the small number of cases under consideration, Bonferroni's correction was not applied for this analysis.

For the examination of the role of environmental factors and of possible gene x environment interactions, the analyses described in the preceding two paragraphs were repeated while taking $PM_{2.5}$ levels and pesticide consumption (kg/hectare) as covariates.

To assess the possible magnitude of each of the observed correlations, the following guideline values were used: $\varrho < 0.3$, weak correlation; $\varrho = 0.3$ to 0.59, fair correlation; $\varrho = 0.6$ to 0.79, moderate correlation; $\varrho \geq 0.8$, strong correlation [114].

5. Conclusions

Despite certain inherent methodological limitations, the current study provides some support for a meaningful relationship between depressive disorders and the subsequent risk of Parkinson's disease and Alzheimer's disease, and also suggests that this relationship may be at least partly related to functional variants of the α-synuclein gene *SNCA*, in combination with exposure to environmental toxins. Though these results cannot be taken as definitive, they highlight the need for a further investigation of three facets of this relationship: (a) the specific associations between different types of depressive disorder and the subsequent risk of neurodegenerative disorders, (b) the role of *SNCA* gene variants, and their functional consequences (such as reduced synaptic plasticity), in

the pathogenesis of depression and in predicting the subsequent risk of Parkinson's disease or Alzheimer's disease in patients with depression, and (c) possible interactions between *SNCA* gene polymorphisms and environmental risk factors in influencing the transition from depressive disorders to neurodegeneration. It is hoped that these results will be of value to those examining the shared pathophysiological basis of these conditions.

Supplementary Materials: None.

Author Contributions: Not applicable.

Funding: This research received no external funding from any source.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data used in this study was obtained from public domain databases which have been referenced in the manuscript. A complete data sheet is available from the author on request.

Conflicts of Interest: The author declares no conflict of interest.

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