

FEATURED ARTICLE

Pre-diagnostic cognitive and functional impairment in multiple sporadic neurodegenerative diseases

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Abstract

Introduction: The pathophysiological processes of neurodegenerative diseases begin years before diagnosis. However, pre-diagnostic changes in cognition and physical function are poorly understood, especially in sporadic neurodegenerative disease.**Methods:** UK Biobank data were extracted. Cognitive and functional measures in individuals who subsequently developed Alzheimer's disease (AD), Parkinson disease, frontotemporal dementia, progressive supranuclear palsy, dementia with Lewy bodies, or multiple system atrophy were compared against individuals without neurodegenerative diagnoses. The same measures were regressed against time to diagnosis, after adjusting for the effects of age.**Results:** There was evidence for pre-diagnostic cognitive impairment and decline with time, particularly in AD. Pre-diagnostic functional impairment and decline were observed in multiple diseases.**Discussion:** The scale and longitudinal follow-up of UK Biobank participants provides evidence for cognitive and functional decline years before symptoms become obvious in multiple neurodegenerative diseases. Identifying pre-diagnostic functional and cognitive changes could improve selection for preventive and early disease-modifying treatment trials.

KEYWORDS

Alzheimer's disease, cognition, dementia, dementia with Lewy bodies, frontotemporal dementia, multiple system atrophy, neurodegenerative disease, Parkinson disease, physical function, pre-diagnostic, progressive supranuclear palsy, sporadic, UK Biobank

1 | INTRODUCTION

Neurodegenerative diseases present a significant health, social, and economic burden. Disease-modifying therapies and effective preventive strategies are lacking.¹ Treatment trials are typically conducted after symptoms have emerged, which may be too late in the disease process to alter its course.^{2,3} Understanding the earliest, pre-diagnostic phase in neurodegenerative disease could open opportu-

nities for more effective preventive and treatment trials. A better characterization of pre-diagnostic differences in cognition, day-to-day function, and pathological biomarkers, such as cerebrospinal fluid (CSF) amyloid beta 42 ($A\beta_{42}$) and phosphorylated tau (p-tau), is critical to these efforts. In this study we focus on cognitive and day-to-day functional measures.

Studies of genetic dementia cohorts suggest that disease biomarkers change in neurodegenerative diseases years before symptoms are

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RESEARCH IN CONTEXT

1. **Systematic Review:** Studies of genetic dementia cohorts provide evidence for pre-diagnostic changes in disease biomarkers and cognitive function in several genetic neurodegenerative diseases. The pre-diagnostic phase of sporadic neurodegenerative disease has been less well studied. It is unclear whether early functional or cognitive changes are detectable in sporadic neurodegenerative disease.
2. **Interpretation:** We have established an approach to identify cognitive and functional pre-diagnostic markers of neurodegenerative disease years before diagnosis. We found disease-relevant patterns of pre-diagnostic cognitive and functional impairment and observed a pre-diagnostic linear decline in a number of cognitive and functional measures.
3. **Future Directions:** Our approach can form the basis for pre-diagnostic cognitive and functional screening to recruit into trials of disease prevention and disease-modifying therapies for neurodegenerative diseases. A screening panel based on cognition and function could be followed by disease-specific biomarkers to further improve risk stratification.

obvious. In genetic frontotemporal dementia (FTD), structural brain changes are detectable 10 years before symptom onset,^{4–6} with pre-symptomatic alterations in functional brain network organization⁷ and microRNA (miRNA) expression.⁸ In genetic Alzheimer's disease (AD), CSF and neuroimaging changes may be seen 15 to 25 years before symptom onset.^{9–11}

The pre-diagnostic phase of sporadic neurodegenerative disease is more challenging to assess. There is indirect evidence that A β neuropathology is present several years before symptom onset in sporadic AD and is associated with cognitive decline.¹² There is also evidence for a pre-symptomatic reduction in the monoaminergic nuclei MRI (magnetic resonance imaging) signal.¹³

These studies suggest early pathological changes, but it remains less certain whether this translates into impaired cognition or day-to-day function. There is evidence for pre-diagnostic accelerated forgetting in familial AD mutation carriers,¹⁴ whereas apathy and executive dysfunction appear early in individuals who carry mutations for FTD.^{5,15} However, global cognitive and behavioral functions remain near normal if supported by a reorganization of the brain's functional network.^{7,16,17} It remains unclear whether changes in cognition and physical function in sporadic neurodegenerative diseases are detectable before symptom onset and how long before a diagnosis they are identifiable.

The UK Biobank¹⁸ offers a rare opportunity to analyze pre-diagnostic changes across a wide range of sporadic neurodegenerative

diseases. It includes more than 500,000 individuals 40 to 69 years of age recruited between 2006 and 2010 from the general population, from whom health-related data were collected. This offers a rich data set of prospective cognitive and functional data from a large pool of individuals, some of whom have gone on to develop a neurodegenerative disease. As a proof-of-concept, we recently published an analysis of pre-diagnostic data on the cohort in the UK Biobank who went on to develop progressive supranuclear palsy (PSP).¹⁹

We present an analysis of the data extracted from the UK Biobank, testing whether cognitive and functional changes are detectable in individuals who subsequently develop a neurodegenerative disease, the majority of which are sporadic. This provides an overview of the early manifestations of multiple rare and common neurodegenerative diseases.

2 | METHODS

2.1 | Data extraction from UK biobank

Data extracted from the UK Biobank included participant demographics, diagnoses of neurodegenerative diseases (Table 1), and a set of cognitive and functional measures (Table 2). Ethics approval for the study is covered under the UK Biobank, which has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank. Data were obtained from the UK Biobank under an approved application (ID 46620). Where applicable for demographic data, pairwise comparisons were performed between each diagnostic group and controls using linear or multinomial logistic regression, with *P*-values adjusted for multiple comparisons using the Benjamini-Hochberg procedure^{20,21} within each diagnosis.

Diagnoses and dates of diagnosis were compiled from hospital inpatient data, primary care data, death certificate data, and self-reported diagnoses. These data were extracted on May 23, 2021. Primary care data were available for $\approx 45\%$ of the UK Biobank cohort and covered up to 2017. Codes associated with the following diagnoses were searched for: AD, FTD, Parkinson disease (PD), PSP, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Codes associated with other cognitive neurodegenerative diseases were also searched for and labeled as "Others." The most recent diagnosis was used. Where multiple diagnoses were present on the most recent date, the rarer diagnosis was used as the most likely diagnosis (e.g., it is common for people with PSP to first receive a diagnosis of PD). Where ambiguity remained, the label "Multiple" was used. The date of the earliest recorded diagnosis was used as a proxy for the actual date of diagnosis. To identify pre-diagnostic individuals only, those with a diagnosis date pre-dating the baseline assessment visit were excluded. Individuals with a self-reported diagnosis of neurodegenerative disease at any time but without a formal diagnosis and individuals whose diagnoses were labeled as "Multiple" or "Others" were excluded. The remaining individuals without a diagnosis during follow-up were designated as controls.

TABLE 1 Demographics of individuals included from the UK Biobank from each diagnostic group

	Ctrl	AD	FTD	PD	PSP	DLB	MSA
Number	493,735	2778	211	2370	133	40	73
Years to diagnosis from baseline	–	8.3 (3.0)	7.7 (3.0)	7.4 (3.2)	7.6 (3.0)	4.7 (2.1)	6.5 (3.3)
Age	56.4 (8.1)	64.7* (4.2)	61.2* (5.9)	62.8* (5.4)	63.6* (5.3)	65.4* (3.7)	60.8* (6.3)
BMI	27.4 (4.8)	27.4 (4.8)	27.2 (5.0)	27.8* (4.5)	29* (4.8)	27.5 (4.4)	26.6 (4.2)
Sex							
Male	44.3%	45.3%	49.8%	60.3%*	60.9%*	67.5%*	39.7%
Female	52.9%	50.7%	47.4%	36.1%*	35.3%*	30%*	58.9%
Handedness							
Right	88.7%	89.3%	91.5%	88.4%	90.2%	92.5%	90.4%
Left	9.3%	8.2%	6.2%	9.3%	6%	7.5%	6.8%
Ambidextrous	1.7%	2.1%	2.4%	1.9%	3%	0%	2.7%
Ethnicity							
White	93.9%	95.5%*	96.7%	95.8%*	96.2%*	100%*	93.2%*
Afro-Caribbean	1.6%	1.4%	0.9%	0.8%*	0%	0%*	2.7%
Asian	2.3%	1.4%*	0.9%	1.8%	1.5%	0%*	1.4%
Mixed	0.5%	0.3%	0%	0.3%	0%*	0%	2.7%
Others	0.9%	0.4%*	0.5%	0.5%*	0%*	0%*	0%*
Smoking Status							
Never	40%	37%*	34.1%	39.3%*	34.6%*	32.5%	46.6%
Previous	34.3%	41.9%*	40.3%	39.9%*	48.1%*	47.5%	27.4%
Current	10.6%	9%	11.4%	6.7%*	8.3%	2.5%	8.2%

Participants with a diagnosis at baseline were excluded, so the groups here are those who converted during the study. Where appropriate the mean is shown with standard deviation in parentheses. Where the values differ from controls with an adjusted P -value $< .05$, they are marked with an asterisk. Where percentages do not add up to 100% the remaining data were missing. Ctrl = Controls, AD = Alzheimer's disease, FTD = frontotemporal dementia, PD = Parkinson disease, PSP = progressive supranuclear palsy, DLB = dementia with Lewy bodies, MSA = multiple system atrophy.

2.2 | Analysis of baseline assessment data

A set of cognitive and functional outcome measures (Table 2) recorded at baseline assessment were compared between pre-diagnostic individuals and controls using Bayesian regression analysis.

2.3 | Multiple imputation

We used multiple imputation, generating five sub-data sets to account for the 5% of cases with incomplete data among the imputed categories.^{22,23}

Imputation was performed using the *mice* package in R (version 4.0.3).²⁴ "Prospective memory," "fluid intelligence score," "numeric memory," and "smoking pack-years" were not imputed and were excluded as predictors for imputation because a large proportion of the data were missing. All other data fields including demographic data were used as predictor variables and imputed according to the default method for the respective data type as defined in *mice* (Table 2).

2.4 | Bayesian regression modeling

We used the *brms* package in R.^{25,26} Each cognitive or functional outcome measure was fitted to a model with diagnosis category and age as predictors, and to a null model with age as the sole predictor. Handedness was included as an additional predictor when analyzing hand grip strength. Model families were selected based on the characteristics of the data, and weakly informative Cauchy priors centered at zero were used for the regression coefficients (Table 2). For each outcome measure, the regression model was fitted separately to each of the five imputed sub-data sets. The posterior draws from the resulting sub-models were then aggregated to obtain a combined model with 50,000 post-warm-up iterations.

All models converged, with no divergent transitions or other diagnostic warnings. Diagnostic trace plots showed good mixing of sampling chains. \hat{R} convergence diagnostic values were all ≈ 1.00 , and less than 1.05. Simulated data drawn from each model's posterior predictive distributions agreed well with the observed data across the diagnostic categories analyzed (see [Supplementary Material](#)).

TABLE 2 The cognitive and functional outcome measures used in this study and information relevant to the statistical analysis

Cognitive/functional measure	Data-field no.	Type of data	Imputation method	Model family	Regression coefficient prior
Fluid intelligence score	20016	Numeric	N/A	Gaussian	Cauchy (0,13)
Reaction time (mean time to correctly identify matches)	20023	Numeric	Predictive Mean Matching	Shifted Log normal	Cauchy (0,5)
Numeric memory (max no. of digits remembered)	4282	Numeric	N/A	Gaussian	Cauchy (0,10)
Prospective memory	20018	Ordinal	N/A	Cumulative ordinal	Cauchy (0,5)
Pairs Matching (no. of incorrect matches in rounds 1 and 2)	399	Numeric	Predictive Mean Matching	Negative Binomial	Cauchy (0,5)
Overall health rating	2178	Ordinal	Proportional Odds Model	Cumulative ordinal	Cauchy (0,5)
Falls in last year	2296	Ordinal	Proportional Odds Model	Cumulative Ordinal	Cauchy (0,5)
Left/right hand grip strength	46, 47	Numeric	Predictive Mean Matching	Skewed normal	Cauchy (0,90)
Weight change compared to 1 year ago	2306	Categorical	Polytomous Logistic regression	Categorical	Cauchy (0,5)

Full descriptions are available by keying in the corresponding data-field number at biobank.ndph.ox.ac.uk/showcase/search.cgi. Where missing data were imputed, we report the imputation method used. We also report the *BRMS* family used to specify the Bayesian model, and the prior specified for the regression coefficient.

We chose Bayesian regression modeling to assess differences between diagnostic groups given the marked differences in group sizes, the ability to accept or reject the null and model hypothesis based on data precision, and the ability to assess difference between groups based on effect size. Bayesian analysis is a principled approach for handling smaller sample sizes, as the posterior probability distributions of the difference between groups directly represent the uncertainty of the estimates, which is affected by sample size. Our inferences took this posterior uncertainty into account. To assess the evidence for group differences, we obtained the 95% credible interval (CrI) of the posterior distribution for the regression coefficient of each diagnostic group relative to controls, and compared it to a pre-defined region of practical equivalence (ROPE) (see Figures 1 and 2).

For numerical data, the ROPE was defined as the values ranging between ± 0.1 of the standard deviation (SD) around the control mean.²⁷ For logistic regression, the ROPE was defined as a multiplicative effect of $e^{\pm 0.18}$.²⁸ For pairs matching data, which was modeled using a negative binomial distribution, the ROPE was defined as a multiplicative effect 0.9 to 1.1 on the number of incorrect matches. It has been suggested that if the CrI falls entirely outside the ROPE, there is strong evidence to reject the null hypothesis; if the CrI falls entirely within the ROPE there is strong evidence for accepting the null hypothesis.²⁷

2.5 | Regression analysis over time prior to diagnosis

To look for linear change in the years prior to diagnosis, we used classical linear regression. This analysis included a set of cognitive and functional measures (Table 2) recorded during baseline assessment and any subsequent visits pre-dating diagnosis.

For numerical data, we first regressed out the data on age, and then within each diagnosis we regressed the residuals against years to diagnosis. In cases where more than five individuals had multiple data points, we used a linear mixed-effects model with the individual as a random effect (using the *lmer* function). Otherwise, simple linear regression was used.

For categorical and ordinal data, we were unable to generate a valid random effects model that took into account individual variation due to the paucity of data points from the same individual. Ordinal logistic regression was performed for ordinal data (see Table 2) using the *polr* function from the *MASS* library. Data were regressed on age, and then within each diagnosis data they were regressed against years to diagnosis, with age multiplied by the coefficient determined from the first regression model as an offset term. *P*-values were approximated by comparing the generated *t*-values against the standard normal distribution.

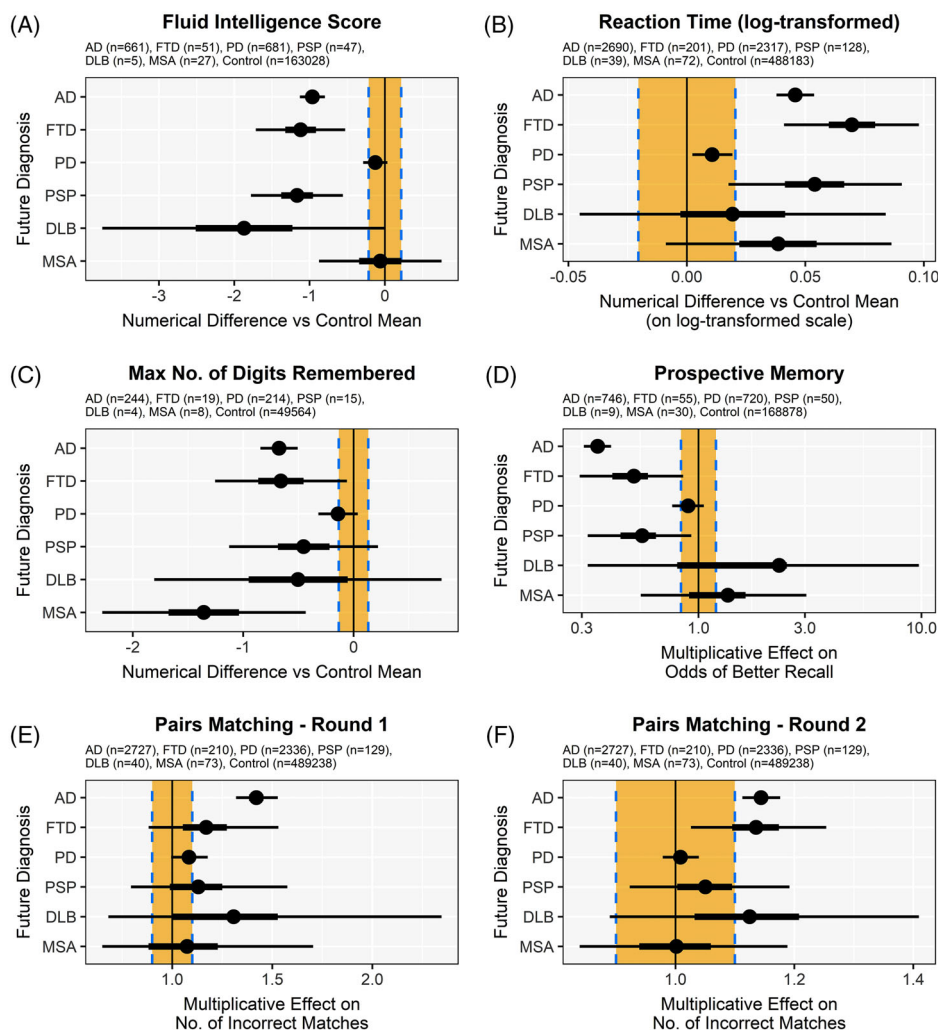


FIGURE 1 Baseline cognitive measures in UK Biobank participants who go on to develop neurodegenerative disease. The Bayesian posterior probability distributions of the difference relative to controls are plotted, with the mean the shaded circle, 50% credible interval the thicker black line, and 95% credible interval the thinner black line. The yellow rectangle represents the region of practical equivalence (ROPE), with a vertical black line denoting the point of zero difference from the control mean or odds depending on the data type, as indicated on the x-axis. The sample sizes shown indicate the number of available raw data points prior to imputation

Multinomial logistic regression for categorical data was performed using the *multinom* function from the *nnet* library. Data were regressed on age, and then within each diagnosis data they were regressed against years to diagnosis, with age multiplied by the coefficient determined from the first regression model as an offset term. *P*-values were calculated using two-tailed Wald *z*-tests.

P-values were grouped by diagnosis and further separated into those that applied to functional and cognitive measures. Within each of these 12 groups, *P*-values were adjusted using the Benjamini-Hochberg method.^{20,21} We report both uncorrected and adjusted *P*-values.

2.6 | Code availability

Search queries and processing scripts are available on Gitlab gitlab.developers.cam.ac.uk/ns651/neurodegeneration.

3 | RESULTS

3.1 | Pre-diagnostic cognitive differences

We assessed whether people who subsequently developed a range of neurodegenerative diagnoses demonstrated reduced cognitive function at their pre-diagnostic baseline assessment. The time between baseline assessment and diagnosis varied between 4.7 years for DLB and 8.3 years for AD (Table 1). There was strong evidence of decreased fluid intelligence in pre-AD (raw score difference = -0.96 , 95% CrI -0.80 to -1.13), FTD (-1.12 , CrI -0.53 to -1.71), and PSP (-1.17 , CrI -0.56 to -1.78); in these groups the CrI lay outside the ROPE (Figure 1A). There was weaker evidence of a difference in DLB (-1.87 , CrI -3.75 to 0.00) where the mean lay outside the ROPE, but with an overlapping CrI. There was strong evidence *against* reduced fluid intelligence in PD (-0.13 , CrI -0.29 to 0.03) and MSA (-0.06 , CrI -0.88 to

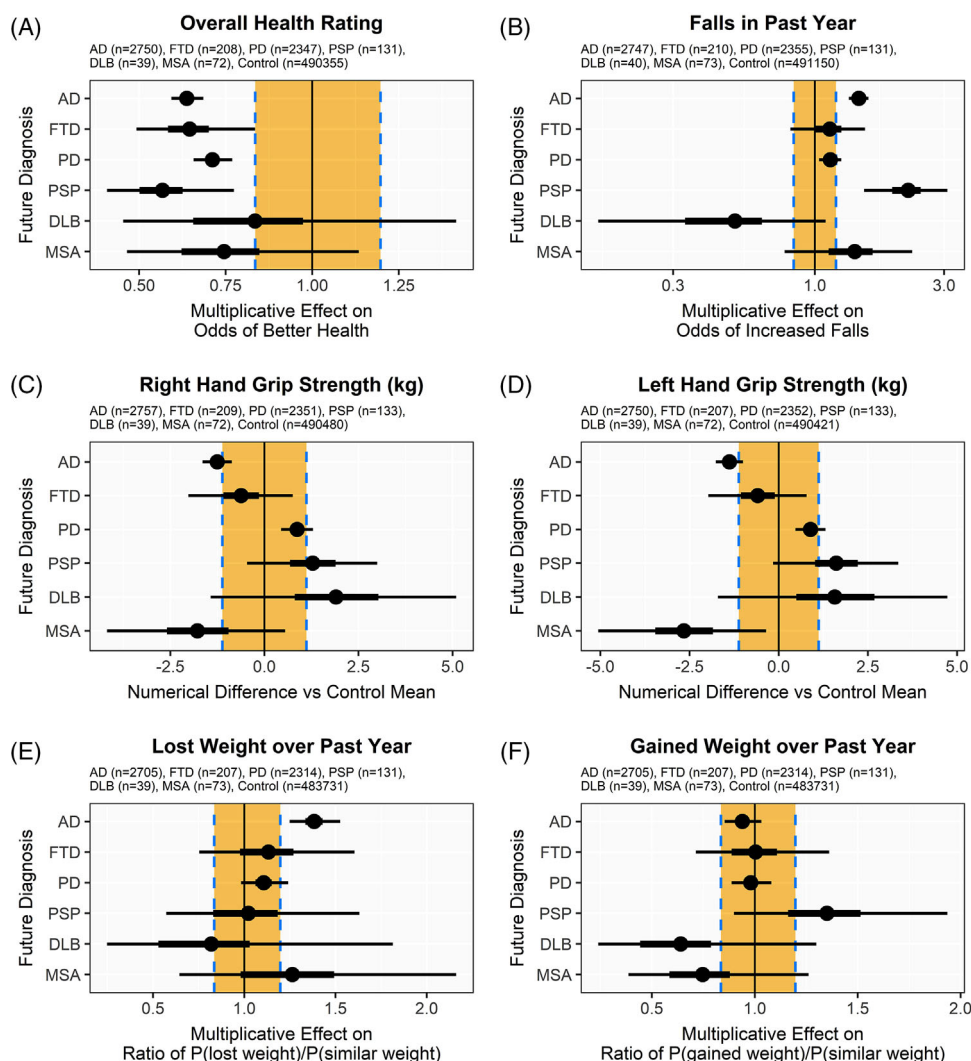


FIGURE 2 Physical measures in pre-diagnosis individuals. Posterior probability distributions of the difference relative to controls are plotted, with the mean and shaded circle, 50% credible interval the thicker black line, and 95% credible interval the thinner black line. The yellow rectangle represents the region of practical equivalence (ROPE), with a vertical black line denoting the point of zero difference from the control mean or odds depending on the data type, as indicated on the x-axis. The sample sizes shown indicate the number of available raw data points prior to imputation

0.75), with the mean and majority of the CrI overlapping the ROPE in both cases.

There was strong evidence of slower reaction time in pre-AD (difference on log-transformed scale = 0.046, CrI 0.038 to 0.054) and FTD (0.070, CrI 0.041 to 0.098) (Figure 1B). There was moderate evidence for slower reaction time in PSP (0.054, CrI 0.018 to 0.091) and MSA (0.039, CrI -0.009 to 0.086). There was strong evidence of *no difference* in reaction time in PD (0.011, CrI 0.002 to 0.019), and indeterminate evidence in DLB (0.019, CrI -0.045 to 0.084).

Poorer numeric memory was observed in pre-AD (difference in digits remembered = -0.67, CrI -0.84 to -0.51) and MSA (-1.36, CrI -2.28 to -0.43) (Figure 1C), with some evidence of a difference in FTD (-0.66, CrI -1.25 to -0.06). The evidence in PD (-0.14, CrI -0.32 to 0.04), PSP (-0.45, CrI -1.13 to 0.22), and DLB (-0.50, CrI -0.81 to 0.80) was indeterminate.

Poorer prospective memory was observed in pre-AD (multiplicative effect on odds of better recall = 0.35, CrI 0.31 to 0.41) (Figure 1D). There was weaker evidence to support differences in FTD (0.51, CrI 0.29 to 0.85) and PSP (0.56, CrI 0.32 to 0.93). There was moderate evidence that prospective memory was *not impaired* in PD (0.90, CrI 0.76 to 1.06), and indeterminate evidence in DLB (2.30, CrI 0.32 to 9.74) and MSA (1.35, CrI 0.55 to 3.04). An increase in incorrectly matched pairs was observed in pre-AD in rounds 1 (multiplicative effect = 1.42, CrI 1.3 to 1.53) (Figure 1E) and 2 (1.14, CrI 1.1 to 1.18) (Figure 1F). In FTD, the evidence was indeterminate for round 1 (1.17, CrI 0.88 to 1.53) but there was some evidence of worse performance in round 2 (1.14, CrI 1.03 to 1.25). In PD, there was weak evidence in round 1 (1.08, CrI 0.9 to 1.18) and strong evidence in round 2 (1.01, CrI 0.98 to 1.04) that there was *no difference* in performance. In PSP, the evidence was indeterminate for round 1 (1.13, CrI 0.79 to 1.58) but there was some evidence

in round 2 that there was *no difference* in performance (1.05, CrI 0.92 to 1.19). The evidence was indeterminate in DLB (round 1: 1.31, CrI 0.68 to 2.35; round 2: 1.12, CrI 0.89 to 1.41) and MSA (round 1: 1.07, CrI 0.65 to 1.70; round 2: 1.00, CrI 0.84 to 1.19).

3.2 | Pre-diagnostic functional differences

In addition we assessed for early impairment in day-to-day function. Worse overall health was reported relative to controls in pre-AD (multiplicative effect on odds of better rating = 0.64, CrI 0.59 to 0.69), FTD (0.65, CrI 0.49 to 0.84), PD (0.71, CrI 0.66 to 0.77), and PSP (0.57, CrI 0.41 to 0.77) (Figure 2A). The evidence was indeterminate for DLB (0.83, CrI 0.45 to 1.42) and MSA (0.75, CrI 0.46 to 1.13).

An increased number of falls was observed in pre-AD and (multiplicative effect on odds of more falls = 1.45, CrI 1.34 to 1.58) and PSP (2.21, CrI 1.52 to 3.09) (Figure 2B). There was some evidence to suggest *no difference* in the risk of falls for FTD (1.14, CrI 0.81 to 1.53) and PD (1.14, CrI 1.04 to 1.25). The evidence was indeterminate for DLB (0.51, CrI 0.16 to 1.10) and MSA (1.40, CrI 0.77 to 2.29). There was weak evidence for decreased grip strength in pre-AD (right hand −1.25 kg, CrI 1.64 to −0.87; left hand −1.38 kg, CrI −1.76 to −1.00) and MSA (right −1.78 kg, CrI −4.18 to 0.55; left −2.66 kg, CrI −5.06 to −0.35) (Figure 2C,D). There was weak evidence to suggest *no difference* in grip strength in FTD (right −0.62 kg, CrI −2.02 to 0.75; left −0.59 kg, CrI −1.97 to 0.78) and PD (right 0.87 kg, CrI 0.44 to 1.29; left 0.89 kg, CrI 0.47 to 1.31). The evidence was indeterminate for PSP (right 1.28 kg, CrI −0.46 to 3.00; left 1.61 kg, CrI −0.16 to 3.35) and DLB (right 1.90 kg, CrI −1.43 to 5.10; left 1.57 kg, CrI −1.70 to 4.73).

Differences in weight change over the past year are plotted as the multiplicative effect of each diagnosis on the ratios $\frac{p^{(lost\ weight)}}{p^{(similar\ weight)}}$ and $\frac{p^{(gained\ weight)}}{p^{(similar\ weight)}}$. In pre-AD there was an increased tendency toward weight loss over the past year (multiplicative effect of 1.38, CrI 1.25 to 1.53) (Figure 2E), but no difference toward weight gain (0.94, CrI 0.85 to 1.03) (Figure 2F). In FTD, there was weak evidence to suggest *no difference* in the tendency toward weight loss (1.13, CrI 0.75 to 1.60) or weight gain (1.00, CrI 0.71 to 1.36). In PD, there was weak evidence for *no difference* in weight loss (1.11, CrI 0.98 to 1.24) and strong evidence for *no difference* in weight gain (0.98, CrI 0.89 to 1.08). There was some evidence for *no difference* in weight loss in PSP (1.02, CrI 0.57 to 1.63), and indeterminate evidence for weight gain (1.35, CrI 0.90 to 1.94). There evidence was indeterminate for DLB (weight loss 0.82, CrI 0.2 to 1.81) (weight gain 0.64, CrI 0.24 to 1.30) and MSA (weight loss 1.26, CrI 0.64 to 2.16) (weight gain 0.75, CrI 0.39 to 1.26).

3.3 | Cognitive and functional decline prior to diagnosis

A decline was observed for several cognitive and functional measures in the time prior to diagnosis (Table 3). Pre-AD individuals demonstrated worsening fluid intelligence (−0.036/year, $P = 5.6 \times 10^{-5}$)

(Figure 3A), reaction time (2.9 ms/year, $P = 1.1 \times 10^{-9}$) (Figure 3B), prospective memory ($\times 1.1$ /year odds of worse recall, $P = 4.7 \times 10^{-5}$) (Figure 3D), and pairs matching results (0.056 incorrect matches/year in round 2, $P = .014$) (Figure 3E). Reaction time also worsened (7.4 ms/year, $P = .0011$) in pre-PSP individuals (Figure 3C).

Pre-PD individuals exhibited weakening right (−0.089 kg/year, $P = 9.7 \times 10^{-7}$) and left (−0.086 kg/year, $P = 6.4 \times 10^{-7}$) hand grip strength (Figure 3G,I) in the years prior to diagnosis. Pre-PSP individuals exhibited worsening overall health self-rating ($\times 1.2$ /year odds of worse rating, $P = .027$) (Figure 3L), and an increasing falls risk ($\times 1.2$ /year odds of increased falls, $P = .027$) (Figure 3J). Pre-AD individuals demonstrated a significant decrease over time in right (−0.044 kg/year, $P = .021$) and left (−0.045 kg/year, $P = .019$) hand grip strength (Figure 3F,H). Pre-MSA individuals demonstrated worsening overall health self-rating ($\times 1.3$ /year odds of worse rating, $P = .0017$) (Figure 3M) and increasing falls risk ($\times 1.3$ /year odds of increased falls, $P = .029$) (Figure 3K).

4 | DISCUSSION

We demonstrate cognitive and functional antecedents of several idiopathic neurodegenerative syndromes in the years prior to diagnosis. In line with findings of pre-symptomatic cognitive decline in familial mutation carriers of AD and FTD,^{5,14} these changes were identified at a baseline assessment averaging 5 to 9 years before diagnosis. The pre-diagnostic linear decline in a number of measures supports our supposition that these changes represent early progressive neurodegeneration rather than a low cognitive or functional baseline.

Extensive differences in all cognitive assessments and some physical measures were observed in pre-AD individuals. This is consistent with: (1) genetic cohorts highlighting a long prodromal phase of AD identified using neuroimaging,²⁹ (2) the concept of mild cognitive impairment (MCI) as a precursor to AD, and (3) the finding of early visual memory deficits 10 years prior to AD symptoms.³⁰ Our study builds on previous evidence that individuals with MCI are at greater risk of AD. We present evidence for impairment in specific cognitive domains across the pre-AD population, and show that impairment pre-AD extends to physical function. More speculatively, our data perhaps demonstrate why MCI is more identifiable in AD than in other neurodegenerative diseases, given that the pre-AD group exhibited more extensive cognitive impairment than the other diseases.

We identified syndrome-relevant changes in other diseases. Pre-PSP individuals demonstrated an increased falls risk and reduced fluid intelligence scores, reflecting the typical Richardson syndrome of PSP of early falls and a dysexecutive cognitive impairment.³¹ The poorer numeric memory in pre-MSA patients is noteworthy because cognitive impairment is not a dominant symptom in MSA. Nevertheless, cognitive impairment has been identified consistently in a portion of patients with MSA,^{32,33} with frontal-executive dysfunction being the most common cognitive feature.³⁴ Furthermore, the pre-MSA and pre-PSP groups exhibited a rapid functional decline in falls risk and overall health rating leading up to the time of diagnosis. In these other

TABLE 3 Data from regression of cognitive and functional measures against years to diagnosis, after adjusting for the effect of age

Diag Measure	n	Coef	SE	P-value	Adj P
Fluid intelligence score	729	−0.036	0.0086	2.8e-05	5.6e-05
Reaction time (ms)	2766	2.9	0.45	1.8e-10	1.1e-09
Max no. of digits remembered	246	−0.00056	0.015	.97	0.97
Prospective memory	824	−0.1	0.024	1.6e-05	4.7e-05
Pairs matching round 1 errors	2742	0.0056	0.0069	.42	0.51
AD	2791	0.056	0.022	.0093	0.014
Pairs matching round 2 errors					
Overall health rating	2833	−0.014	0.012	.24	0.48
Falls in past year	2830	0.012	0.013	.36	0.51
Right hand grip strength (kg)	2844	−0.044	0.016	.0069	0.021
Left hand grip strength (kg)	2837	−0.045	0.015	.0032	0.019
Weight loss over past year	2789	0.013	0.016	.42	0.51
Weight gain over past year	2789	0.0075	0.015	.63	0.63
Fluid intelligence score	56	−0.0079	0.035	.82	0.82
Reaction time (ms)	206	1	1.6	.53	0.64
Max no. of digits remembered	21	0.056	0.049	.27	0.64
Prospective memory	60	−0.073	0.083	.38	0.64
Pairs matching round 1 errors	213	−0.019	0.019	.32	0.64
FTD	212	0.052	0.07	.45	0.64
Pairs matching round 2 errors					
Overall health rating	213	0.0099	0.043	.82	0.92
Falls in past year	215	0.018	0.053	.74	0.92
Right hand grip strength (kg)	214	−0.059	0.062	.34	0.92
Left hand grip strength (kg)	210	−0.029	0.058	.61	0.92
Weight loss over past year	212	−0.14	0.07	.04	0.24
Weight gain over past year	212	−0.0054	0.054	.92	0.92
Fluid intelligence score	754	−0.003	0.0085	.73	0.74
Reaction time (ms)	2395	0.52	0.38	.17	0.52
Max no. of digits remembered	220	−0.022	0.012	.066	0.4
Prospective memory	801	−0.02	0.026	.44	0.74
Pairs matching round 1 errors	2359	−0.0023	0.0057	.7	0.74
PD	2395	−0.0059	0.018	.74	0.74
Pairs matching round 2 errors					
Overall health rating	2432	−0.024	0.012	.046	0.068
Falls in past year	2439	0.03	0.015	.043	0.068
Right hand grip strength (kg)	2432	−0.089	0.017	3.2e-07	9.7e-07
Left hand grip strength (kg)	2433	−0.086	0.016	1.1e-07	6.4e-07
Weight loss over past year	2395	0.019	0.018	.27	0.33
Weight gain over past year	2395	0.0058	0.015	.7	0.7
Fluid intelligence score	49	−0.039	0.033	.25	0.25
Reaction time (ms)	132	7.4	1.9	.00018	0.0011
Max no. of digits remembered	16	−0.085	0.048	.1	0.2
Prospective memory	54	−0.14	0.1	.16	0.24
Pairs matching round 1 errors	131	0.032	0.027	.25	0.25

(Continues)

TABLE 3 (Continued)

Diag Measure	n	Coef	SE	P-value	Adj P
PSP	131	0.21	0.09	.019	0.058
Pairs matching round 2 errors					
Overall health rating	135	−0.16	0.06	.0089	0.027
Falls in past year	135	0.17	0.062	.0063	0.027
Right hand grip strength (kg)	137	0.037	0.08	.64	0.94
Left hand grip strength (kg)	137	−0.02	0.074	.78	0.94
Weight loss over past Year	135	−0.0069	0.092	.94	0.94
Weight gain over past year	135	0.14	0.065	.034	0.069
Fluid intelligence score	5	−0.13	0.15	.47	0.8
Reaction time (ms)	39	−5.6	5.9	.35	0.8
Max no. of digits remembered	4	−0.008	0.014	.64	0.8
Prospective memory	9	−0.15	0.35	.67	0.8
Pairs matching round 1 errors	40	0.0053	0.093	.95	0.95
DLB	40	−0.2	0.25	.42	0.8
Pairs matching round 2 errors					
Overall health rating	39	0.098	0.19	.61	0.91
Falls in past year	40	−0.16	0.26	.54	0.91
Right hand grip strength (kg)	39	0.0077	0.18	.97	0.97
Left hand grip strength (kg)	39	−0.02	0.16	.9	0.97
Weight loss over past year	39	0.5	0.26	.059	0.36
Weight gain over past year	39	−0.24	0.25	.34	0.91
Fluid intelligence score	29	−0.042	0.037	.26	0.59
Reaction time (ms)	74	2.1	1.8	.23	0.59
Max no. of digits remembered	8	−0.07	0.099	.51	0.76
Prospective memory	32	0.049	0.14	.73	0.88
Pairs matching round 1 errors	74	−0.00033	0.026	.99	0.99
MSA	74	0.096	0.091	.29	0.59
Pairs matching round 2 errors					
Overall health rating	74	−0.28	0.077	.00028	0.0017
Falls in past year	75	0.24	0.091	.0096	0.029
Right hand grip strength (kg)	74	−0.17	0.089	.061	0.091
Left hand grip strength (kg)	74	−0.11	0.084	.21	0.25
Weight loss over past year	75	0.2	0.099	.046	0.091
Weight gain over past year	75	0.071	0.093	.44	0.44

"Prospective memory" and "overall health rating" were analyzed using ordinal regression, and log-odds of better outcomes were regressed. "Falls in past year" was analyzed with ordinal regression, and log-odds of a greater number of falls were regressed. Weight loss was analyzed as the log of the ratio Probability(weight loss)/Probability(weight unchanged), and weight gain was similarly analyzed. n = number of data points, Coef = regression coefficients, SE = standard error, Adj P = P-values adjusted using the Benjamini-Hochberg procedure, AD = Alzheimer's disease, FTD = frontotemporal dementia, PD = Parkinson disease, PSP = progressive supranuclear palsy, DLB = dementia with Lewy bodies, MSA = multiple system atrophy.

diseases, we provide preliminary evidence characterizing the MCI and physical decline understood to precede these diseases.

Conversely, we demonstrate that pre-PD individuals have preserved pre-symptomatic cognition and good evidence of preserved outcomes on some measures. Our study focused on cognition and function, so we did not capture the well-recognized early systemic features seen in a proportion of people with PD.³⁵

Identifying early subtle changes in cognition and function could enable stratification into prevention trials targeting known risk factors.³⁶ Studies of prevention are ongoing, with some evidence that treating blood pressure in middle age reduces cerebral white matter disease,^{37,38} and that a multidomain preventive approach may reduce the risk of cognitive decline in a population 60 to 77 years of age.³⁹ However, most lifestyle factors are targeted at the vascular risk

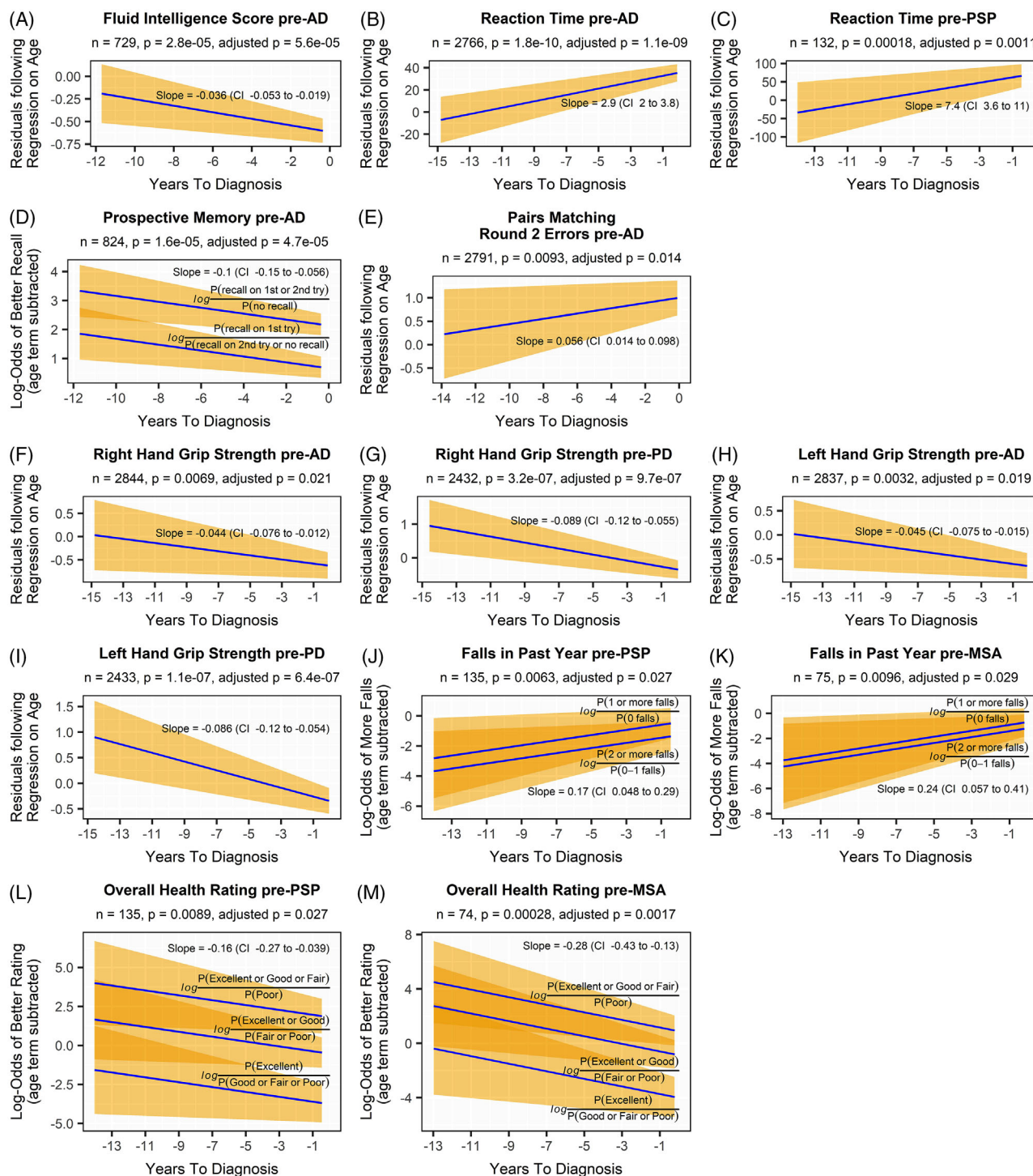


FIGURE 3 Cognitive and functional measures regressed on years to diagnosis after removing the effect of age. Blue lines indicate the estimated regression coefficient, the yellow shaded area represents the 95% confidence interval. Adjusted *P*-values were calculated using the Benjamini-Hochberg method. Log-odds are plotted for D, J, K, L, and M as these measures were analyzed using ordinal regression. *n* = number of data points, CI = 95% confidence interval, AD = Alzheimer's disease, PD = Parkinson disease, PSP = progressive supranuclear palsy, MSA = multiple system atrophy

factors associated with AD, whereas other pathologies such as tau and α -synuclein are not associated with such risk.

In these other pathologies, early disease-modifying treatments are being pursued. Given the toxicity of many such treatments,⁴⁰ one would need to be confident in identifying specific pathologies, and initiating treatment at a time that maximizes the risk-benefit ratio. The most common changes we identified were in fluid intelligence, memory, and reporting of overall health. Screening of these domains may guide the development of pathology-specific biomarker assessments such as positron emission tomography (PET) scans or CSF or blood-based biomarkers.^{41–48} The combination of cognitive and functional measures with associated biomarkers could improve predictive models, facilitating more targeted preventative and treatment trials at a time when they may be of greater benefit.^{2,3}

Our study has several limitations. Analysis of the FTD ($n = 211$), PSP ($n = 133$), DLB ($n = 40$), and MSA ($n = 73$) groups was limited by the smaller sample size available. In DLB, this partly reflected the recording of the diagnosis in the UK Biobank, as it was only possible to search for DLB within the primary care data set. Pre-diagnostic functional and cognitive differences in these diseases may be estimated more precisely in further studies with a larger sample size. Although the UK Biobank is population based, it is biased toward a population with a lower risk of disease in general,⁴⁹ and is not representative of ethnic and socioeconomic diversity in the United Kingdom. This may limit the generalizability of our results. Moreover, the restricted mid-life age range of the UK Biobank cohort may exclude the age at which some risk factors apply most strongly. Further analysis of risk factors can potentially improve our understanding of disease pathophysiology and guide preventative strategies. In conclusion, our study identifies pre-diagnostic functional and cognitive differences in multiple neurodegenerative diseases. Better characterization of the pre-diagnostic stage will improve risk stratification for prevention and disease-modifying treatment studies.⁵⁰

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CONFLICT OF INTEREST

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