Prediction of manifest Huntington disease with clinical and imaging measures: A 12-year prospective observational study

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Abstract

BACKGROUND—Although correlation between cytosine-adenine-guanine (CAG) repeat length and age of Huntington disease (HD) onset is well known, improved prediction of onset would be advantageous for clinical trial design and prognostic counseling. We compared genetic, demographic, motor, cognitive, psychiatric, functional and imaging measures for tracking progression and predicting conversion to manifest HD.

METHODS—N=1078 research participants with the gene mutation for HD, but without a rating of 4 on the Diagnostic Confidence Level (DCL) following administration of the 15-item motor assessment of the Unified Huntington's Disease Rating Scale. Participants were from 33 world wide sites and followed for up to 12 years (mean=5, SD=3·3) over the period 2001–2013. A subset of 225 participants prospectively converted to manifest HD according to the DCL ("meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder in a subject at risk for HD" with 99% confidence). Joint modeling of longitudinal and survival data was used to examine the extent to which baseline and change of 40 variables analyzed separately was predictive of CAG-adjusted age at motor diagnosis.

FINDINGS—Cross-sectional and longitudinal clinical and imaging measures were significant predictors of motor diagnosis beyond CAG repeat length and age. The strongest predictors in the top three phenotypic domains were total motor score (motor), putamen volume (imaging), and Stroop word test (cognitive). A one standard deviation (SD) difference in total motor score increased the risk of a motor diagnosis by 3·1 times (95% CI=[2·3,4·2]), one SD loss in putamen volume increased risk by 3·3 times ([2·4,4·7]) and one SD cognitive decline increased risk by 2·3 ([1·9,2·9]).

INTERPRETATION—Prediction of HD diagnosis can be considerably improved beyond that obtained by CAG repeat length and age alone. Such knowledge about potential predictors of manifest HD should inform discussions about revisions to guidelines for diagnosis, and prognosis, and counselling, and might be useful in guiding selection of participants and outcome measures for clinical trials.

INTRODUCTION

Huntington disease (HD) is an autosomal dominant neurodegenerative disease caused by expansion of the trinucleotide cytosine-adenine-guanine (CAG) in the first exon of the *Huntingtin* gene. There is a well-known relationship between the length of the CAG mutation and the age at disease onset[1] although there is also substantial individual variation. Over the past decade, Neurobiological Predictors of Huntington's Disease (PREDICT-HD; NS040068) and other studies[2–11] documented disease-related changes of clinical features and biomarkers in persons with the CAG expansion, but not yet diagnosable with HD.[12,13] Useful clinical and biological markers should be predictive of landmark events, such as clinical motor diagnosis. In this study we compare genetic, demographic, motor, cognitive, psychiatric, functional, and imaging measures for predicting conversion to manifest HD in the largest study of gene mutation premanifest participants, culminating in 225 prospectively diagnosed HD patients. Improved predictability of HD diagnosis could advance research design, experimental trials, and clinical care through improved prognosis and earlier intervention.

METHODS

Participants

Participants were 1078 HD gene-expanded (CAG>35) individuals from the PREDICT-HD study who had less than the highest rating on the Diagnostic Confidence Level (DCL) (DCL< 4) of the Unified Huntington's Disease Rating Scale (UHDRS) at the beginning of the study (see Table 1). Data were collected from 2001 to 2013, and all participants had prior and independent genetic testing for HD. Exclusion criteria included presence of other central nervous system disease, injury, or developmental disorder, or evidence of an unstable medical or psychiatric illness. All participants provided informed written consent (with full study approval by 33 site institutional review boards) and were treated consistent with ethical standards. Mean years in the study was five (SD=3·3) with a range from one to twelve. There were 959 participants (89%) who had two or more waves (years) of data, and 118 who had only one time point (11%) (see web extra material for additional details). A subset of 225 HD gene-expanded participants received a motor diagnosis during the study, according to the DCL ("meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder in a subject at risk for HD" with 99% confidence). The DCL is administered by a movement disorder specialist after conducting the 15-item standardized motor assessment. PREDICT-HD also had $N = 305$ non-gene-expanded controls who were used only for an ancillary analysis reported in the web extra material. All abnormalities in clinical and imaging data were forwarded to clinical investigators at the relevant site for additional review and discussion. When the data were found to suggest abnormalities in function or brain imaging, follow-up clinical investigations were encouraged. Findings were reviewed by the Executive Committee, who made decisions regarding use of the data in the study: if a control participant was found to

have a previously undetected neurological diagnosis, the participant and all of his or her data were excluded.

Measures

The web extra material details the 40 longitudinal measures, which were selected based on their sensitivity to the detection and progression of disease.[12] Motor variables were total motor score (TMS) from the UHDRS and the chorea, bradykinesia, oculomotor, dystonia and rigidity subdomains from the 15-item standardized motor assessment. Cognitive variables included the Stroop Color and Word Test (three measures), the Symbol Digit Modalities Test, University of Pennsylvania Smell Identification Test, emotion recognition, speeded tapping, time production or paced tapping, and the Trail Making Test. Psychiatric measures included four subscales of the Symptom Checklist 90 (SCL90), the Beck Depression Inventory (BDI), and three subscales of the Frontal Systems Behavioral Scale. Imaging measures included intracranial-corrected volumes (ICV) for putamen, accumbens, caudate, hippocampus, thalamus, globuspallidus, cerebral spinal fluid, lobar white and gray matter. Functional outcome variables included the total functional capacity (TFC) and functional activity scale from the UHDRS, the World Health Organization Disability Assessment Schedule, and the Everyday Cognition Rating Scale (ECOG). Motor diagnosis was defined as a rating of "4" on the Diagnostic Confidence Level (DCL) of the UHDRS.

Statistical analyses

The primary goal was to examine the ability of each variable to predict time to motor diagnosis (first occurrence) over and above CAG repeat length, age, and their interaction. Time to diagnosis and longitudinal change were simultaneously modeled using joint modeling for survival and longitudinal data[14,15] (see web extra material for details). The intent was to model progression over the entire lifespan by using the time metric of age adjusted for CAG expansion.

The survival model was a Cox regression model and the longitudinal model was a linear mixed effects regression (LMER) model. The time metric for both was age adjusted for genetic burden (CAG expansion), known as the CAG-Age Product (CAP), $CAP = age \times (CAG - 33 \cdot 66)$.[16] CAP reflects the cumulative exposure to the effects of mutant huntingtin, and is similar to other CAG and age based measures.[17–19] CAP at motor diagnosis or censoring was used for the observation time in the Cox model, and CAP was the longitudinal time metric for the LMER model. It is emphasized that CAP as specified in this analysis is time-varying and represents age adjusted for CAG expansion. Because of the variability in age at study entry, the annual measurements span virtually the entire adult age range, which allows inferences about motor diagnosis risk over the HD lifespan. The natural CAP intercept (baseline) is CAP=0, denoting birth. Predictive power is meaningless at birth because the clinical variables are not measured. We chose the baseline cross-section of CAP=290 as the intercept because this is the value at which motor signs begin to appear in the PREDICT-HD cohort.[6] At this baseline the predictors might have sufficient variability to correlate with later motor diagnosis. CAP=290 corresponds to the rounded ages of 40, 35, and 28 for individuals with the CAG sample quartile values of 41, 42, and 44, respectively.

Each outcome was standardized and cubic splines based on five knots (1, 25, 50, 75, 99 percentiles) were used in the LMER portion to model nonlinear change.[12,13,20,21] Two joint models were fit for each variable: a reduced model that provided information about a marker's baseline prediction of the hazard for motor diagnosis (at CAP=290), and a full model that incorporated change of the marker in the prediction. A statistically significant γ estimate meant a variable accounted for variability in the timing of diagnosis over and above CAG expansion and age. The covariates in all models were gender and education. For cognitive variables, depression (BDI) was added to account for mood changes. For imaging variables, field strength was added because some sites updated their scanners during the study. The Hazard Ratio (HR) was computed as exp (γ) and served as the primary effect size (HR^{-1} was used when the γ estimate was negative). A significant HR indicates a variable that adds to prediction beyond that of CAG and age (the latter variables being indexed by CAP).

A subsequent analysis was performed to characterize the risk of motor diagnosis over the lifespan. Individual fitted values from the LMER spline model were used to obtain baseline values at CAP=290. The baseline information was used in a separate (not joint) Cox model to predict time to diagnosis along with the covariates. The cumulative hazard was estimated based on the fitted models for various baseline predictor values.

An ancillary analysis examined the natural history of key variables from the premanifest phase through diagnosis. All converters were used for this analysis. The time metric was years to diagnosis and cubic spline curves were used with LMER models to allow for nonlinear trends over time.

Role of the funding source

The study sponsors had no role in study design, in the collection, analysis, and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Figure 1 shows age at diagnosis as a function of CAG expansion for the converters who obtained a motor diagnosis during the study. The squared correlation between CAG repeat length and age at HD diagnosis was $r^2=0.53$. For every CAG stratum the figure shows variation for age of diagnosis. Considering CAG=40, the range of diagnosis age is 31 years, and the difference between the first and third quartile is 15 years. Table 1 shows descriptive statistics for converters, non-converters, and the combined sample at study entry. Additional information is listed in the web extra material. Mean CAP at motor diagnosis was 447, which for the sample CAG quartiles of 41, 42, and 44, represents the rounded ages of 61, 54, and 43, respectively.

Table 2 shows the joint modeling results (each variable was tested separately). The longitudinal variables are grouped by domain and sorted within domain based on the

absolute Z-value of γ from the full model. N/A indicates the full model could not be estimated due to a lack of variability in the individual rate of change over time.

The column of reduced model γ estimates shows that the baseline information was a significant predictor of the hazard for 37 of 40 variables. A comparison shows that the full model γ estimates were larger in absolute value for every variable that had a full model estimated. Thus, prediction of motor diagnosis based on baseline and longitudinal change information was stronger than using only the former.

Regarding the full model results, the largest motor domain effect size was for TMS (Z=7·23, p<0·0001). The TMSHR indicates a one SD difference increased the risk of diagnosis by 3·07 times (95% CI=[2·26,4·16]) For the imaging domain, putamen volume was the strongest predictor (Z=−6·95, p<0·0001), and a one SD difference increased the risk of diagnosis by 3·32 times ([2·37,4·65]). The strongest cognitive variable was Stroop word (Z= −7·79, p < 0·0001), which increased the risk of diagnosis by 2·32 ([1·88,2·87]). The best psychiatric variable was executive functioning (Z=6·64, p<0·0001) with an increased risk of diagnosis of 1·86 ([1·55,2·23]). TFC was the strongest functional variable (Z=−6·34, p<0·0001), with an increased risk of diagnosis of 1·84 ([1·52,2·22]).

Figure 2 illustrates the Table 2 results for putamen volume, total motor score, and Stroop word test. Each variable was the strongest predictor within the three strongest domains (functional and psychiatric variables, though significant, had weaker prediction in terms of the estimated HR; see Table 2). The figure shows the cumulative hazard (accumulated risk rate) as a function of CAP for the three variables and a model with no predictor (solid black line). The no-predictor model represents the cumulative hazard associated with only CAG expansion and age (both variables are indexed by CAP). As indicated in the figure, the baseline was set to CAP=290, and the predictor curves were generated for values of the variables representing no deterioration (dash-dot lines) and advanced deterioration (solid lines). The no deterioration values (total motor score=0, putamen volume (ICV-corrected)=0·008, Stroop word=183) were the most extreme values in the sample (minimum for total motor score, and maximum for the others). The advanced values (total motor score=15, putamen volume (ICV-corrected)=0·0038, Stroop word=85) were the medians for DCL=3 of the sample. The figure shows when there is advanced deterioration at baseline, the cumulative hazard for the predictors accelerates at a rate faster than when the covariates are ignored. Conversely, when there is no deterioration at baseline, the cumulative hazard for the predictors accelerates at a slower rate than when the covariates are ignored.

Figure 3 shows individual empirical curves (dashed lines) and fitted spline curves (solid lines) with 95% CIs for the converters. The vertical line in each panel denotes year of diagnosis (set to year=0). The two strongest predictors in each domain (based on absolute Z-values) from Table 2 were selected for graphing. The web extra material lists descriptive information on all the variables for the converters at study entry and time of diagnosis.

DISCUSSION

The current findings show several clinical and biological measures that can improve the prediction of HD diagnosis above and beyond that obtained by CAG repeat length and age alone. The strongest predictors (in terms of absolute Z-values in Table 2) were in the domains of motor (total motor score was the strongest predictor), imaging (putamen volume), and cognitive (Stroop word test). Psychiatric and functional variables were significant but relatively weak predictors in the sense of having estimated hazard ratios less than two. Findings suggest models of HD onset prediction can be considerably improved using straightforward clinical assessment. Volumetric MRI measures provide additional powerful predictors.

Figure 2 summarizes the statistical results in illustrating the importance of using putamen volume, total motor score, or Stroop word test in estimating the risk of future motor diagnosis in addition to CAG and age (and their interaction; see CAP definition above). The no-predictor curve represents the risk that is associated with CAP alone. Because CAP is age adjusted for CAG, the cumulative risk increases as CAP elapses because the likelihood of motor diagnosis increases as people age. As a result, the no-predictor curve represents the accumulated risk rate that one would predict based only on CAG and age (and their interaction). On the other hand, when a predictor from Table 2 is considered, the risk profile is modified based on the predictor value at baseline. The modification can result in a very different risk profile compared to using CAP alone. Figure 2 indicates for people with advanced deterioration at baseline, the risk of motor diagnosis is greater when a predictor is used, whereas for people with no or little deterioration, the risk is less. Thus, information from a clinical predictor is informative for future motor diagnosis risk assessment over and above CAG and age. Further research is critical to detect additional genetic, environmental, and biological contributions that may lead to new avenues for intervention.

A follow-up analysis not reported showed that using the composite of the three variables in Figure 2 did not improve upon using the variables alone. A complication of Figure 2 is that the maximum Stroop word value may not represent the absence of deterioration, but rather an advanced education level and/or advanced level of intelligence. The converse also holds for low Stroop word scores. However, the relation of Figure 3 still holds; superior or inferior Stroop word test performance at baseline alters the future risk assessment (similar comments regarding putamen volume and TMS also apply).

As expected, the best motor predictor of HD diagnosis was TMS, since diagnosis is based on motor findings. This underscores the value of the motor examination, even in the premanifest period. This result is consistent with previous findings of subtle motor abnormalities years before diagnosis, which may accelerate just prior to diagnosis.[6,22] Subdomains for chorea, bradykinesia, and oculomotor abnormalities were also predictive.

The strongest cognitive variable was the Stroop word test, a timed reading task. Previously, we documented 19 cognitive tasks that showed significant longitudinal change prior to motor diagnosis.[12] The present results suggest that performance on just one of the most robust of these tests can significantly improve diagnostic prediction. The most robust

cognitive measures require just a few minutes to administer and can be used in a variety of settings, making them valuable for research design and clinical practice.

The utility of brain imaging markers in the detection of HD has been documented in several studies over the past decade.[2,23,24] Striatal volume consistently distinguishes gene-mutation positives from negatives and tracks disease progression. The current study demonstrates imaging variables were among the best predictors of diagnosis in premanifest HD, and their preeminence offers biological validity for the models presented. The use of imaging variables may translate to advances in clinical trial design used either in selection criteria or as an outcome measure. Imaging may also be useful in clinical care and education, although broad dissemination of imaging predictors would require standardization of acquisition and analysis protocols for clinical care.

Findings validate and extend results from other studies using smaller samples, shorter follow-up and varying endpoints.[2–11] The integration of these findings with the literature provide strong evidence that cognitive, motor, and imaging deficits are evident prior to traditional motor diagnosis and may provide an opportunity for earlier intervention, treatment and support. The predictive utility of the markers suggested by this research can be immediately integrated into clinical trial design and can be used to begin to advance clinical care through refined diagnostic and prognostic guidelines.

There is considerable evidence that the diagnosis of HD is made relatively late in the disease course, after a high proportion of persons already show significant cognitive decline,[13,25] psychiatric abnormalities,[26–28] motor impairment,[6,22] and at a time when over half of their striatal volume is lost.[2] Notably, many persons are diagnosed after major changes in functioning have occurred (loss of usual employment or driving) as well as a reduction in basic activities of daily living (requiring financial or care assistance).[29–32] It is possible that an earlier diagnosis might be more beneficial to intervention and life planning.[33,34] Our analysis concerned the predictive ability of individual markers, and it might be possible to translate these findings into revised diagnostic and prognostic criteria for HD, which could advance research and clinical care.

The trajectories illustrated in Figure 3 suggest some interesting models regarding the course of the disease. Using the largest known sample of prospectively followed converters (N=225), the graphs suggest that many of the clinical markers of disease progression (i.e., cognitive, sensory, and psychiatric variables) progress in a near linear fashion and decline in concert with biological markers of brain imaging abnormalities. Additionally, it suggests motor and functional variables progress in a nonlinear fashion, which is reflected by the fact that motor signs and functional impairment become evident only at certain points of disease progression. There are several possible explanations for the variations in disease progression. One explanation may be that atrophy of each individual brain region proceeds relatively linearly, beginning with the striatum, but as additional brain regions begin to undergo degeneration and dysfunction, their combined effect causes acceleration of the clinical expression of disease. An alternative threshold hypothesis is that at some point, a threshold is surpassed, triggering acceleration of motor and functional deficits. Researchers making the critical choice of outcome measures for clinical trials might benefit from the data

provided so study designs can enhance the possibility of documenting therapeutic effects, should they occur. Given the variation in motor and functional changes across the disease course, it is likely that subject selection at varying disease epochs could drastically alter interpretations made about an intervention.

It is important to consider qualifications of these research findings. The baseline for prediction was defined at a point for which it is known the PREDICT-HD sample has the earliest detectable change in motor signs.[6] Should other samples suggest the examination of additional cross sections in the premanifest period, the estimates may vary accordingly. It is encouraging to note, however, that the present findings mirror those reported by studies of smaller samples followed for shorter duration.[11] Replication with other samples will continue to refine these predictive models. Translation of these models into clinical care may require further research to determine how such information can be integrated into genetic counseling in a safe and productive manner to promote understanding. Advances in diagnosis and prognosis will require clinical consensus as well as a white paper to best communicate standard criteria and clinical care practices. Implementation of new diagnostic and prognostic criteria requires patient-centered clinical outcome research to document best practices for HD families who choose to have greater prognostic information

Additional caveats concern the variability observed in this study. The graphs of converters (Figure 3) indicate a relatively wide range of values associated with motor diagnosis (time=0), especially for TMS (min=2, max=56). As discussed in the methods section, individuals might have had different motor examiners over time, which could inflate the TMS variability. Early in the study, substantial TMS variation was noted and efforts were made to help assure data integrity as outlined in the web extra material. Another source of heterogeneity was introduced by the upgrading of scanners at the sites (1.5T to 3T). Scanner strength was adjusted for, both in the image processing and the statistical analysis (see web extra material). It is noted that despite the substantial observed variability, both the TMS and the imaging variables were among the strongest predictors. Thus, sources of variance such as different raters and scanners did not overcome the predictive power of the variables. Future studies that constrain sources of variance by having the same scanners or the same motor raters might show even larger effect sizes than reported here.

The detection and tracking of early clinical signs and symptoms in HD is critical to choosing outcome measures useful for clinical trials. Treatments with face validity (impacting on symptoms of disability in motor, cognitive, psychiatric and functional domains) can be essential components of clinical trials and often mandated by regulatory agencies. The predictive measures reported here might have value in the selection of specific types of research participants and might help choose outcomes that are associated with a critically meaningful endpoint – that of being diagnosed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet. 1993; 4:398–403. [PubMed: 8401589]

2. Aylward EH, Liu D, Nopoulos PC, et al. Striatal volume contributes to the prediction of onset of Huntington disease in incident cases. Biol Psychiatry. 2012; 71:822–828. [PubMed: 21907324]

3. Brandt J, Inscore AB, Ward J, et al. Neuropsychological deficits in Huntington's disease gene carriers and correlates of early "conversion". J Neuropsychiatry Clin Neurosci. 2008; 20:466–472. [PubMed: 19196932]

4. Harrington DL, Smith MM, Zhang Y, Carlozzi NE, Paulsen JS. PREDICT-HD Investigators of the Huntington Study Group. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. J Neurol Neurosurg Psychiatry. 2012; 83:612–619. [PubMed: 22451099]

5. Langbehn DR, Paulsen JS. Huntington Study Group. Predictors of diagnosis in Huntington disease. Neurology. 2007; 68:1710–1717. [PubMed: 17502553]

6. Long JD, Paulsen JS, Marder K, et al. Tracking motor impairments in the progression of Huntington's disease. Mov Disord. 2014; 29:311–319. [PubMed: 24150908]

7. Marder K, Gu Y, Eberly S, et al. Relationship of Mediterranean diet and caloric intake to phenoconversion in Huntington disease. JAMA Neurol. 2013; 70:1382–1388. [PubMed: 24000094]

8. Paulsen JS, Zhao H, Stout JC, et al. Clinical markers of early disease in persons near onset of Huntington's disease. Neurology. 2001; 57:658–662. [PubMed: 11524475]

9. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. J Clin Exp Neuropsychol. 2002; 24:133–145. [PubMed: 11992196]

10. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord. 2008; 23:1830–1836. [PubMed: 18785217]

11. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol. 2013; 12:637–649. [PubMed: 23664844]

12. Paulsen JS, Long JD, Johnson HJ, et al. Clinical and Biomarker Changes in Premanifest Huntington Disease Show Trial Feasibility: A Decade of the PREDICT-HD Study. Front Aging Neurosci. 2014; 6:78. [PubMed: 24795630]

13. Paulsen JS, Smith MM, Long JD. PREDICT-HD investigators and coordinators of the Huntington Study Group. Cognitive decline in prodromal Huntington Disease: implications for clinical trials. J Neurol Neurosurg Psychiatry. 2013; 84:1233–1239. [PubMed: 23911948]

14. Diggle PJ, Sousa I, Chetwynd AG. Joint modelling of repeated measurements and time-to-event outcomes: the fourth Armitage lecture. Stat Med. 2008; 27:2981–2998. [PubMed: 18041047]

15. Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics. 1997; 53:330–339. [PubMed: 9147598]

16. Zhang Y, Long JD, Mills JA, et al. Indexing disease progression at study entry with individuals at-risk for Huntington disease. American Journal of Medical Genetics Part B-Neuropsychiatric Genetics. 2011; 156B:751–763.

17. Langbehn DR, Hayden MR, Paulsen JS. PREDICT-HD Investigators. CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B:397–408. [PubMed: 19548255]

18. Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. Ann Neurol. 1997; 41:689–692. [PubMed: 9153534]

19. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014; 10:204–216. [PubMed: 24614516]

20. Paulsen JS, Hayden M, Stout JC, et al. Preparing for preventive clinical trials: the Predict-HD study. Arch Neurol. 2006; 63:883–890. [PubMed: 16769871]

21. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry. 2008; 79:874–880. [PubMed: 18096682]

22. Biglan KM, Ross CA, Langbehn DR, et al. Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study. Mov Disord. 2009; 24:1763–1772. [PubMed: 19562761]

23. Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. Brain Res Rev. 2008; 58:209–225. [PubMed: 18486229]

24. Kloppel S, Henley SM, Hobbs NZ, et al. Magnetic resonance imaging of Huntington's disease: preparing for clinical trials. Neuroscience. 2009; 164:205–219. [PubMed: 19409230]

25. Duff K, Paulsen J, Mills J, et al. Mild cognitive impairment in prediagnosed Huntington disease. Neurology. 2010; 75:500–507. [PubMed: 20610833]

26. Beglinger LJ, Paulsen JS, Watson DB, et al. Obsessive and compulsive symptoms in prediagnosed Huntington's disease. J Clin Psychiatry. 2008; 69:1758–1765. [PubMed: 19012814]

27. Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC. Predict-HD Investigators of the Huntington Study Group. Psychiatric symptoms in Huntington's disease before diagnosis: the Predict-HD study. Biol Psychiatry. 2007; 62:1341–1346. [PubMed: 17481592]

28. Epping EA, Mills JA, Beglinger LJ, et al. Characterization of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study. J Psychiatr Res. 2013; 47:1423–1431. [PubMed: 23790259]

29. Beglinger LJ, O'Rourke JJ, Wang C, et al. Earliest functional declines in Huntington disease. Psychiatry Res. 2010; 178:414–418. [PubMed: 20471695]

30. Downing NR, Kim JI, Williams JK, et al. WHODAS 2.0 in prodromal Huntington disease: measures of functioning in neuropsychiatric disease. Eur J Hum Genet. 2013

31. Williams J, Downing N, Vaccarino AL, Guttman M, Paulsen JS. Self Reports of Day-to-Day Function in a Small Cohort of People with Prodromal and Early HD. PLoS Curr. 2011; 3:RRN1254. [PubMed: 21901173]

32. Paulsen JS, Wang C, Duff K, et al. Challenges assessing clinical endpoints in early Huntington disease. Mov Disord. 2010; 25:2595–2603. [PubMed: 20623772]

33. Rothstein M, Siegal G. Health Information Technology and Physicians' Duty to Notify Patients of New Medical Developments. Hous J Health L & Policy. 2012; 12:93–136.

34. Williams JK, Erwin C, Juhl A, et al. Personal factors associated with reported benefits of Huntington disease family history or genetic testing. Genetic Testing and Molecular Biomarkers. 2010; 14:629–636. [PubMed: 20722493]

> ***Panel:* Research in context**
>
> **Systematic review**
>
> On August 25, 2014, we searched PubMed and Medline for English-language articles with human participants age 19 or older with the following search terms: "Huntington disease", "longitudinal", "prospective", "onset", and "diagnosis". Reference lists of found articles were also reviewed. Since no previous PREDICT-HD study examined comprehensive prediction of diagnosis, they were excluded. Seven publications were found using prospective data to predict HD diagnosis based on motor criteria. Sample sizes for participants prospectively diagnosed were 21 to 70 and number of years followed were from 2.5 to 5.
>
> **Interpretation**
>
> Number of converters prospectively followed in the literature were smaller in size by over 320% and number of years followed was from 2.5 to 5. Four of the seven found studies only considered cognitive predictors, one study only considered dietary predictors, and the remaining two studies examined various comprehensive predictors of prospective diagnosis. Using data from the Huntington Study Group, Langbehn and Paulsen[5] found cognitive, motor and self-reported symptoms to be predictive of traditional motor diagnosis. Although traditional motor criteria for diagnosis was not examined in Tabrizi,[11] findings suggest cognitive, quantitative motor and imaging predictors of motor onset. The current study is the first to use comprehensive longitudinal assessments to prospectively predict traditional motor diagnosis in HD. Joint modeling of longitudinal change and time to HD diagnosis revealed several significant phenotypic and biologic predictors that might be useful as endpoints in clinical trials and for selecting samples. Findings fill a gap in the literature by identifying predictors that are important for HD diagnosis over and above CAG expansion and age, demonstrating that baseline status and longitudinal change are important in prediction of a relevant outcome in the progression of HD. Illustrations of our statistical analysis reveal cumulative relative risk of diagnosis profiles for persons in extremes of the disease course (far from diagnosis at baseline versus close to diagnosis at baseline). Our results provide insights regarding the nature of HD progression and show that a relatively brief clinical assessment can enhance prediction of motor diagnosis.
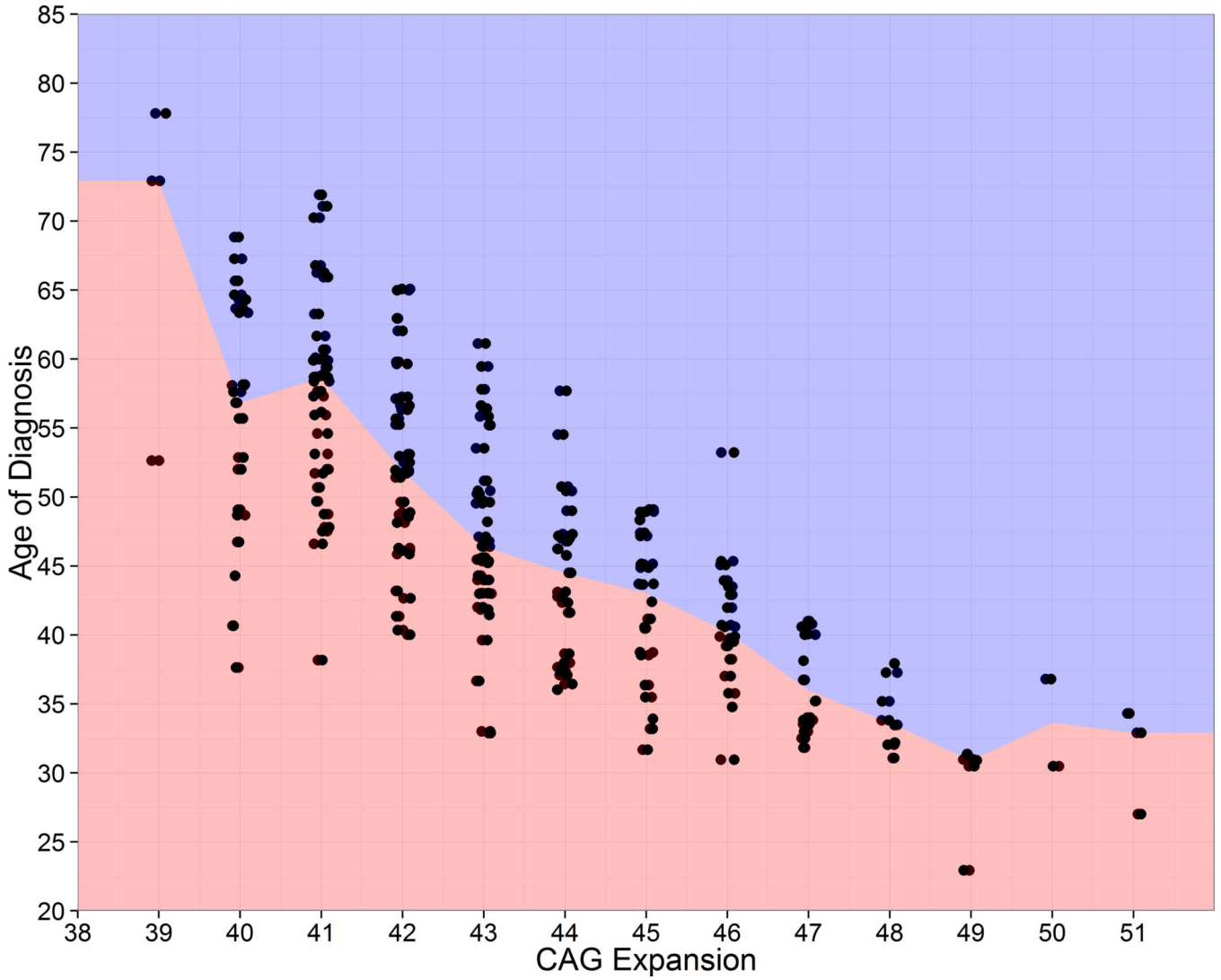
Figure 1. Observed age of diagnosis by CAG expansion for N=225 prospective converters. Observations were slightly jittered horizontally to reveal overlapping cases

Figure 1 shows age of diagnosis as a function of CAG expansion for the N=225 people who obtained a motor diagnosis during the 12-year PREDICT-HD study (i.e., the converters). None of the individuals in Figure 1 were diagnosed at study entry and all have repeated measures, some with up to 12 years of observations (mean=5 years). The color change is at the median age for each CAG. As seen in the figure, the age at diagnosis can vary widely for individuals with the same CAG expansion. Considering CAG=40, the range is 31 years, and the difference between the first and third quartile is 15 years. The variability is indicative of the need to include variables in addition to CAG expansion with the goal of improving the accuracy of predicting the time of diagnosis. The main goal of this study is to improve predictive accuracy by identifying variables that are correlated with diagnosis, over and above CAG expansion. CAG=cytosine-adenine-guanine.
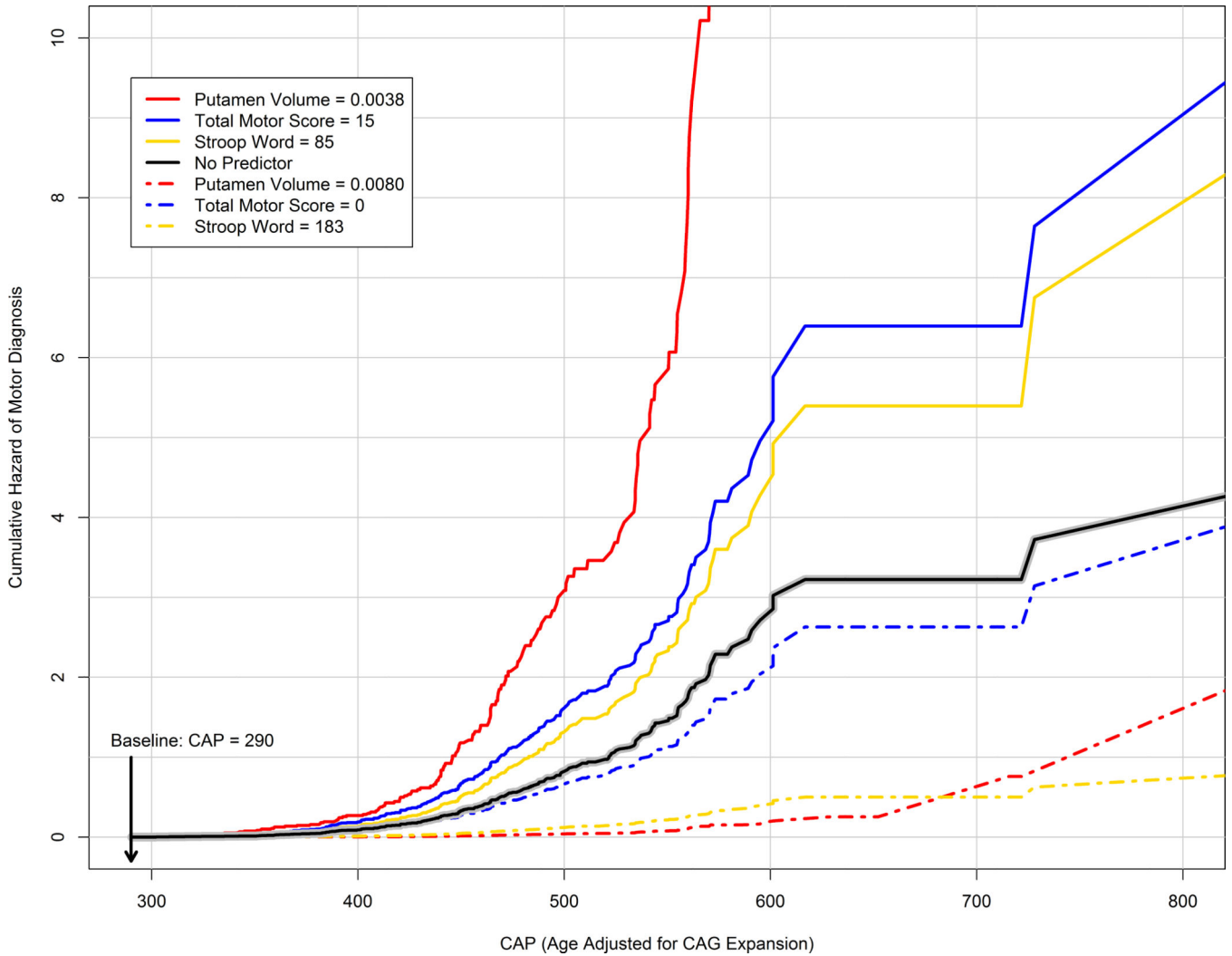
Figure 2. Cumulative hazard (accumulated risk rate) of motor diagnosis by CAG-Age Product (CAP) for various baseline predictor values

CAP is age corrected for CAG expansion and is the time metric of the horizontal axis. The solid black line denotes the cumulative hazard for a model with no predictor representing prediction based only on CAG and age (as summarized by CAP). The dash-dot lines are risk profiles for predictors representing no deterioration at baseline (e.g., Total Motor Score=0), whereas the colored solid lines are risk profiles for predictors representing advanced deterioration at baseline (e.g., Total Motor Score = 15). Putamen volume is ICV-corrected. As a reference, CAP=290 corresponds to age 31 and CAP=600 corresponds to age 64 for a person with CAG=43 (the sample mean). CAP=Age $\times$ (CAG − 33·66).CAG=cytosine-adenine-guanine.
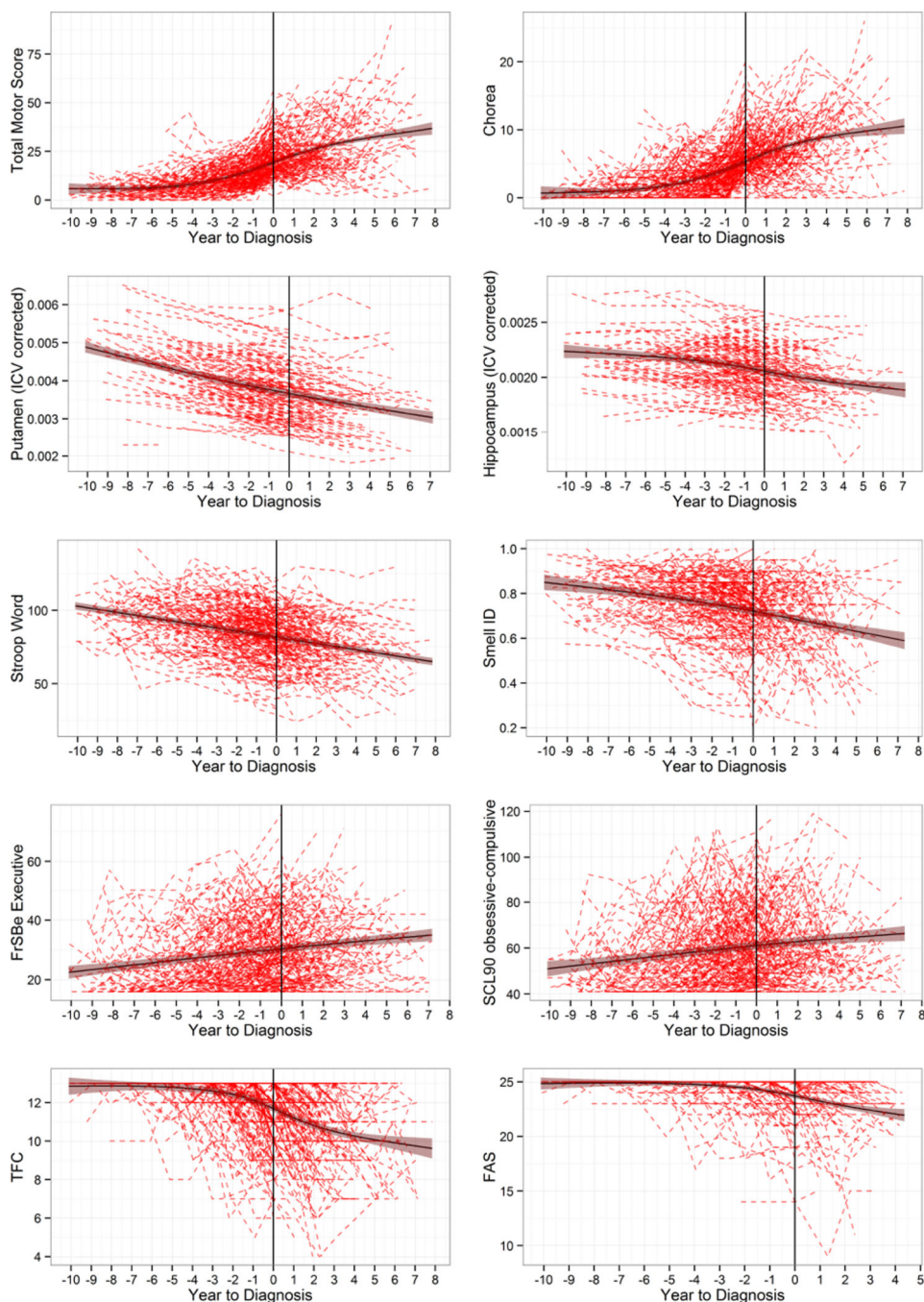
Figure 3. Trajectories of motor, imaging, cognitive, functional, and psychiatric variables for N=225 converters

The top-two strongest predictors in each domain were selected (see Table 2).Dashed lines are individual empirical data, and solid lines are cubic spline curves (shading shows 95% confidence interval). ICV=Intracranial-corrected volumes. Smell ID=Smell Identification (University of Pennsylvania Smell Identification Test). FrSBe=Frontal Systems Behavior Scale. SCL90=Symptom Checklist 90. TFC=total functional capacity. FAS=functional activity scale.

Table 1

Descriptive statistics for non-converters, converters, and the combined sample (mean (SD) or counts (%)).

	Non-Converters	Converters	Combined
N	853	225	1078
CAG[a]	42·21 (2·58)	43·57 (2·85)	42·49 (2·69)
Age[a]	38·92 (10·24)	43·03 (10·31)	39·78 (10·39)
CAP[a]	334·89 (82·74)	436·59 (81·82)	356·12 (92·30)
Duration	4·28 (3·31)	6·66 (2·48)	4·78 (3·30)
Education[a]	14·56 (2·62)	14·08 (2·50)	14·46 (2·60)
Female N	540 (63%)	147 (65%)	687 (64%)

[a]Measured at study entry. Age and education are expressed in years. Duration=years in the study.

CAG=cytosine-adenine-guanine expansion length. CAP=(Age at Baseline) × (CAG 33·66).

Table 2

Joint modeling results. Within each domain, variables are ranked by absolute Z-value for the association parameter (γ) of the full model.

Variable	Domain	N	N*	Event	Cross-Sectional Prediction (Reduced Model)			Longitudinal Prediction (Full Model)		
					γ(SE)	Z-value(p)	HR or HR^{-1} (95% CI)	γ(SE)	Z-value(p)	HR or HR^{-1} (95% CI)
TMS	Motor	1073	3661	225	0·98(0·16)	6·20(<·0001)	2·65(1·95,3·61)	1·12(0·16)	7·23(<·0001)	3·07(2·26,4·16)
Chorea	Motor	1073	3661	225	1·09(0·17)	6·53(<·0001)	2·99(2·15,4·15)	1·16(0·16)	7·08(<·0001)	3·19(2·31,4·40)
Brady	Motor	1073	3661	225	0·76(0·15)	5·05(<·0001)	2·14(1·59,2·87)	0·89(0·13)	6·80(<·0001)	2·44(1·89,3·16)
Ocular	Motor	1073	3661	225	0·73(0·19)	3·94(<·0001)	2·07(1·44,2·98)	0·82(0·20)	4·07(<·0001)	2·28(1·53,3·39)
Rigidity	Motor	1073	3661	225	0·29(0·18)	1·61(0·1073)	1·33(0·94,1·88)	0·36(0·17)	2·17(0·0298)	1·44(1·04,2·00)
Dystonia	Motor	1073	3661	225	0·66(0·25)	2·57(0·0101)	1·93(1·17,3·17)	N/A	N/A	N/A
Putamen	Imaging	980	1774	147	−1·11(0·15)	−7·36(<·0001)	3·03(2·25,4·06)	−1·20(0·17)	−6·95(<·0001)	3·32(2·37,4·65)
Hippocampus	Imaging	980	1774	147	−0·58(0·11)	−5·29(<·0001)	1·78(1·44,2·21)	−0·64(0·11)	−6·02(<·0001)	1·90(1·54,2·35)
Lobar Gray	Imaging	967	1703	146	−0·59(0·14)	−4·38(<·0001)	1·81(1·39,2·36)	−0·75(0·13)	−5·95(<·0001)	2·11(1·65,2·69)
CSF	Imaging	985	1785	148	0·38(0·08)	4·87(<·0001)	1·47(1·26,1·71)	0·48(0·09)	5·50(<·0001)	1·62(1·36,1·92)
Accumbens	Imaging	980	1774	147	−0·87(0·19)	−4·48(<·0001)	2·39(1·63,3·49)	−1·00(0·18)	−5·48(<·0001)	2·71(1·90,3·88)
Globus	Imaging	980	1774	147	−1·11(0·26)	−4·29(<·0001)	3·04(1·83,5·04)	−1·29(0·25)	−5·19(<·0001)	3·64(2·23,5·92)
Caudate	Imaging	980	1774	147	−0·73(0·18)	−4·11(<·0001)	2·07(1·46,2·92)	−0·85(0·18)	−4·84(<·0001)	2·34(1·66,3·29)
Thalamus	Imaging	980	1774	147	−0·34(0·14)	−2·49(0·0129)	1·40(1·07,1·84)	−0·35(0·14)	−2·60(0·0093)	1·42(1·09,1·85)
Lobar White	Imaging	952	1659	143	−0·09(0·08)	−1·08(0·2795)	1·09(0·93,1·29)	−0·12(0·07)	−1·67(0·0946)	1·13(0·98,1·31)
Stroop-Wo	Cognitive	979	2879	178	−0·75(0·11)	−7·13(<·0001)	2·12(1·72,2·61)	−0·84(0·11)	−7·79(<·0001)	2·32(1·88,2·87)
Smell-ID	Cognitive	962	2139	159	−0·45(0·08)	−5·59(<·0001)	1·57(1·34,1·83)	−0·54(0·08)	−6·87(<·0001)	1·72(1·47,2·00)
SDMT	Cognitive	979	2876	178	−0·68(0·12)	−5·84(<·0001)	1·97(1·57,2·48)	−0·72(0·12)	−6·20(<·0001)	2·05(1·63,2·57)
Stroop-Co	Cognitive	979	2877	178	−0·73(0·15)	−4·98(<·0001)	2·09(1·56,2·78)	−0·81(0·13)	−6·15(<·0001)	2·25(1·74,2·91)
Stroop-In	Cognitive	979	2869	178	−0·76(0·15)	−4·89(<·0001)	2·13(1·57,2·89)	−0·77(0·13)	−5·88(<·0001)	2·17(1·68,2·81)
Timing	Cognitive	759	1391	104	0·44(0·12)	3·58(0·0003)	1·55(1·22,1·97)	0·59(0·11)	5·43(<·0001)	1·81(1·46,2·23)
Sp-Tapping	Cognitive	764	1392	104	0·38(0·10)	3·67(0·0002)	1·47(1·20,1·80)	0·46(0·09)	4·86(<·0001)	1·58(1·32,1·91)
EmoRec	Cognitive	765	1406	103	−0·42(0·14)	−2·99(0·0028)	1·52(1·15,1·99)	−0·52(0·14)	−3·73(0·0002)	1·68(1·28,2·21)
TMT-A	Cognitive	974	2217	167	0·18(0·07)	2·50(0·0124)	1·20(1·04,1·38)	0·21(0·08)	2·55(0·0109)	1·24(1·05,1·45)
TMT-B	Cognitive	970	2197	165	0·16(0·09)	1·89(0·0592)	1·18(0·99,1·40)	N/A	N/A	N/A

Variable	Domain	N	N*	Event	Cross-Sectional Prediction (Reduced Model)			Longitudinal Prediction (Full Model)		
					γ(SE)	Z-value(p)	HR or HR⁻¹ (95% CI)	γ(SE)	Z-value(p)	HR or HR⁻¹ (95% CI)
F-Exc-C	Psychiatric	1002	3071	191	0·53(0·09)	5·77(<·0001)	1·69(1·42,2·03)	0·62(0·09)	6·64(<·0001)	1·86(1·55,2·23)
S-OC-C	Psychiatric	1009	3120	195	0·56(0·10)	5·34(<·0001)	1·75(1·42,2·15)	0·64(0·11)	5·93(<·0001)	1·90(1·54,2·35)
F-Apa-C	Psychiatric	1002	3071	191	0·37(0·08)	4·53(<·0001)	1·45(1·23,1·70)	0·46(0·08)	5·37(<·0001)	1·58(1·34,1·86)
S-GSI-C	Psychiatric	988	2943	184	0·46(0·09)	4·89(<·0001)	1·58(1·32,1·90)	0·51(0·10)	5·34(<·0001)	1·67(1·38,2·02)
F-Dis-C	Psychiatric	1002	3071	191	0·36(0·09)	3·84(0·0001)	1·43(1·19,1·72)	0·42(0·09)	4·56(<·0001)	1·52(1·27,1·81)
S-Hos-C	Psychiatric	1009	3120	195	0·35(0·11)	3·35(0·0008)	1·42(1·16,1·75)	0·35(0·10)	3·38(0·0007)	1·42(1·16,1·75)
S-Dep-C	Psychiatric	987	2942	184	0·45(0·12)	3·75(0·0002)	1·57(1·24,1·99)	N/A	N/A	N/A
S-Anx-C	Psychiatric	988	2943	184	0·39(0·10)	3·94(<·0001)	1·48(1·22,1·80)	N/A	N/A	N/A
BDI	Psychiatric	816	2297	137	0·25(0·10)	2·43(0·0149)	1·28(1·05,1·56)	N/A	N/A	N/A
TFC	Functional	1071	3626	225	−0·53(0·10)	−5·15(<·0001)	1·70(1·39,2·08)	−0·61(0·10)	−6·34(<·0001)	1·84(1·52,2·22)
FAS	Functional	827	2326	137	−0·36(0·11)	−3·39(0·0007)	1·43(1·16,1·76)	−0·40(0·10)	−3·90(<·0001)	1·49(1·22,1·83)
ECOG-C	Functional	602	911	101	0·37(0·13)	2·76(0·0058)	1·44(1·11,1·87)	0·43(0·13)	3·22(0·0013)	1·54(1·18,2·00)
WHODAS-C	Functional	529	736	67	0·48(0·21)	2·25(0·0245)	1·61(1·06,2·44)	N/A	N/A	N/A
ECOG-P	Functional	678	1093	120	0·45(0·09)	5·12(<·0001)	1·57(1·32,1·86)	N/A	N/A	N/A
WHODAS-P	Functional	581	850	63	0·42(0·14)	3·11(0·0019)	1·53(1·17,1·99)	N/A	N/A	N/A

N=number of subjects. N^*=total number of observations summed over subjects and time. Event=number of conversions. HR=hazard ratio (HR^{-1}= inverse HR). TMS=total motor score. Brady=bradykinesia. CSF=cerebrospinal fluid. Hippo=hippocampus. Stroop-Wo=Stroop Color and Word Test – word condition. Stroop-In=Stroop Color and Word Test – interference condition. Stroop-Co=Stroop Color and Word Test – color condition. SDMT=Symbol Digit Modalities Test. Smell-ID=University of Pennsylvania Smell Identification Test (UPSIT). EmoRec=emotion recognition test. Sp-Tapping=speeded tapping. TMT-A=Trail Making Test, Part A. TMT-B=Trail Making Test, Part B. S-OC-C=Symptom Checklist 90. F-Exc-C=Frontal Systems Behavioral Scale – executive subscale – companion rating. S-GSI-C=Symptom Checklist 90 – Global Severity Index – companion rating. F-Apa-C=Frontal Systems Behavioral Scale – apathy subscale – companion rating. F-Dis-C=Frontal Systems Behavioral Rating Scale – disinhibition subscale – companion rating. S-Hos-C=Symptom Checklist 90 – hostility subscale – companion rating. S-Dep-C=Symptom Checklist 90 – depression subscale – companion rating. S-Anx-C=Symptom Checklist 90 – anxiety subscale – companion rating. BDI=Beck Depression Inventory. TFC=total functional capacity. FAS=functional activity scale. ECog-C=Everyday Cognition Rating Scale – Companion Rating. WHODAS-C=World Health Organization Disability Assessment Schedule – companion rating. ECog-P=Everyday Cognition Rating Scale – Participant Rating. WHODAS-P=World Health Organization Disability Assessment Schedule – participant rating. Psych=Psychiatric. All measures in the Imaging Domain were corrected for intracranial volume. N/A=not available because full model could not be estimated.