Title: Association of neurodevelopmental conditions with Alzheimer's disease and related dementias and Parkinson's disease

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Abstract

Background: Neurodevelopmental conditions (NDC), including attention deficit/hyperactivity disorder (ADHD) and autism, are associated with increased rates of neurodegenerative diseases, including Alzheimer's disease and related dementias (ADRD) and Parkinson's disease. Such associations are unstudied in diverse populations and while controlling for a range of important covariates. The purpose of this study was to examine the association of ADRD and Parkinson's disease with NDCs in a diverse sample of adults.

Methods: This case-control study used data from the U.S. All of Us Research Program 2018-2023 from approximately 600,000 adults in the U.S. We matched on ADRD and Parkinson's disease status in order to examine the association of these conditions with NDCs.

Results: NDC was more prevalent in ADRD cases than in non-ADRD controls (7.8% versus 2.4%) and among Parkinson's disease cases than non-Parkinson's disease controls (4.5% versus 1.8%). After adjustment for sex, age, education level, body mass index, cardiometabolic conditions, and psychiatric conditions, individuals with ADRD had significantly higher odds of having an NDC compared with controls (adjusted odds ratio, 2.68; 95% CI, 2.40–2.99). Similarly, Parkinson's disease cases had 2.09 times the odds of having an NDC as non-Parkinson's disease controls (95% CI 1.66, 2.59) in adjusted models.

Conclusions: As the population of individuals with NDCs ages, and more older adults find themselves in the care of clinicians with experetise in ADRD and Parkinson's disease, it is imperative to understand the support needs of this population, and to provide targets for reducing ADRD prevalence in younger or middle adulthood.

Key words: autism, attention deficit/hyperactivity disorder, All of Us, electronic health record

Introduction

Neurodevelopmental conditions (NDCs), including autism, attention-deficit hyperactivity disorder (ADHD), and intellectual disability, are lifelong conditions with increasing prevalence over the past several decades, with the exception of intellectual disability, which has remained stable. [1,2] In the U.S., the current estimated prevalence in adults is 2% for autism, 4% for ADHD, and 1% for intellectual disability. [2-4] As the population of individuals with NDCs ages, researchers, advocates, and funding agencies have called for more focus on the health and experiences of adults with NDCs across the lifespan. [5-7]

Emerging evidence suggests that certain NDCs are associated with an increased risk of developing neurodegenerative diseases. For example, Parkinson's disease appears to be more common in individuals with ADHD[8-10] and autism[11-13] than in individuals without these conditions. Similarly, Alzheimer's disease and related dementias (ADRD) may be diagnosed more frequently in autistic adults[11,14,15] and adults with ADHD. [10,16] The observation that ADRD is also more often diagnosed in patients with a first or second degree autistic relative[17] suggests a genetic basis for this association. However, the link between NDCs and neurodegenerative disease is not well established, largely due to reliance on small-scale studies and few large-scale longitudinal studies examining the links between specific NDCs and the risk of ADRD or Parkinson's disease. Most of these studies come from international samples that lack the racial and ethnic diversity of the U.S. Furthermore, existing studies largely do not control for potential confounders, including education level, which are difficult to ascertain through health records.

Beyond primary neurological factors, cardiometabolic and psychiatric conditions are also recognized as important contributors to neurodegeneration, often serving as risk factors or prodromes for ADRD or Parkinson's disease. [18,19] Individuals with NDCs have higher rates of

cardiometabolic diseases and higher average body max index (BMI) than individuals without NDCs, conditions which are established risk factors for ADRD. [11,20] Yet, the potential influence of cardiometabolic diseases and BMI on the relationship between NDCs and neurodegenerative diseases have been minimally explored. Similarly, individuals with NDCs experience higher rates of certain psychiatric conditions than individuals without NDCs, including schizophrenia, depression, anxiety, and bipolar disorder, that are associated with ADRD. [11,21] While some prior work in Medicaid and Medicare populations have controlled for co-occurring psychiatric diagnoses, finding a positive association between NDCs and ADRD, [14,15] a comprehensive examination accounting for a broader range of co-occurring conditions is needed.

Leveraging a large, racially diverse sample of adults from the U.S. National Institutes of Health's All of Us Research Program, the current study aims to examine the association of NDCs with ADRD and Parkinson's disease. We hypothesize that NDCs will occur more frequently in individuals with ADRD or Parkinson's disease than among individuals without these conditions.

Methods

Data

This case-control study used data from the All of Us Research Program, supported by the U.S. National Institutes of Health (NIH). All of Us is a longitudinal cohort study that combines electronic health records, surveys, laboratory assessments, physical measurements, and genetic data on adults in the United States. [22] The expressed intent of the study is to recruit a target sample of 1,000,000 adults that represents the diversity of the U.S. in terms of race and ethnicity, geography, illness, and age in order to perform studies on the health of adults. Details on the

research program and the participants are available elsewhere.[22] Briefly, participants are recruited through a combination of direct participant engagement on the website where anyone can sign up to participate, advertisement by more than 100 participating health care provider organizations across the United States, and recruitment through community events and organizations by provider and community partners. Participation is voluntary and was more common among women than men, and participants come from all 50 states, Washington D.C., and five U.S. territories.[23] Data used in this study included a combination of surveys and electronic health records (EHR) from All of Us Controlled Tier Dataset V8 (C2024Q3R4; released 2/3/2025) for adults ages 18 years and older (eFigure 1). We selected only participants with available EHR data, physical measurements, and survey responses (n=384,420, 61% of all participants). Participants entered the study between May 1, 2018, and October 1, 2023, and the length of follow up for the EHR was variable depending on the length of an individual's inclusion in an EHR. We used STROBE case-control reporting guidelines for study reporting. Cells sizes under n=20 are required to be suppressed due to All of Us data censorship and safety requirements.

Exposures

The main exposure of interest in this study was the presence of an NDC in EHR using OMOP Concept ID codes (Observational Medical Outcomes Partnership Common Data Model Version 5), which standardizes input across data types. Individuals were identified as having an NDC if they had an OMOP concept code for autism, ADHD, or intellectual disability (eTable 1). OMOP is an international, standardized vocabulary for identifying conditions for research purposes that combines several sources of data, including ICD codes, survey results, and EHR entries.[24] Though NDCs are often diagnosed in childhood, many older adults, such as would be included in

this study, have been diagnosed in adulthood. [25,26] Further, the inclusion of NDCs in the EHR is typically ongoing, as individuals receive medical, prescription, and behavioral health services in support of the condition. The Chronic Conditions Warehouse produces algorithms for identifying these conditions using claims data, supported by the Centers for Medicaid and Medicare Services and this approach has been used in prior research. [27]

Outcome

The two main outcomes of interest were ADRD and Parkinson's disease, which were identified through OMOP Concept ID codes identified from diagnoses recorded in the EHR during the study period. ADRD included Alzheimer's disease, dementia associated with another disease, senile dementia, mild dementia, presenile dementia, subcortical dementia, and any dementia with an OMOP Concept ID nested under these. Parkinson's disease included anyone with a diagnosis of primary Parkinson's disease and excluded those with secondary parkinsonism, including parkinsonism due to drug and postencephalitic parkinsonism. OMOP Concept ID codes for all included diagnoses are in eTable 2.

Covariates

Covariates included sex at birth, race, ethnicity, highest education level reported at the time of survey, body mass index (BMI) at the time of physical measurement for study participation, age as of January 1, 2025, cardiometabolic conditions in the EHR, and psychiatric conditions in the EHR. Participants self-reported their biological sex at birth using categories including female, male, intersex, none of these, and prefer not to answer. Due to small cell counts, responses were collapsed into three categories: female, male, and all other. Race was also self-reported, and options included Asian, Black or African American, Middle Eastern or North African, more than

one population, none of these, and White. Ethnicity (Latino, not Latino) was captured separately from race. Education level was self-reported as the highest grade or year of school completed. BMI calculations were made with height and weight from one of two sources: in-person visits with All of Us personnel to provide physical measurements, and self-report if that was unavailable. Cardiometabolic and psychiatric conditions were identified from the EHR using Observational Medical Outcomes Partnership (OMOP) Common Data Model Concept ID codes (listed in eTable 2). Cardiometabolic conditions included type 2 diabetes, stroke, atrial fibrillation, heart failure, ischemic heart disease, and myocardial infarction. Psychiatric conditions included anxiety disorders, posttraumatic stress disorder, psychotic disorders including schizophrenia, bipolar disorder, and major depressive disorder (eTable 3). The first date of any condition on the electronic health record was recorded as the start date, which was used to determine timing of onset relative to ADRD and Parkinson's disease. Conditions with a start date after the start date of ADRD or of Parkinson's disease were excluded from consideration.

Sample selection and control matching

We conducted two separate case-control matching procedures, one for ADRD and one for Parkinson's disease. For ADRD, all individuals with an ADRD diagnosis were classified as cases (n=7,941). We frequency-matched controls at a 5:1 ratio to cases on sex at birth and age in five-year categories for a total of n=39,705 matched controls without ADRD. The matching ratio was chosen because it was the largest ratio that allowed for matches across all strata. This procedure was repeated for all Parkinson's cases (n=2,530) with a control match of 10:1 (n=25,300 controls). Individuals who had both ADRD and Parkinson's disease were included in both case

groups (n=494). Individuals with Down Syndrome were excluded from the sample before matching.

Statistical analysis

First, we characterized the distribution of NDC and covariates among the cases and the frequency matched controls. Second, we used a sequence of unconditional logistic regression models to examine the association of any NDC (autism or ADHD or intellectual disability) with ADRD and Parkinson's disease within the respective case-control samples. Model 1 controlled for the matching variables (sex at birth and residual age) and the matching strata as suggested in prior research. [28] Residual age was included to account for the coarsening of age categories used in the matching process. For example, a person aged 60 in a category with a center age of 62 would have a residual age of -2. Model 2 controlled for Model 1 covariates plus the highest level of education, while Model 3 further adjusted for BMI, cardiometabolic conditions, and psychiatric conditions.

Models 1-3 were fitted for 2 parallel analyses. Models 1A-3A examined the association of having any of autism, ADHD, or intellectual disability with ADRD and Parkinson's disease. Models 1B-3B examined the association of specific NDCs (autism, ADHD, and intellectual disability) with ADRD and with Parkinson's disease by mutually adjusting for autism, ADHD, and intellectual disability in each model.

Results

Table 1 displays characteristics of individuals with ADRD and their matched controls, and individuals with Parkinson's disease and their matched controls. NDC was more prevalent in ADRD cases than in non-ADRD controls (7.8% versus 2.4%). Each individual NDC was about

three times more common among ADRD cases than controls. The majority (58.1%) of ADRD cases were female and the average age of ADRD cases was 68.2 years. Education varied by ADRD case status, with advanced education less common in ADRD cases than non-ADRD controls. Both cardiometabolic and psychiatric conditions were more common among ADRD cases than non-ADRD controls. Among Parkinson's disease cases, NDC was more common than among non-Parkinson's disease controls (4.5% versus 1.8%). The sample size was too small to export all individual NDCs results due to censorship rules (cell size of n<20). Most Parkinson's disease cases were male (57.4%), and the mean age of Parkinson's disease cases was 74.3 years. Advanced levels of education were similar in Parkinson's disease cases and in non-Parkinson's disease controls. Psychiatric conditions were more common among Parkinson's disease cases than non-Parkinson's disease controls.

After adjustment for sex, age, education level, body mass index, cardiometabolic conditions, and psychiatric conditions, individuals with ADRD had significantly higher odds of having an NDC compared with controls (adjusted odds ratio, 2.68; 95% CI, 2.40–2.99; Figure 1, top panel). Similarly, Parkinson's disease cases had 2.09 times the odds of having an NDC as non-Parkinson's disease controls (95% CI 1.66, 2.59; Figure 1, bottom panel) in adjusted models. Figure 1 presents results separately for each NDC, as shown in the Model B results. ADRD cases had 1.42 (95% CI 0.95, 2.09; autism) to 2.62 (95% CI 1.90, 3.62; intellectual disability) times the odds of each NDC compared to non- ADRD controls. Similarly, Parkinson's disease cases had two to four times the odds of each type of NDC compared to non-Parkinson's disease controls. Fitting sequential regression models (Table 2) showed that the addition of education in adjusted models did not materially change the odds ratio of the association between NDCs and ADRD or

Parkinson's disease. The addition of cardiometabolic and psychiatric conditions attenuated results slightly.

Discussion

Our study, using a diverse sample of U.S. adults, demonstrates increased odds of NDC diagnoses among individuals with ADRD or Parkinsons's disease, compared to controls without these conditions. These associations were consistent across individual NDC diagnoses (autism, ADHD, and intellectual disability) even after accounting for potential sources of confounding. This finding is consistent with existing evidence, which indicates higher rates of dementia and Parkinson's disease in individuals with autism and individuals with ADHD, [8,11-16,29-31] and an increased prevalence of dementia in individuals with intellectual disability and learning disabilities compared to those without these conditions. [32]

Prior literature often highlights education as a potential confounder or player in the causal pathway in the associations. [19,33] Because individuals with NDCs may, on average, have lower educational attainment than individuals without these conditions, and lower educational attainment increases risk of neurodegeneration, [34,35] this may explain an NDC-ADRD association. However, our findings indicated that in this sample, the inclusion of education in regression models did not attenuate the association between ADRD or Parkinsons' disease and NDCs. [36] Other structural factors, including measures of socioeconomic status like employment and living situation, may also be driving associations with poorer health outcomes. [19,37,38] Further, social isolation is a potentially modifiable risk factor for ADRD that is more commonly experienced in adults with NDC than adults without NDC. [19,39,40]

In contrast, the inclusion of cardiometabolic and psychiatric conditions somewhat attenuated the observed associations, though not to the null. The exact relationship between cardiometabolic and psychiatric conditions and the development of ADRD is not known, but many of these conditions are identified as modifiable risk factors for ADRD. [19] For instance, the treatment of depression may reduce ADRD risk, suggesting broader social factors could influence the causal pathway. [41] Given the higher rates of cardiometabolic and psychiatric conditions in individuals with NDCs, further examination of their role in the development of ADRD and Parkinson's disease in this population is warranted. [11,18,20] Our findings suggest they are influential to ADRD and Parkinson's disease development, but do not explain the whole association between NDCs and neurodegenerative conditions.

As the field progresses to understand the needs of the aging NDC population, several other hypotheses about the relationship of NDCs and neurodegeneration are worth exploring. [42] First, the clinical complexity of diagnosing dementia among patients with pre-existing cognitive differences or low IQ, coupled with potential for diagnostic overlap with NDC, is a significant challenge. Some features of NDCs, including reduced working memory and increased inhibition, may be mistaken for signs of neurocognitive disorders. [31,43] Furthermore, a lack of clinical tools designed to identify cognitive decline in non-speaking adults (a significant portion of autistic adults) poses a considerable barrier. [44,45] Future studies and clinical training should address the potential for diagnostic substitution among these conditions.

Additionally, shared biological mechanisms or etiologies between ADRD, Parkinson's disease, and NDCs may exist, including common genetic underpinnings[46,47] and shared neuroanatomic involvement. [48] One hypothesized mechanism suggests that individuals with NDCs experience accelerated biological and cognitive aging, [49,50] although evidence against this hypothesis in

autistic adults[51] and attenuation by increasing levels of education have also been reported. [50] The role of neuroinflammation, critical in ADRD neuropathology, is another area of convergence, as it may also be evident in NDCs. [52-54] Similar convergent pathological mechanisms include dysregulated neurotransmitter systems and altered synaptic pruning and maturation, seen in both NDCs and neurodegenerative diseases. [55-59]

Strengths and limitations

There are several notable strengths to this study. Our study features a new U.S. data source, adding evidence to supplement the existing literature predominantly from international populations. All of Us participants make up a large sample of older adults that is diverse in race and ethnicity by design of the study. [22] The large sample in All of Us allows for the examination of associations among relatively rare conditions. Furthermore, our analysis accounted for several factors not always examined in prior research, including education, BMI, cardiometatolic conditions, and psychiatric conditions.

Several limitations are also important to highlight. First, the participation of individuals with NDCs in All of Us, especially autism and intellectual disability, may not be representative of the population with these conditions. Participants with neurodevelopmental conditions are likely at the higher end of the functional spectrum for these disorders, as would be required for study consent and participation. Further, the diagnostic criteria for ADHD and autism have changed in the last several decades, which may impact the generalizability of these findings to younger generations. Second, limited follow-up time may impact the detection of new ADRD and Parkinson's disease cases, as the length of study participation was 2018-2023 (with variable length of EHR history). Future follow-up will likely yield more cases and enable additional longitudinal analysis. Further, the incidence of ADRD and Parkinson's diseases at the time of

study enrollment was not determined, though similarly to NDCs, we expect participants with greater cognitive decline would not be able to enroll in the study, thus limiting the likelihood of dementia diagnosis at the time of enrollment. Third, despite the large sample size, smaller numbers of ascertained Parkinson's disease cases led to uncertainty and wide confidence intervals when examining individual NDCs. Fourth, dementia was not examined by subtype (e.g., Alzheimer's disease) although prior studies have found differences in subtype prevalence by NDC status.[31] Nonetheless, diagnostic differentiation of dementias is clinically difficult and individuals often present with muliple dementia pathologies. Finally, several of these considerations point to the possibility that this study may suffer from selection and information biases. Future work may consider designs such as the use of negative controls to address these limitations. The identification of a negative control for this research question is difficult due to the linkage of ADRD risk factors (such a traumatic brain injury and psychiatric conditions) with NDCs. However, the selection of an appropriate control could help address detection bias related to increased health care use in people with NDCs.

Conclusions

The current study, drawing from a diverse set of older U.S. adults within the All of Us Study, found an increased odds of neurodevelopmental conditions (NDC) in individuals with ADRD and Parkinson's disease. This increased risk was observed even after adjustment for important confounders that prior studies were unable to consider. However, the exact mechanisms underlying this increased risk are unknown and warrant further investigation. As the population of individuals with NDCs ages, and more older adults find themselves in the care of clinicians with experetise in ADRD and Parkinson's disease, it is imperative to understand the support

needs of this population, and to provide targets for reducing ADRD prevalence in younger or middle adulthood.

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Disclosures

MB is employed at the Swedish Medical Products Agency, SE-751 03 Uppsala, Sweden. The views expressed in this paper do not necessarily represent the views of this Government agency.

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Figure 1 title: Adjusted logistic regression models examining the association between ADRD and NDC (top panel) and Parkinson's disease and NDC (bottom panel).

Figure 1 legend: All models control for age (by controlling for the residual of age as the distance of the age from the center point of the five-year age group, sex, the matching strata, education level, BMI category, cardiometabolic conditions, and psychiatric conditions. Graph shows 95% confidence interval. ADRD=Alzheimer’s disease and related dementias; NDC = neurodevelopmental condition.

Table 1. Select characteristics of individuals with and without ADRD Parkison's disease, including presence of neurodevelopmental conditions, on frequency matched sample

	ADRD cases and matched controls		Parkinson's cases and matched controls	
	ADRD (n=7941)	No ADRD (n=39705)	Parkinson's disease (n=2530)	No Parkinson's disease (n=25300)
	N (%)	N (%)	N (%)	N (%)
Sex at birth*				
Female	4616 (58.1%)	23080 (58.1%)	1036 (40.9%)	10360 (40.9%)
Male	3190 (40.2%)	15950 (40.2%)	1453 (57.4%)	14530 (57.4%)
Other	135 (1.7%)	675 (1.7%)	41 (1.6%)	410 (1.6%)
Age* (mean (SD))	68.2 (16.8)	67.6 (16.6)	74.3 (10.3)	73.8 (10.3)
Any NDC	621 (7.8%)	995 (2.5%)	114 (4.5%)	451 (1.8%)
Autism	44 (0.6%)	84 (0.2%)	--	--
Intellectual disability	80 (1.0%)	88 (0.2%)	--	--
ADHD	533 (6.7%)	873 (2.2%)	101 (4.0%)	431 (1.7%)
Race				

American Indian or Alaska Native	123 (1.5%)	462 (1.2%)	23 (0.9%)	248 (1.0%)
Asian	122 (1.5%)	911 (2.3%)	31 (1.2%)	464 (1.8%)
Black or African American	1174 (14.8%)	5854 (14.7%)	150 (5.9%)	3375 (13.3%)
Middle eastern or north African	42 (0.5%)	178 (0.4%)	**	**
More than one population	387 (4.9%)	1478 (3.7%)	88 (3.5%)	787 (3.1%)
Other or none indicated	1369 (17.3%)	7307 (18.4%)	459 (18.2%)	4049 (18.2)
White	4724 (59.5%)	24993 (62.9%)	1867 (73.8%)	17164 (67.8%)
Latino	1249 (15.7%)	5423 (13.7%)	300 (11.9%)	2639 (10.4%)
BMI (mean (SD))				
Underweight	105 (1.3%)	440 (1.1%)	23 (0.9%)	218 (0.9%)
Healthy weight	1850 (23.3%)	10002 (25.2%)	576 (22.8%)	5890 (23.3%)
Overweight	2359 (29.7%)	12644 (31.8%)	887 (35.1%)	8793 (34.8%)
Obese	3096 (39.0%)	14943 (37.6%)	882 (34.9%)	9333 (36.9%)

Missing	531 (6.7%)	1676 (4.2%)	162 (6.4%)	1066 (4.2%)
Education level				
Advanced degree	1525 (19.2%)	9784 (24.6%)	758 (30.0%)	7048 (27.9%)
College graduate	1554 (19.6%)	9111 (22.9%)	574 (22.7%)	5995 (23.7%)
College 1-3 years	2268 (28.6%)	10103 (25.4%)	653 (25.8%)	6210 (24.5%)
12 years or GED	1522 (19.2%)	6735 (17.0%)	338 (13.4%)	3777 (14.9%)
9-11 years	449 (5.7%)	1826 (4.6%)	80 (3.2%)	927 (3.7%)
8 or fewer years	411 (5.2%)	1232 (3.1%)	73 (2.9%)	770 (3.0%)
missing	212 (2.7%)	914 (2.3%)	54 (2.1%)	573 (2.3%)
Any cardiometabolic	3830 (48.2%)	14363 (36.2%)	1101 (43.5%)	10738 (42.4%)
Any psychiatric	4270 (53.8%)	12711 (32.0%)	1029 (40.7%)	7706 (30.5%)

**matched variable. --cells under n=20 censored for data security. **included in the "other or none indicated" group. NDC = neurodevelopmental condition. ADRD = Alzheimer's disease and related dementias. ADHD = attention deficit / hyperactivity disorder*

Table 2. Logistic regression models to examine the association between ADRD and NDCs and Parkinson's and NDCs

	ADRD			Parkinson's		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
	OR (95%CI)	aOR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	aOR (95%CI)
Model A (includes the single variable "any NDC")						
Any NDC (autism, ADHD, intellectual disability)	3.45 (3.10, 3.83)	3.56 (3.20, 3.96)	2.68 (2.40, 2.99)	2.64 (2.13, 3.25)	2.62 (2.11, 3.22)	2.09 (1.66, 2.59)
Model B (mutually adjusting for individual NDCs)						
Autism	1.63 (1.10, 2.40)	1.67 (1.12, 2.45)	1.42 (0.95, 2.09)	5.11 (2.13, 11.50)	5.07 (2.11, 11.43)	3.90 (1.56, 9.03)
ADHD	3.20 (2.86, 3.59)	3.36 (3.00, 3.77)	2.55 (2.26, 2.87)	2.55 (2.03, 3.18)	2.51 (2.00, 3.13)	2.03 (1.60, 2.55)
Intellectual disability	3.90 (2.85, 5.34)	3.40 (2.48, 4.66)	2.62 (1.90, 3.62)	2.25 (0.96, 4.65)	2.35 (1.00, 4.88)	1.89 (0.76, 4.06)

Model 1 controls for age (by controlling for the residual of age as the distance of the age from the center point of the five-year age group (e.g. the residual for a 30-year-old is -2, as 32 is the middle of the five-year age group)) and sex, the matching variables, and the matching strata.

OR = Odds ratio; 95% CI = 95% confidence interval. Model 2 additionally controls for education. Model 3 additionally controls for BMI, cardiometabolic conditions, and psychiatric conditions.