Estimating the causal effects of modifiable, non-genetic factors on Huntington Disease progression using propensity score weighting

Beth Ann Griffin PhD[1], Marika Suttorp Booth MS[2], Monica Busse PhD[3], Edward J Wild PhD[4], Claude Setodji PhD[5], John H. Warner PhD[6], Cristina Sampaio MD[7], and Amrita Mohan PhD[8]

Paper Word Count: 3,435

Key Words: Huntington's Disease, non-genetic factors, observational studies, propensity scores, disease progression

[1] Corresponding Author, RAND Center for Causal Inference, RAND Corporation, 1200 South Hayes Street, Arlington, VA, USA. bethg@rand.org, +1(703)-413-1100x5188

[2] RAND Corporation, 1776 Main Street, Santa Monica, CA, USA.

[3] Centre for Trials Research, Cardiff University, Neuadd Merionydd, Heath Park, CF14 4XN, Cardiff, UK.

[4] Huntington's Disease Centre, UCL Institute of Neurology, London WC1N 3BG

[5] RAND Center for Causal Inference, RAND Corporation, 4570 Fifth Ave #600, Pittsburgh, PA, USA.

[6] CHDI Management/CHDI Foundation, 155 Village Boulevard, Suite 200, Princeton, NJ, USA.

[7] CHDI Management/CHDI Foundation, 155 Village Boulevard, Suite 200, Princeton, NJ, USA.

[8] CHDI Management/CHDI Foundation, 155 Village Boulevard, Suite 200, Princeton, NJ, USA.

ABSTRACT

Introduction

Despite being genetically inherited, it is unclear how non-genetic factors (e.g., substance use, employment) might contribute to the progression and severity of Huntington's Disease (HD).

Methods

We used propensity score (PS) weighting in a large (n=2,914) longitudinal dataset (Enroll-HD) to examine the impact of education, employment status, and use of tobacco, alcohol, and recreational and therapeutic drugs on HD progression. Each factor was investigated in isolation while controlling for 19 other factors to ensure that groups were balanced at baseline on potential confounders using PS weights. Outcomes were compared several years later using doubly robust models.

Results

Our results highlighted cases where modifiable (non-genetic) factors - namely light and moderate alcohol use and employment - would have been associated with HD progression in models that did not use PS weights to control for baseline imbalances. These associations did not hold once we applied PS weights to balance baseline groups. We also found potential evidence of a protective effect of substance use (primarily marijuana use), and that those who needed antidepressant treatment were likely to progress faster than non-users.

Conclusions

Our study is the first to examine the effect of non-genetic factors on HD using a novel application of PS weighting. We show that previously-reported associated factors – including light and moderate alcohol use – are reduced and no longer significantly linked to HD progression after PS weighting. This indicates the potential value of PS weighting in examining non-genetic factors contributing to HD as well as in addressing the known biases that occur with observational data.

Introduction

Despite being a genetically inherited disorder, it is still not clear how non-genetic factors—such as education, substance use, exercise, diet—might contribute to the progression and clinical severity of HD.[1-6] Previous studies have sought to identify non-genetic, potentially modifiable contributors to HD progression using observational data, with mixed findings.[7-15] The broader application of results from these studies in developing lifestyle interventions has remained challenging due to the unmeasured confounding that likely exists in the observed associations. For example, genetic attributes, such as the number of cytosine-adenine-guanine (CAG) repeats, which are known to have a strong correlation with HD onset and severity [4], are often either unmeasured or not controlled for in a robust fashion in typical analyses and could yield potentially meaningful differences between individuals in different groups of interest in a study. Such differences could occur by chance, or systematically (e.g., if rapid progressors were more likely to engage in the behavior under investigation, or if retrospective recall of risk factor exposure were affected by disease severity). This could lead to spurious positive findings if robust statistical methods are not used.

While randomized controlled clinical trials are the gold standard for estimating the effects of non-genetic factors on disease progression, observational studies together with robust statistical methods to restrict confounding can be used to help improve our understanding of the role of nongenetic factors play in disease progression. Our study illustrates the use of one such method – namely propensity score balancing and doubly robust (DR) outcome analyses – with a composite clinical endpoint to examine the relationships between seven non-genetic factors (education, employment status, and use of tobacco, alcohol, recreational drugs, antidepressants, and statins) and HD progression.

Methods

Study design and participants

Our analyses utilized data from Enroll-HD, a registry-based study of HD gene expansion carriers at over 160 clinical sites worldwide.[16] Enroll-HD provides prospective data (demographics, medications, medical history, clinical features, family history and genetic characteristics) on ~16,000 participants. The dataset used comes from the third version of Enroll-HD's public use data set, released in December 2016. We included adult individuals with the HD gene (e.g., those with CAG ≥ 36 and age ≥ 18, referred to here as "HD-positive" individuals) with late premanifest or Stage 1 or 2 manifest HD at intake into the study (see Appendix A).We defined late premanifest using a CAG Age Product (CAP) score, a measure of disease burden for HD that is a function of age and CAG. The formula is defined by $\mathrm{CAP_i} = \mathrm{Age_i} * (\mathrm{CAG_i} - 30)/6.49$

whereby CAP measures an individual's cumulative exposure to mutant huntingtin. Thus, among premanifest individuals, high CAP scores would denote individuals who have larger exposure and are, on average, closer to motor onset. In our analysis, late (versus early) premanifest was defined based on having a CAP score over 80. Stage 1 and 2 manifest HD were defined using Total Functional Capacity (TFC; ranges from 0 to 13) which is a broad measure of functional capacity that rates a person's functional capacity and level of independence in five domains: occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for level of care. Greater scores indicating higher functioning for an HD individual.[17, 18] We define manifest stage 2 individuals had TFC > 6 and <=10 while manifest stage 1 is >10 and <=13 as recommended by Shoulsan and Fang staging. See Appendix A for more justification on these categorizations. [19]

The data used in our analyses are longitudinal, with annual one-year follow-up visits planned as part of the study (though there is variability in the length of time between visits for participants). In our outcome analyses, we used data from individuals who have at least two follow-ups of data (73 percent of the eligible baseline sample). We refer to "baseline" as a label for the assessments done at the first visit when the participant joined the study. We also excluded three cases that had CAG over 70, which is an extreme count for CAG; Enroll-HD data administrators do not release exact CAG count for such individuals due to privacy concerns.

Candidate non-genetic factors from baseline

Substance use was measured as yes/no responses to "Does the participant currently use drugs?" *Alcohol use* by self-reported "units per week", which we categorized into four bins: "abstainers" (<1 drink per month), "light drinkers" (1-13 drinks per month), "moderate drinkers" (4-14 units per week), and "heavy drinkers" (>2 units per day). *Smoking* by a yes/no indicator measuring current use; *education groups* using the International Standard Classification of Education coding (nursery/primary/comprehensive school, sixth form/high school; college; and university/tertiary studies/advance studies); *employment status* using an indicator for full- or part-time job; *antidepressant* and *statin use* using Anatomical Therapeutic Chemical Classification System (ATC) coding groups such that antidepressants begin with the ATC code N06A and statins, C10AA.

These seven non-genetic factors were selected *a priori* during the design phase of the study. We designed the analysis to examine factors that had already been explored in the literature (education, employment, substance use, alcohol use, and tobacco use) and to additionally examine evidence of effects on HD for certain medications often used by individuals with HD (antidepressants and statins). We also were restricted to factors for which Enroll-HD has data. Thus, while physical activity and nutrition would be two factors of high interest in a study such as this, they are not available in the Enroll-HD survey, so we could not explore their potential role in HD progression.

Outcomes

We used seven common measures of HD severity to form a composite outcome measuring overall disease severity: the *Total Motor Score* (TMS; Huntington Study Group, 1996); *Total Functional Capacity (TFC*); *Functional Assessment Score (FAS)*[18, 20]; *Symbol Digital Modality Test (SDMT)*[21]; *Stroop Word Reading Test (SWRT*); and two *Verbal Fluency Test (VFT)* measures (Category (C) and Letters (L)). Consistent with current practice, we used a principal component analysis (PCA) to derive a unified composite measure of HD severity summarizing these seven outcomes (see Appendix B). The composite measure ranges from -2.8 to 3.4 and is such that higher values represent more severe HD. [22, 23]

Statistical Analysis

There were low rates of missing data with a mean of 3%, so we imputed missing values to help minimize the impact of missing data when fitting our outcome models. We did a single imputation in proc MI in SAS version 9.4, which imputes missing data using predicted values from multivariate regression models. Responders in our data looked representative of the original baseline sample, so we did not use nonresponse weights.

We designed the study to investigate each candidate non-genetic factor in isolation while simultaneously controlling for the others to guarantee that individuals within different levels of a given factor (e.g., education levels) are comparable to individuals in the other levels on all potential confounders. Thus, we implemented a "pseudo-randomized" trial for each non-genetic factor, whereby we created comparable groups of individuals on baseline characteristics using propensity score (PS) weighting. To illustrate, consider the binary measure of substance use. Here the "exposed" group comprises those individuals who say they are currently using substances (primarily marijuana), and the "nonexposed," or control, group comprises those who are not using substances. To assess whether substance use has an impact on progression of HD, we need to ensure our two groups are well balanced (comparable) at the start of our study (baseline) in terms of known confounders, such as CAG repeats, age, and HD severity at baseline, as well as the list of potential non-genetic factors being considered here (education, employment status, smoking, alcohol, statin use, and antidepressant use).

In general, with observational studies like Enroll-HD (in which randomization is not used to study non-genetic factors), we end up with groups who look very different from one another at baseline. For example, with substance users, we found that our substance users were younger (mean age of 47.6 years versus 52.2 years) and healthier in terms of their HD symptoms (e.g., lower total motor score and higher SDMT, SWRT, and functioning) than nonsubstance users at baseline. To correct for these notable differences between the groups, we utilized PS weights, which weight the groups so that they are comparable on all observed confounders that are used in the PS model. To estimate PS weights, we used the covariate balancing PS (CBPS),[24] which

fits a penalized logistic regression model that is optimized to obtain good balance between the exposed and unexposed samples. We used the cbps() command in R v3.4.1. The CBPS models were logistic regressions for each non-genetic factor as the dependent variable with 19 explanatory variables . The 19 variables are age, CAG, stage, baseline measure of HD severity (TMS, TFC, FAS, SDMT, SWRT, VFT-C, VFT-L and the composite), gender, minority status, and the other non-genetic factors being studied. PS weights were derived using the inverse of the fitted probabilities from these regressions for each individual. A separate CBPS model and set of PS weights were derived for each non-genetic factor under consideration. For our categorical non-genetic factors that have more than 2 categories (namely, education and alcohol use), CBPS estimates multinomial PS weights. Comparability between groups after PS weighting was assessed across a number of diagnostic criteria. We focus on reporting standardized effect size (ES) differences in this manuscript, assuming ES < 0.20 are small. Our PS weights controlled for nineteen covariates: age, CAG, stage, baseline measures of HD severity (TMS, TFC, FAS, SDMT, SWRT, and the two verbal fluency measures) and the other non-genetic factors being studied. We note that all confounders controlled for in the PS model are taken from the baseline survey in Enroll. This is critical to ensure we have a proper "pseudo-randomization" at the beginning of our study, giving us proper temporal ordering for estimating potential causal effects (see Appendix C).

We originally aimed to estimate Average Treatment Effects (ATE) across the population using ATE PS weight for all the non-genetic factors considered here. Unfortunately, high quality ATE weights could not be obtained for substance use and statin use since the group of individuals using these were small in sample size (74 and 279, respectively) as well as notably different from the set of individuals not using substances or statins. Thus, we opted to estimate Average Treatment Effects on the Treated (ATT) for these two non-genetic factors which aim to balance to non-substance users and non-statin users to look like the substance and statin users, respectively. ATT measures the average effect of a non-genetic factor for those individuals with similar characteristics to the treated group (here substance users or statin users).

After estimation of the PS weights, we used doubly robust (DR) outcome models to estimate the impact of each nongenetic factor on the HD severity composite score. We modeled the composite HD severity score measured at visit 1, 2 and 3 simultaneously. Our DR models simultaneously controlled for covariates in a multivariate regression model of the HD outcome along with the PS weights. As such, DR models guarded against bias that may result if either the outcome model (with covariates) or the PS model was incorrect.[25] Thus, our outcome models looked similar to outcome analyses that have traditionally been used in HD research to examine the effects of environmental and behavioral factors, with one noted addition. First, we fit a multivariate regression model to the outcome that controlled for confounding using multivariate regression adjustment in a more traditional way, but then we added the PS weight to the regression model as a sampling weight to ensure we had balanced groups for the non-genetic

factor under consideration. The confounders controlled for in our DR regression models included age via the CAP score, stage of the disease (late premanifest versus stage 1 versus stage 2), CAG, days since baseline, and a residualized version of the baseline level of the outcome (HD severity composite score). See Appendix B for more details. We used the meglm command in Stata Version 15. We reported estimates from two different versions of the outcome models to illustrate the impact of using PS weights: (1) unweighted multivariate estimates, and (2) PS weighted multivariate estimates (or DR estimates). The results shown in (1) represent findings from approaches that rely solely on traditional covariate adjustment; the PS weight is not included as a covariate in these models. We reported findings from secondary analyses in Appendix D for the individual outcomes used in our composite (TMF, SDMT, SWRT, FAS, TFC, and the two VFT measures).

Results

Cohort

Table 1 shows descriptive statistics for our cohort at the baseline visit while Figure 1 shows mean values of the HD composite (our primary outcome) overtime in the cohort. As expected, all three HD groups experienced increases over time in the HD composite, and the mean severity scores were always lowest for late pre-manifest individuals and highest for stage 2 individuals.

Effect of propensity score weighting

Appendix E shows the ability of the PS weights to create more comparable groups for each nongenetic factor. As shown in all the figures, the absolute ES for each potential confounder decreased substantially after weighting, with most falling well below the 0.20 cut-off point considered important for comparability between exposure groups.

Examination of detailed balance tables showed there were significant baseline differences in HD severity between the exposed and unexposed group for several of the confounders prior to PS weights; these notable differences disappeared once PS weights were applied, suggesting that the PS weighting created suitably balanced baseline groups.

Effect of PS weighting on analysis of non-genetic factors and HD progression

Figure 2 shows the findings from our outcome models as effect size comparisons between levels of each non-genetic factor and the reference category indicated. In several cases (light and moderate alcohol use, substance use, employment, education) significant associations with progression rate were found using the unweighted models (shown in blue), which were reduced when we used PS weights (shown in red). For example, light and moderate alcohol consumption were found to have a protective effect on HD progression over time compared to abstaining in the unweighted models (light drinking effect estimate = –0.11 [95% CI –0.19, –0.03]; moderate

drinking = –0.13 [95% CI = –0.20, –0.05]), but such effects are reduced and no longer statistically significant once we add PS weights to the models (e.g., light drinking = 0.09 [–0.19,0.02]), implying that the apparent association in part reflects baseline imbalance. Only antidepressant use remained statistically significant after adjusting for the PS weights, suggesting that antidepressant users in the sample have faster progression rates than PS weighted participants who did not take antidepressants (ES difference = 0.13; 95% confidence interval = 0.05,0.21).

For descriptive purposes, Figure 3 illustrates the size of the impact of each non-genetic factor by plotting the PS weighted baseline means of the composite HD severity measure versus the predicted means of the HD severity composite overtime from the doubly robust outcome model . As such, statistically significance will not align directly with the fully adjusted DR model results shown in Figure 2. Nonetheless, several interesting patterns can be noted. First, for all factors, the PS weighted composite value at baseline is highly similar between the compared groups, which is expected given we balanced on the baseline value of the HD composite in our PS weights. Of note, we see that on average HD severity is worsening for all groups over time and that antidepressant users experienced greater mean levels of HD severity at subsequent follow-up visits than matched non-users. We also see the potential protective effect of substance use (here, primarily marijuana use) with substance users having lower mean levels of HD severity at subsequent follow-up visits than non-users.

Appendix D provides the generally-consistent DR regression results for exploratory regression analyses fit each outcome component used in the PCA.

Discussion

To our knowledge, our study is the first to use propensity score methods to assess the effect of modifiable, non-genetic factors on HD progression. Prior work has primarily used multivariate regressions to draw inferences about the effects of non-genetic factors on HD progression. Such methods are susceptible to baseline imbalance and our findings highlight the potential of PS weighting in understanding the effect these factors have on HD. In several cases (light and moderate alcohol use and employment), we replicated previously reported effects of factors using unweighted models, but these associations were reduced and no longer statistically significant once we applied PS weights to balance baseline groups. The shift is not surprising given the imbalances seen prior to using PS weights (e.g., alcohol abstainers had higher HD severity scores than light and moderate drinkers at intake into the study, a pattern for which previous reports have not adjusted[8, 13-15]). In contrast to several studies on the effects of substance use (all of which rely on multivariate regression and age of motor as the outcome)[8, 13-15] we found weak evidence of a protective effect of substance use on HD progression. With

only 74 substance users (primarily marijuana), we found a trend suggesting a large estimated protective effect (ES = -0.24; 95% CI = -0.51,0.03).

Our findings must be considered alongside their limitations with several possible explanations for the absence of statistically significant findings for most of our factors. First, non-genetic factors may have only minor effects undetectable over the time period examined (median length of follow-up was ~2 years) that we did not have power to detect. Second, our non-genetic factors are very coarse and could be masking the true (and complex) underlying relationships between our modifiable non-genetic factors and HD progression effects; more detailed measures of each factor would be useful in future studies. While coarse, studies like this provide opportunities to highlight to data registries like Enroll-HD where and why richer measures are needed. Next, our outcome may not able to capture the effect such factors have on HD even though it is still an improvement over age of motor onset that has predominantly been used in past research. Finally, our results may still be biased by our inability to control for unmeasured factors. While we have a meaningful set of observed factors in our PS model, we cannot guarantee that our analysis omits some important factor.

Surprisingly our analysis identified a significant detrimental association between antidepressants and HD progression which corresponds to individuals taking antidepressants on average having 35% more change on the outcome between visits than similarly matched individuals who did not take antidepressants (95% CI = 13% to 55%) . Preclinical studies in HD models have suggested, if anything, that antidepressants could be neuroprotective through the restoration of depleted BDNF.[26-29] However, this issue has not previously been examined in humans. It is biologically plausible that antidepressants could accelerate the pathological progression of HD: for instance, increased serotonin in synapses due to antidepressants could increase glutamate release,[30] exacerbating excitotoxic damage to neurons, which is one proposed mechanism for HD progression.[30, 31] However, these results require cautious consideration since, uniquely among the exposures investigated, antidepressants are prescribed as a symptomatic treatment for a common feature of HD that, if left untreated, can lead to serious morbidity or mortality through self-neglect or self-harm.[32] Ethically, a study of this kind cannot include a comparison group of depressed HD gene carriers for whom antidepressants are indicated but withheld. It is therefore possible that, even though the antidepressant treated and untreated groups were well-balanced on the 20 observed measures used in our PS model, the treated group had more severe depression or were already on a more severe disease trajectory that could not be detected or balanced for by *any* statistical methodology. The apparent negative influence of antidepressants in this analysis could reflect this occult imbalance.

We therefore cautiously propose that our work shows that the previously reported neuroprotective effect of antidepressants in HD models is not evident in humans. If our work

provides evidence of a harmful effect of antidepressant use on HD progression as measured via our composite outcome, that must be weighed against the likely positive symptomatic effects of antidepressant use, and protection against self-harm and self-neglect in individuals with depression due to HD.[32] A suitably designed prospective clinical trial is required to determine how this finding might influence the clinical management of HD patients with mood disturbance. The present findings should not be used to guide such decisions. But they do suggest that use of antidepressants should be considered an important confounder when designing RCTs in HD.

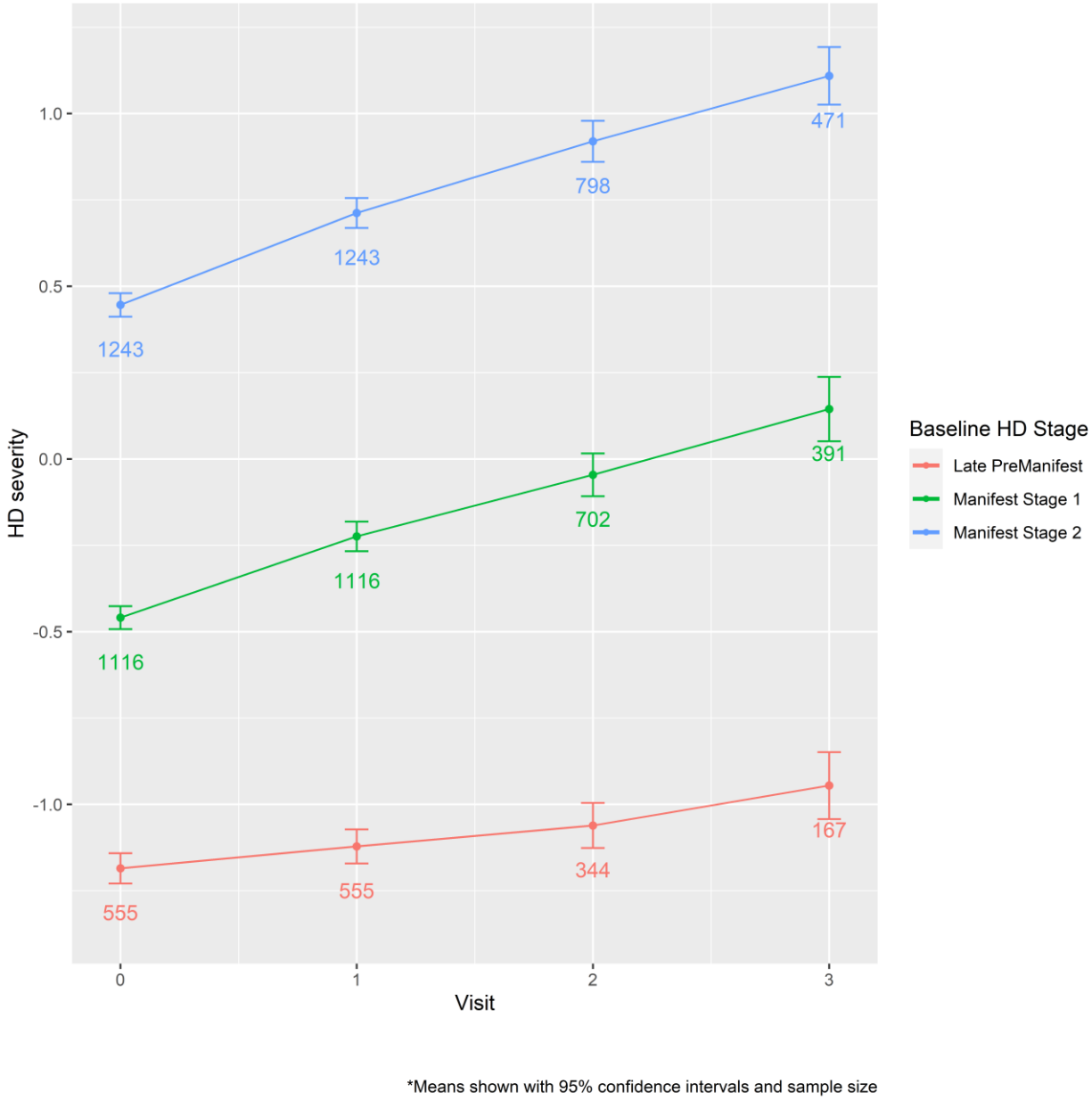
Despite our study's limitations, we believe the work showcases the potential value of PS weighting for analyzing observational data, highlighting important methodological and substantive findings for all neurodegenerative disease as we broaden healthcare options to include lifestyle factors and disease modifications.

Table 1. Summary Statistics for the Environmental and Behavioral Factors at Baseline in Our Analytic Sample, Key Control Covariates, and Intake Values of HD outcomes (N = 2,914)

Factor	N (%)
Current substance use	74 (3%)
Alcohol use	
Abstainer	1,527 (52%)
Light user	560 (19%)
Moderate user	619 (21%)
Heavy user	208 (7%)
Tobacco use	
Current tobacco use	772 (26%)
Mean pack years (SD) (for smokers only)	23 (18)
Education	
Nursery/primary/comprehensive school	673 (23%)
Sixth form [High school]	874 (30%)
College	481 (17%)
University/tertiary studies/ adv res qual	886 (30%)
Antidepressant use	1,260 (43%)
Statin use	279 (10%)
Employed	1,079 (37%)
Mean age (SD)	51 (12)
Mean CAG (SD)	44 (3)
Stage	
Late premanifest	555 (19%)
Stage 1	1116 (38%)
Stage 2	1243 (43%)
Mean SDMT (SD)	31 (14)
Mean SWRT (SD)	68 (22)
Mean VFT: Category (SD)	15 (6)
Mean VFT: Letters (SD)	26 (14)
Mean TMS (SD)	24 (16)
Mean TFC (SD)	11 (2)
Mean FAS (SD)	22 (3)
Mean Composite Outcome (SD)	–0.21 (0.9)
Female N (%)	1,465 (50%)

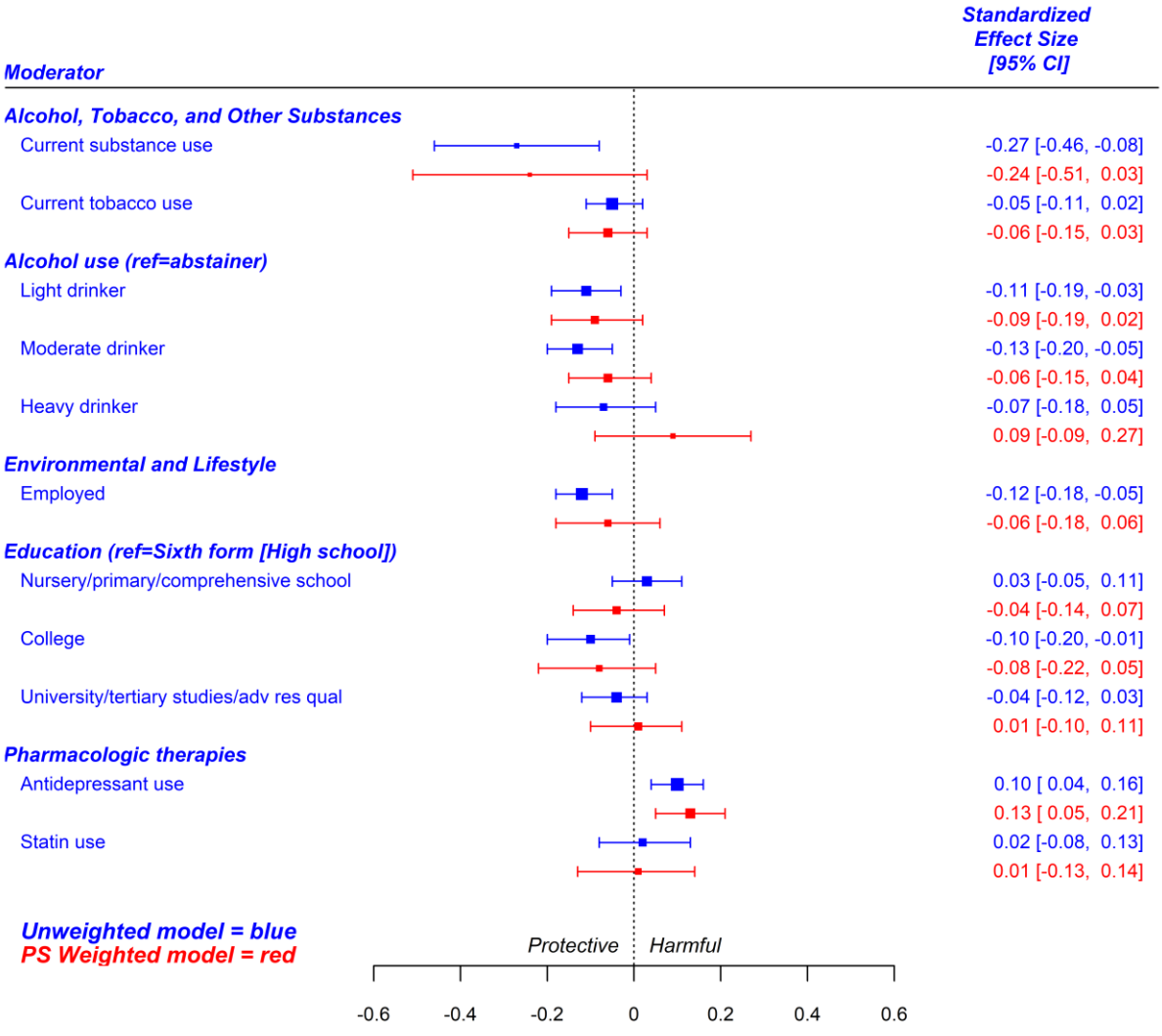
Race/Ethnic Minority Status N (%)	149 (5)%

Figure 1. Mean Composite Outcome with 95% Confidence Intervals Over Time by HD Severity Groups



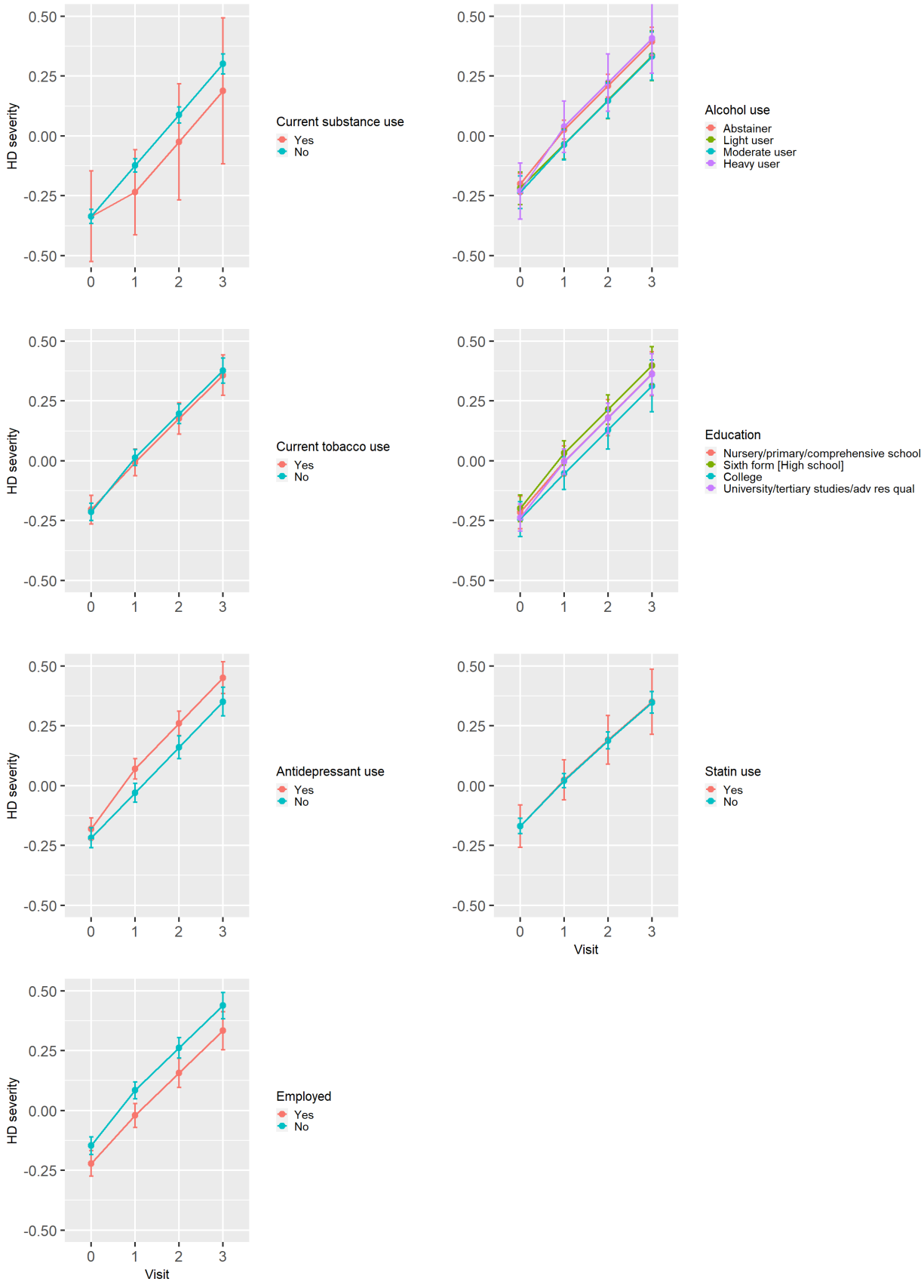
*Means shown with 95% confidence intervals and sample size

Figure 2. Doubly Robust Effect Size Estimates and 95-Percent Confidence Intervals for Each Non-Genetic Factor



The numbers represent standardized effect estimates that highlight the size of the effect for each candidate factor on change in HD severity between follow-ups.

Figure 3. Plot of PS weighted baseline means of the composite HD severity measure versus the predicted means from the doubly robust outcome model overtime for all non-genetic factors


HD severity
0.50
0.25
0.00
-0.25
-0.50
0
1
2
3
Visit
Current substance use
Yes
No
Alcohol use
Abstainer
Light user
Moderate user
Heavy user
Current tobacco use
Yes
No
Education
Nursery/primary/comprehensive school
Sixth form [High school]
College
University/tertiary studies/adv res qual
Antidepressant use
Yes
No
Statin use
Yes
No
Employed
Yes
No

References

[1] S.E. Andrew, Y.P. Goldberg, B. Kremer, H. Telenius, J. Theilmann, S. Adam, E. Starr, F. Squitieri, B. Lin, M.A. Kalchman, The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease, Nature genetics 4(4) (1993) 398-403.
[2] R. Brinkman, M. Mezei, J. Theilmann, E. Almqvist, M. Hayden, The likelihood of being affected with Huntington disease by a particular age, for a specific CAG size, American journal of human genetics 60(5) (1997) 1202.
[3] M. Duyao, C. Ambrose, R. Myers, A. Novelletto, F. Persichetti, M. Frontali, S. Folstein, C. Ross, M. Franz, M. Abbott, Trinucleotide repeat length instability and age of onset in Huntington's disease, Nature genetics 4(4) (1993) 387-392.
[4] D.R. Langbehn, M.R. Hayden, J.S. Paulsen, CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches, American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 153(2) (2010) 397-408.
[5] R.G. Snell, J.C. MacMillan, J.P. Cheadle, I. Fenton, L.P. Lazarou, P. Davies, M.E. MacDonald, J.F. Gusella, P.S. Harper, D.J. Shaw, Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease, Nature genetics 4(4) (1993) 393-397.
[6] N.S. Wexler, Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset, Proceedings of the National Academy of Sciences of the United States of America 101(10) (2004) 3498-3503.
[7] K. Marder, Y. Gu, S. Eberly, C.M. Tanner, N. Scarmeas, D. Oakes, I. Shoulson, Relationship of Mediterranean diet and caloric intake to phenoconversion in Huntington disease, JAMA neurology 70(11) (2013) 1382-1388.
[8] O. Buruma, W. Van der Kamp, E. Barendswaard, R. Roos, D. Kromhout, E. Van der Velde, Which factors influence age at onset and rate of progression in Huntington's disease?, Journal of the neurological sciences 80(2) (1987) 299-306.

[9] C. Simonin, C. Duru, J. Salleron, P. Hincker, P. Charles, A. Delval, K. Youssov, S. Burnouf, J.-P. Azulay, C. Verny, Association between caffeine intake and age at onset in Huntington's disease, Neurobiology of disease 58 (2013) 179-182.
[10] C. Tanner, K. Marder, S. Eberly, K. Biglan, D. Oakes, I. Shoulson, H.S.G.P.H.A.R.O.S. Investigators, Selected health and lifestyle factors, cytosine-adenine-guanine status, and phenoconversion in Huntington's disease, Mov. Disord. 33(3) (2018) 472-478.
[11] J.L. López-Sendón, A. Royuela, P. Trigo, M. Orth, H. Lange, R. Reilmann, J. Keylock, H. Rickards, S. Piacentini, F. Squitieri, What is the impact of education on Huntington's disease?, Movement Disorders 26(8) (2011) 1489-1495.
[12] M.K. Trembath, Z.A. Horton, L. Tippett, V. Hogg, V.R. Collins, A. Churchyard, D. Velakoulis, R. Roxburgh, M.B. Delatycki, A retrospective study of the impact of lifestyle on age at onset of Huntington disease, Movement Disorders 25(10) (2010) 1444-1450.
[13] R.H. Myers, D.S. Sax, W.J. Koroshetz, C. Mastromauro, L.A. Cupples, D.K. Kiely, F.K. Pettengill, E.D. Bird, Factors associated with slow progression in Huntington's disease, Archives of neurology 48(8) (1991) 800-804.
[14] J.A. Byars, L.J. Beglinger, D.J. Moser, P. Gonzalez-Alegre, P. Nopoulos, Substance abuse may be a risk factor for earlier onset of Huntington disease, Journal of neurology 259(9) (2012) 1824-1831.
[15] J.L. Schultz, J.A. Kamholz, D.J. Moser, S.M. Feely, J.S. Paulsen, P.C. Nopoulos, Substance abuse may hasten motor onset of Huntington disease Evaluating the Enroll-HD database, Neurology 88(9) (2017) 909-915.
[16] B.G. Landwehrmeyer, Enroll-HD: A Prospective Registry Study in a Global Huntington's Disease Cohort, 2012. https://clinicaltrials.gov/ct2/show/NCT01574053.
[17] L.J. Beglinger, J.J. O'Rourke, C. Wang, D.R. Langbehn, K. Duff, J.S. Paulsen, H.S.G. Investigators, Earliest functional declines in Huntington disease, Psychiatry Res. 178(2) (2010) 414-418.
[18] J.S. Paulsen, C. Wang, K. Duff, R. Barker, M. Nance, L. Beglinger, D. Moser, J.K. Williams, S. Simpson, D. Langbehn, Challenges assessing clinical endpoints in early Huntington disease, Mov. Disord. 25(15) (2010) 2595-2603.
[19] I. Shoulson, S. Fahn, Huntington disease: clinical care and evaluation, Neurology 29(1) (1979) 1-1.
[20] L.J. Beglinger, J.J. O'Rourke, C. Wang, D.R. Langbehn, K. Duff, J.S. Paulsen, Earliest functional declines in Huntington disease, Psychiatry research 178(2) (2010) 414-418.
[21] Huntington Study Group, Unified Huntington's Disease Rating Scale: Reliability and Consistency, Movement Disorders 11(2) (1996) 136-142.
[22] D.J.H. Moss, A.F. Pardiñas, D. Langbehn, K. Lo, B.R. Leavitt, R. Roos, A. Durr, S. Mead, P. Holmans, L. Jones, S.J. Tabrizi, Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study, The Lancet Neurology 16(9) (2017) 701-711.
[23] S.A. Schobel, G. Palermo, P. Auinger, J.D. Long, S. Ma, O.S. Khwaja, D. Trundell, M. Cudkowicz, S. Hersch, C. Sampaio, E.R. Dorsey, B.R. Leavitt, K.D. Kieburtz, J.J. Sevigny, D.R. Langbehn, S.J. Tabrizi, Motor, cognitive, and functional declines contribute to a single progressive factor in early HD, Neurology 89(24) (2017) 2495-2502.
[24] K. Imai, M. Ratkovic, Covariate balancing propensity score, Journal of the Royal Statistical Society: Series B (Statistical Methodology) 76(1) (2014) 243-263.

[25] J.D. Kang, J.L. Schafer, Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data, Statistical science (2007) 523-539.
[26] W. Duan, Q. Peng, N. Masuda, E. Ford, E. Tryggestad, B. Ladenheim, M. Zhao, J.L. Cadet, J. Wong, C.A. Ross, Sertraline slows disease progression and increases neurogenesis in N171-82Q mouse model of Huntington's disease, Neurobiology of disease 30(3) (2008) 312-322.
[27] H.E. Grote, N.D. Bull, M.L. Howard, A. Van Dellen, C. Blakemore, P.F. Bartlett, A.J. Hannan, Cognitive disorders and neurogenesis deficits in Huntington's disease mice are rescued by fluoxetine, European Journal of Neuroscience 22(8) (2005) 2081-2088.
[28] S. Jamwal, P. Kumar, Antidepressants for neuroprotection in Huntington's disease: A review, European journal of pharmacology 769 (2015) 33-42 (Supplement C).
[29] T. Renoir, M.S. Zajac, X. Du, T.Y. Pang, L. Leang, C. Chevarin, L. Lanfumey, A.J. Hannan, Sexually dimorphic serotonergic dysfunction in a mouse model of Huntington's disease and depression, PloS one 6(7) (2011) e22133.
[30] J. Kamei, H. Igarashi, Y. Kasuya, Modulation by serotonin of glutamate-induced lethality in mice, Research communications in chemical pathology pharmacology 74(2) (1991) 167-184.
[31] A.M.E. Sánchez, J. Mejía-Toiber, L. Massieu, Excitotoxic neuronal death and the pathogenesis of Huntington's disease, Arch. Med. Res. 39(3) (2008) 265-276.
[32] D. Craufurd, J. Snowden, Neuropsychiatry and neuropsychology, Huntington's Disease 4 (2014) 36-65.

Supplementary Material

Appendix A. Additional technical details

For our inclusion criteria, we defined late premanifest using a CAG Age Product (CAP) score, a measure of disease burden for HD that is a function of age and CAG. The formula, described in the unpublished article "Standardizing the CAP Score in Huntington's Disease I: Predicting Age-at-Onset," by John Warner, for defining CAPs is:

$$CAP_i = Age_i * (CAG_i - 30)/6.49.$$

CAP measures an individual's cumulative exposure to mutant huntingtin. Thus, among premanifest individuals, high CAP scores would denote individuals who have larger exposure and are, on average, closer to motor onset. In our analysis, late (versus early) premanifest was defined based on having a CAP score over 80. A randomly selected Huntington's disease gene expansion carrier with a CAP score of 80 will have a 10-percent change of having already experienced motor onset. Individuals who have not yet experienced motor onset have an expected time to motor onset of about 15 years if their CAG length is 40 and about 7.5 years if their CAG length is 50. Stage 1 and 2 manifest HD were defined using Total Functional Capacity (TFC) which is a broad measure of functional capacity that rates a person's functional capacity and level of independence in five domains: occupation, ability to manage finances, ability to perform domestic chores, ability to perform personal activities of daily living, and setting for level of care. Each domain is given a score that ranges from 0 to 2 or 3 (e.g., 0 = unable, 2 = reduced capacity, 3 = normal). The TFC total scores range from 0 to 13, with greater scores indicating higher functioning for an HD individual [1, 2].

Individuals in Stage 1 of the disease typically maintain marginal to full engagement in jobs and predisease levels of independence in all other basic functions (financial management, domestic responsibilities, and activities of daily living, such as eating and dressing) with need for slight assistance in only one basic function. Individuals in Stage 2 typically are unable to work, require slight assistance in all basic functions, and major assistance in one basic function (University of California–San Diego School of Medicine Huntington's Disease Clinical Research Center, undated). Thus, manifest stage 2 individuals had TFC > 6 and <=10 while manifest stage 1 is >10 and <=13 as recommended by Shoulsan and Fang staging. [3]

The key confounders controlled for in our regression models included age, stage of the disease (late premanifest versus stage 1 versus stage 2), CAG, days since baseline, and a

residualized version of the baseline level of the outcome (HD severity composite score). Age was captured by using the CAP score.

The residualized version of the composite score at baseline was computed by taking the difference between the observed baseline value of our outcome and the predicted value from a regression model that regressed the baseline values of our outcome onto the four quartiles of CAP scores. Thus, the residualized outcome represents whether the individual was doing better or worse than expected at baseline given their CAP score.

Our specific multivariate outcome models (both the unweighted and PS weighted DR version) regressed outcomes at each follow-up, Y_{ij} where *i* denotes subscripts for each individual in our data and *j* denotes whether the outcome comes from the first, second, or third visit (*j* = 1,2, and 3, respectively); Y_{i0} denotes the baseline value of our HD severity measure and $resid_i = Y_{i0} - \hat{Y}_{i0}$ where $\hat{Y}_{i0}$ denotes the predicted value from the regression model that regressed the baseline values of our outcome onto the four quartiles of CAP scores. Specifically, our outcome models were as follows:

$$Y_{ij} - Y_{ij-1} = a_0 + \alpha_1 * KeyExposure_i +$$
$$PreManifest_i * \left(p_{00} + p_{01} * resid_i + DaysSinceBaseline_{ij}(1 + p_{03} * CAGd_i)\right) +$$
$$Stage1_i * \left(p_{10} + p_{11} * resid_i + DaysSinceBaseline_{ij}(1 + p_{13} * CAGd_i)\right) +$$
$$Stage2_i * \left(p_{20} + p_{21} * resid_i + DaysSinceBaseline_{ij}(1 + p_{23} * CAGd_i)\right).$$

where $CAGd_i = CAG_i - 42$ is a version of CAG centered around 42, one of the more common values found in the population for CAG [4]. The outcome models allow the impact of the residualized outcome, days since baseline, and CAG to vary by stage of the patient, given preliminary model runs which showed strong evidence that such interactions where needed in the model. The model allowed for random intercepts by individual; otherwise, all other effects in the model were considered fixed effects. The key parameter of interest for our analyses was α_1, which estimates the PS weighted and multivariate adjusted impact (doubly robust impact) of each environmental and behavioral factor on HD progression in our sample. We note that we standardized the change scores so that results presented are on an effect size scale.

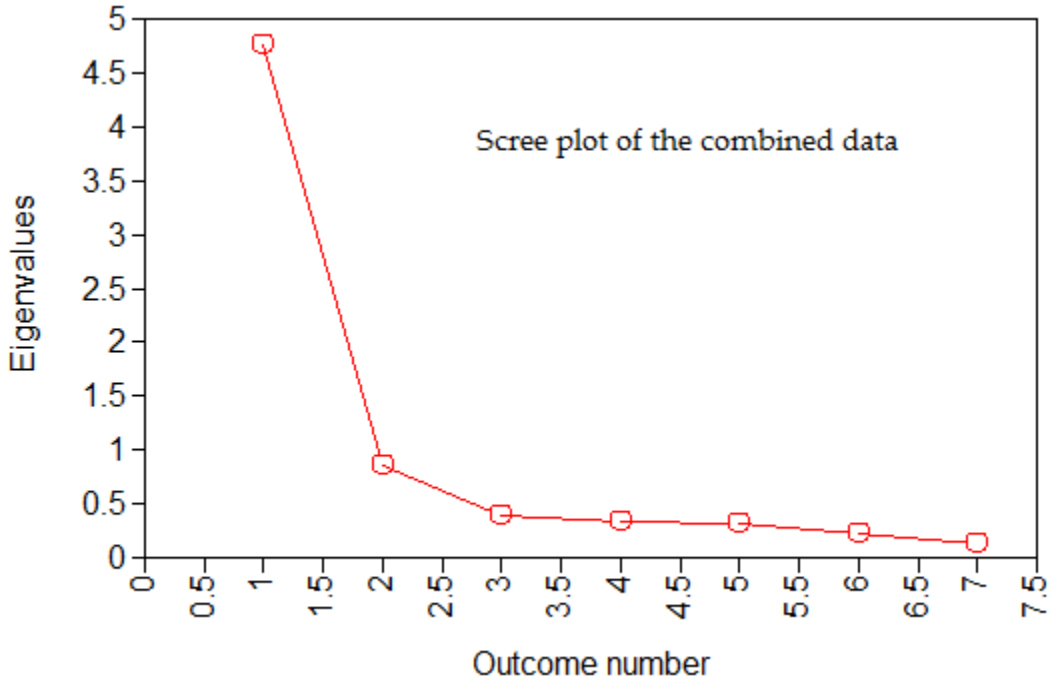
Appendix B. Details on the PCA

As noted in the body of the main report, a PCA was used to derive a single unified composite measure of HD severity summarizing over motor, functioning, and cognitive outcomes listed above. We note that we developed our composite outcome for HD in parallel to the development of the cUHDRS by Schobel et al.[5] As such, we came up with our version of the composite when the cUHDRS was not yet published. We have carefully examined the similarity of our composite to Schobel et al [5] and note they are almost identical (see below). As such, findings from our study will not be impacted by use of the composite derived on our analytic dataset versus use of the formulas promoted in Schobel et al. [5]We opt to retain our version given the careful work that went into its development on our analytic sample and given that our composite score (even though similar to the existing one) might be (marginally) better suitable for our data.

Using our imputed data, we derived PCA severity scores to obtain an overall measure of severity at each visit in the study. This gave a single point severity score based on how advanced a participant was at each time point. We fit the PCA jointly using all available longitudinal data under the assumption that the latent structure's relationship with the different measures is similar from follow-up to follow-up after finding evidence that within visit (i.e., wave) estimates of the PCA were similar to those obtained by jointly estimating the PCA across waves. Here we provide details on our steps to implementing the PCA.

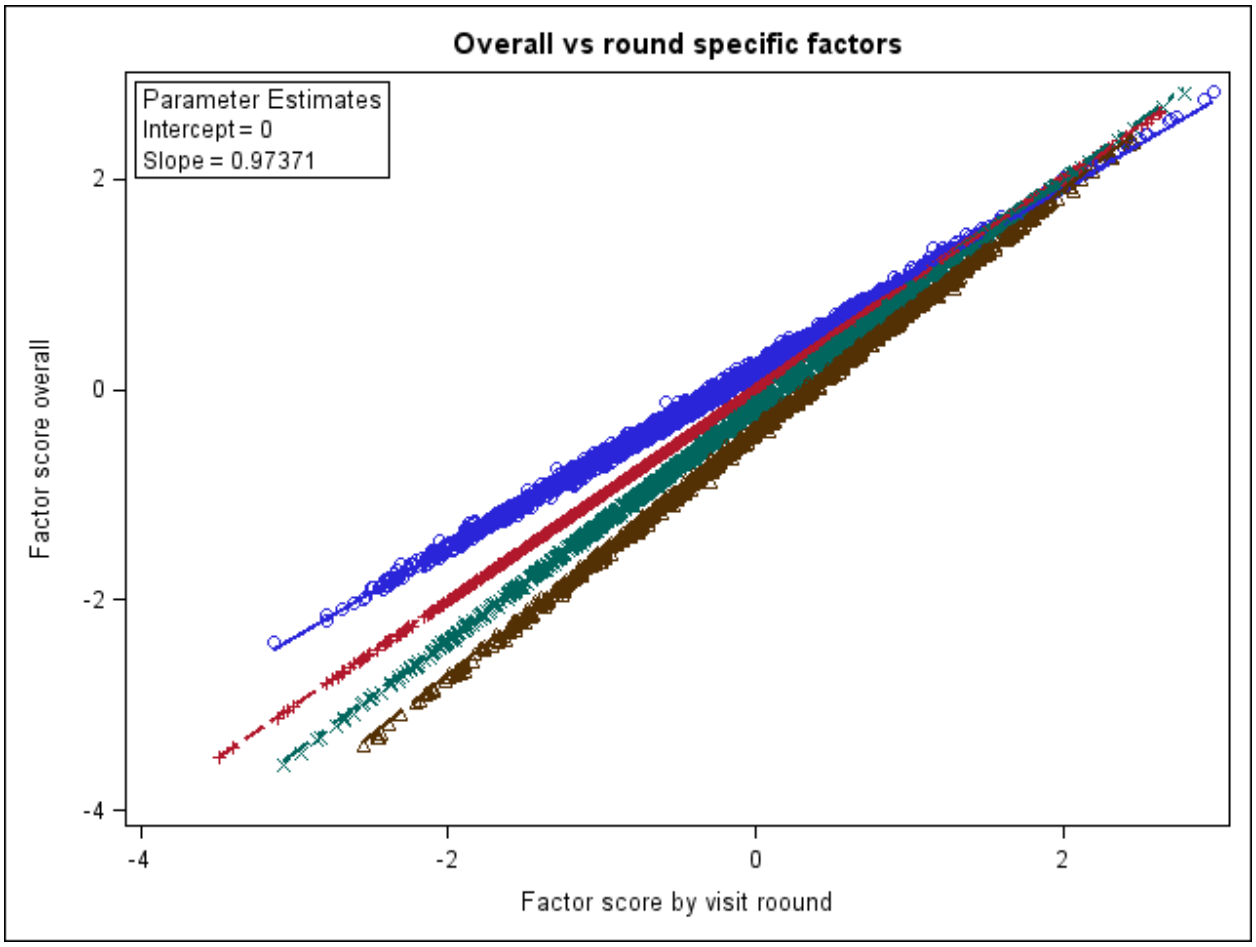
We started with a general PCA where the goal was to see how many latent factors are in the seven outcome measures used to represent cognitive wellbeing, functional capacity, and total motor score of individuals in our dataset. Figure B.1 shows the scree plot of eigenvalues for this analysis. As shown, the first eigenvalue was 4.75 and the next one was 0.85 which lends support to the argument that our seven underlying measures of severity can be used to represent only 1 factor on the basis of the eigenvalues-greater-than-one rule.[6-8] We performed the eigenvalue analysis using the joint longitudinal data simultaneously, assuming that the factor relationship with the measures is similar in each wave. Then, to check such assumptions and assess whether there might be variability in inferences by follow-up wave, we additionally conducted the analysis within each visit. The results were similar, indicating that only one factor is needed within round (result available upon request).

Figure B.1. Scree Plot of Eigenvalues from PCA



Next, we examined the correlation between the factors estimated within visits compared to the one conducted using all visits (including baseline) combined together. Figure B.2 shows the plotted results from a linear regression model which regresses the overall PCA factor score using all waves of data onto the PCA factor score estimates using only one wave of data for each individual. Different colors are used to show the estimated relationship for each wave relative to the jointly estimated PCA factor score. A straight line will be indicative of perfect correlation with just different scaling. As shown, correlations are very high, providing further support to use the overall PCA factor scores as our overall composite severity measure in the study.

Figure B.2. Overall PCA Factor Score Using All Waves Versus PCA Factor Score by Wave



The final formula for the final composite severity measure of HD used in our analyses was:

$$CompositeSeverityScore = 0.176 * TMS - 0.173 * TFC - 0.172 * FAS - 0.167 * VFTc - 0.163 * VFTl - 0.185 * SDMT - 0.176 * SWRT$$

where all the measures in this formula are standardized to have mean 0 and variance 1.Thus, higher values of the composite score represent more severe HD while lower values represent less.

Table B.1 shows the correlation between each of the components used in the PCA. As shown, correlations are high, lending further support for use of the PCA to obtain an overall composite measure. Here is the correlation matrix obtained:

Table B.1. Model Estimated Correlations

	MOTSCORE	TFCSCORE	FASCORE	VERFCT5	VERFLT05	SDMT1	SWRT1
MOTSCORE	1.000						
TFCSCORE	–0.635	1.000					
FASCORE	–0.630	0.618	1.000				
VERFCT5	–0.605	0.594	0.589	1.000			
VERFLT05	–0.584	0.573	0.569	0.546	1.000		
SDMT1	–0.697	0.684	0.679	0.652	0.630	1.000	
SWRT1	–0.651	0.639	0.634	0.609	0.588	0.702	1.000

We performed additional analyses to help validate our PCA outcome. It is important to understand if a true relationship between the PCA outcome we created and HD progression exists over time for individuals in our sample. Naturally, this is nontrivial to establish completely since HD progression is multifaceted and can be difficult to measure. In this study, we do not have other outcomes to cross-check against the PCA outcome. We note that the highly-related studies which motivated our use of the PCA in the Enroll database had MRI images to track against the PCA outcome they created and used the brain images measuring progressive corticostriatal atrophy to show strong correlations between their PCA outcome and HD progression[5, 9]. While we cannot compare our PCA outcome to such images, Table B.2 shows the correlations between change in the individual HD measures used in the PCA and change in our composite to shore up evidence that the PCA outcome is measuring progression well in the sample. As expected, we have positive correlations between change in total motor score and the composite where for both high scores mean worse HD symptoms (ranges from 0.49 to 0.66). Conversely, we have negative correlations observed between changes in the other measures (TFC, FAS, SDMT, SWRT, and the two verbal measures) and the composite (ranging from –0.39 to –0.80) because, in all of these cases, decreasing values of the measure itself indicates worse HD symptoms over time and thus we have a statistically significant correlation whereby as each of these symptoms worsens, the HD composite increases.

Table B.2. Estimated Correlations Between Change in the Composite PCA and Change In Seven HD Severity Measures Used in the Composite at Each Visit Time

	Visit 1	Visit 2	Visit 3
Change in MOTSCORE	0.49	0.60	0.66
Change in TFCSCORE	–0.68	–0.73	–0.79
Change in FASCORE	–0.68	–0.75	–0.80
Change in VERFCT5	–0.48	–0.45	–0.45
Change in VERFLT05	–0.39	–0.48	–0.51
Change in SDMT1	–0.49	–0.53	–0.58
Change in SWRT1	–0.50	–0.56	–0.60

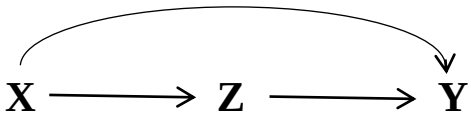
NOTE: All correlations are show are statistically significant with p<0.001.

We also carefully compared our equation for our composite to the recently published paper by Schobel and colleagues (2017), which makes a strong call to the field of HD research to utilize composite PCA outcomes like we are doing. [5] We found that our PCA equation is highly similar to the one they computed using the data from 1,668 individuals across four different longitudinal HD studies. This is a notable finding for the field that our analytic sample can produce similar PCA composite values to one done on a smaller database of HD individuals, suggesting additional evidence that the PCA composite used in this study is reproducible.

Appendix C. Notes on temporality

Figure C.1 illustrates the type of analysis one would ideally do when estimating the causal impact of our environmental and behavioral factors (here labeled with a Z) on HD severity and progression (here labeled Y). In this graphic, X denotes the potential confounding covariates upon which we wish to make the exposure groups comparable, Z denotes the environmental or lifestyle factor of interest, and Y denotes our outcome. Ideally, one should measure X prior to Z and Z prior to Y to estimate causal effects (i.e., one needs a clear temporal alignment between X, Z, and Y, whereby the confounding covariates come prior to the environmental factor and the environmental factor occurs prior to the outcome). In this framework, the goal is to estimate the causal impact of Z on Y, controlling for bias induced by X, which is related to both Z and Y. In our current setup, both X and Z are measured at the baseline visit (the first study visit), because there is not a lot of change over time in many of the environmental factors being considered and we wished to maximize the sample size available for the outcome analyses. Our goal is to create groups (defined by Z) that are comparable with respect to all confounding covariates included in X. Once these groups are created, we then use the later follow-ups of data from the study to measure how Z impacts Y. Here, we focus on longitudinal outcomes measured from up to the first three visits post baseline for individuals in our sample. By creating similar groups for levels of Z on the covariates in X, we are enabling more-robust analyses to tease out the causal impact of Z on outcomes measured at later follow-ups in the study

Figure C.1. Illustration of the Proposed Causal Analyses



NOTE: X denotes our confounding covariates, Z denotes our environmental or lifestyle factor, and Y outcomes.

Appendix D. Secondary analysis results

Table D.1 provides the DR regression results for exploratory regression analyses which fit our outcome models separately to each component used in the PCA. In general, the findings were consistent, though as might be expected, there were some signals of potential effects between our nongenetic factors and the individual HD outcomes, with exploratory evidence of protective effects of light and moderate drinking on the FAS, light drinking on SDMT, substance use (primarily marijuana) on SDMT, employment on TFC, and being in the highest education group on the SWRT. There was also exploratory evidence of a potential harmful impact of heavy drinking on TMS. The results from these analyses are exploratory and of secondary interest so caution should be used when interpreting the findings, given how many tests are being implemented in this analysis.

Table D.1 Doubly Robust Effect Size Estimates and 95-Percent Confidence Intervals for Secondary Analyses Using PS.Expanded Weighted Model

	Total Motor Score	**TFC**	**FAS**	**SDMT**	**SWRT**	**Verbal Freq – C**	**Verbal Freq – L**
Alcohol, Tobacco, and Other Substances							
Current Drug Abuse	–0.19 (–0.44, 0.06)	0.01 (–0.35, 0.38)	0.15 (–0.15, 0.46)	0.25 (0.02, 0.49)	0.24 (–0.03, 0.51)	0.15 (–0.09, 0.40)	0.03 (–0.26, 0.31)
Smoker	–0.04 (–0.14, 0.05)	0.09 (–0.01, 0.18)	0.08 (–0.02, 0.17)	–0.09 (–0.19, 0.01)	0.02 (–0.08, 0.11)	0.04 (–0.05, 0.12)	0.04 (–0.05, 0.14)
Alcohol Use (ref =abstainer)							
Light drinker	0.10 (–0.02, 0.22)	0.06 (–0.05, 0.17)	0.13 (0.02, 0.24)	0.11 (0.01, 0.22)	0.07 (–0.03, 0.17)	0.06 (–0.04, 0.16)	0.00 (–0.12, 0.12)
Moderate drinker	0.06 (–0.04, 0.16)	0.03 (–0.07, 0.13)	0.10 (0.00, 0.20)	0.08 (–0.02, 0.17)	0.04 (–0.07, 0.14)	0.03 (–0.07, 0.14)	–0.01 (–0.11, 0.09)
Heavy drinker	0.20 (0.02, 0.38)	–0.10 (–0.27, 0.07)	–0.09 (–0.26, 0.08)	–0.09 (–0.24, 0.06)	0.05 (–0.13, 0.23)	0.02 (–0.13, 0.18)	0.02 (–0.12, 0.16)
Environmental and Lifestyle							
Employed	0.03 (–0.08, 0.15)	0.12 (0.01, 0.22)	0.04 (–0.15, 0.23)	0.10 (–0.01, 0.21)	0.05 (–0.05, 0.16)	0.02 (–0.10, 0.15)	–0.07 (–0.19, 0.06)
Education (ref = 3)							
0–2	–0.08 (–0.19, 0.02)	0.04 (–0.07, 0.16)	–0.02 (–0.14, 0.09)	–0.04 (–0.14, 0.06)	0.01 (–0.10, 0.12)	0.04 (-–0.08, 0.16)	0.04 (–0.07, 0.16)
4	–0.09 (–0.22, 0.04)	–0.01 (–0.14, 0.13)	–0.02 (–0.17, 0.12)	0.06 (–0.06, 0.19)	0.07 (–0.06, 0.19)	0.10 (–0.02, 0.22)	0.12 (–0.01, 0.24)
5–6	0.04 (–0.07, 0.15)	–0.05 (–0.16, 0.06)	-0.07 (–0.19, 0.05)	0.04 (–0.06, 0.15)	0.11 (0.00, 0.22)	–0.05 (–0.15, 0.06)	0.10 (–0.02, 0.21)

Pharmacologic therapies							
Antidepressants	0.05 (–0.03, 0.12)	–0.11 (–0.19, –0.03)	–0.10 (–0.18, –0.01)	–0.05 (–0.13, 0.02)	–0.12 (–0.20, –0.04)	–0.07 (–0.15, 0.00)	–0.05 (–0.13,0.03)
Statins	–0.03 (–0.17, 0.10)	–0.03 (–0.16, 0.11)	0.06 (–0.07, 0.19)	–0.01 (–0.14, 0.11)	–0.02 (–0.15, 0.11)	0.04 (–0.10, 0.18)	–0.14 (–0.29, 0.00)

Appendix E. Diagnostic Summaries for Propensity Score Weight

Figure E.1. Maximum pairwise effect size (ES) before and after PS weighting for alcohol using groups

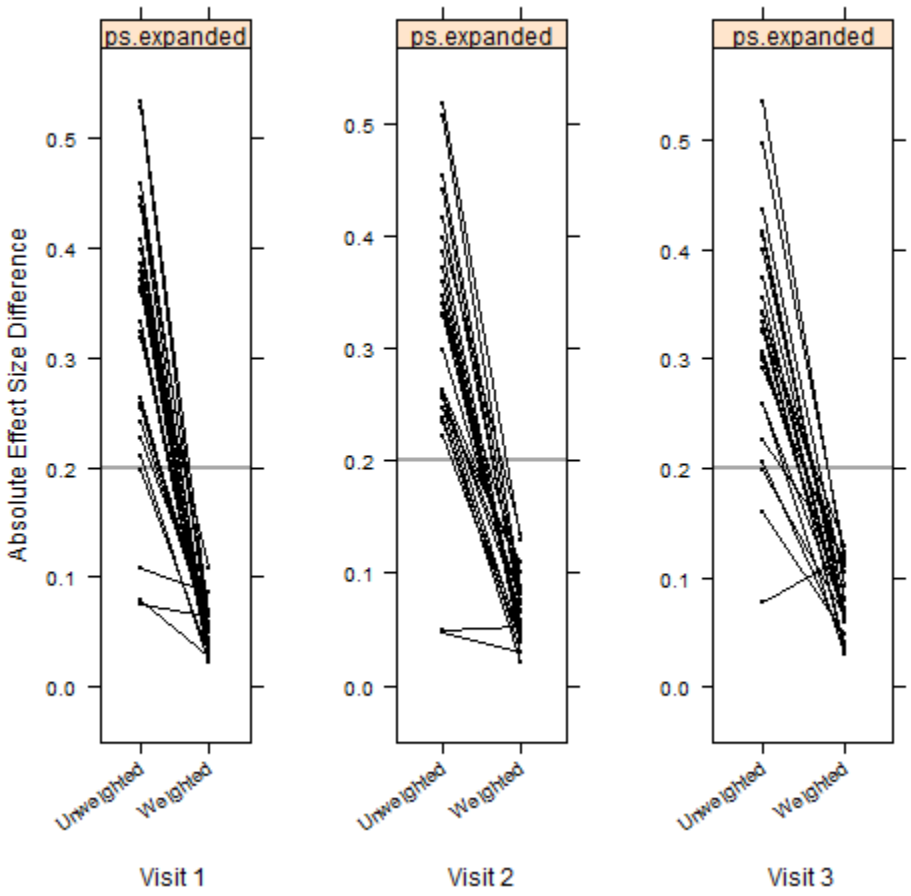


Figure E.2. Absolute ES for PS.Expanded Before and After Weighting for Indictor of Current Substance Use (ATT Weights)

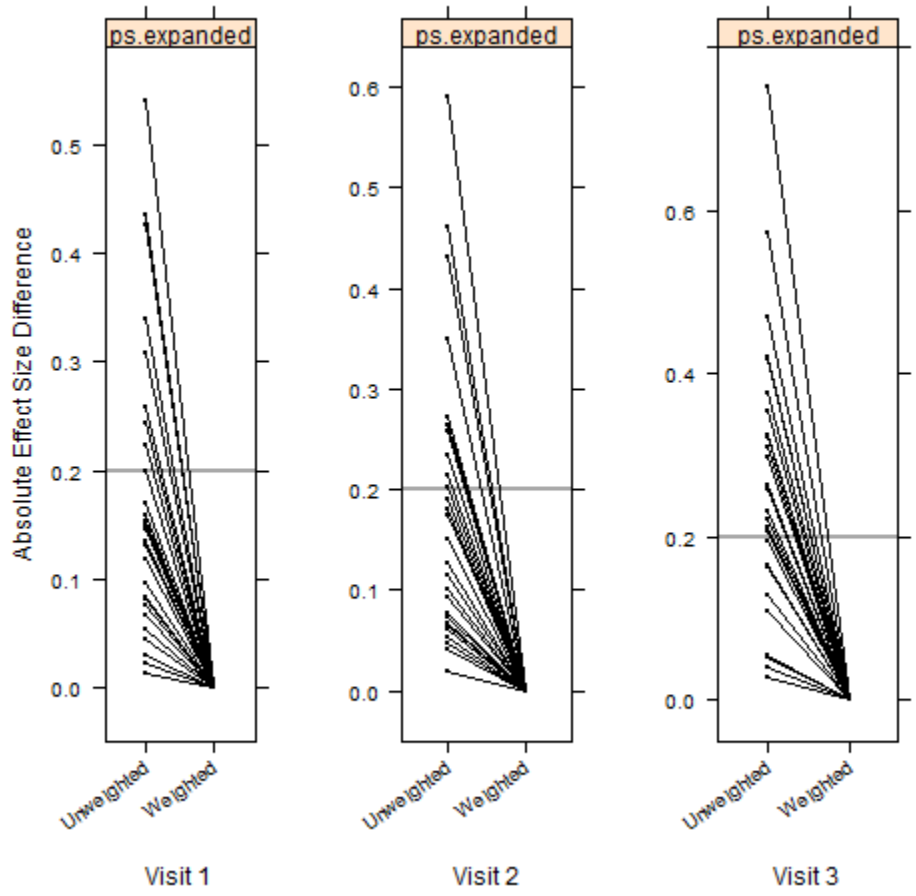


Figure E.3. Absolute ES for PS.Expanded Before and After Weighting for Binary Indictor of Smoking

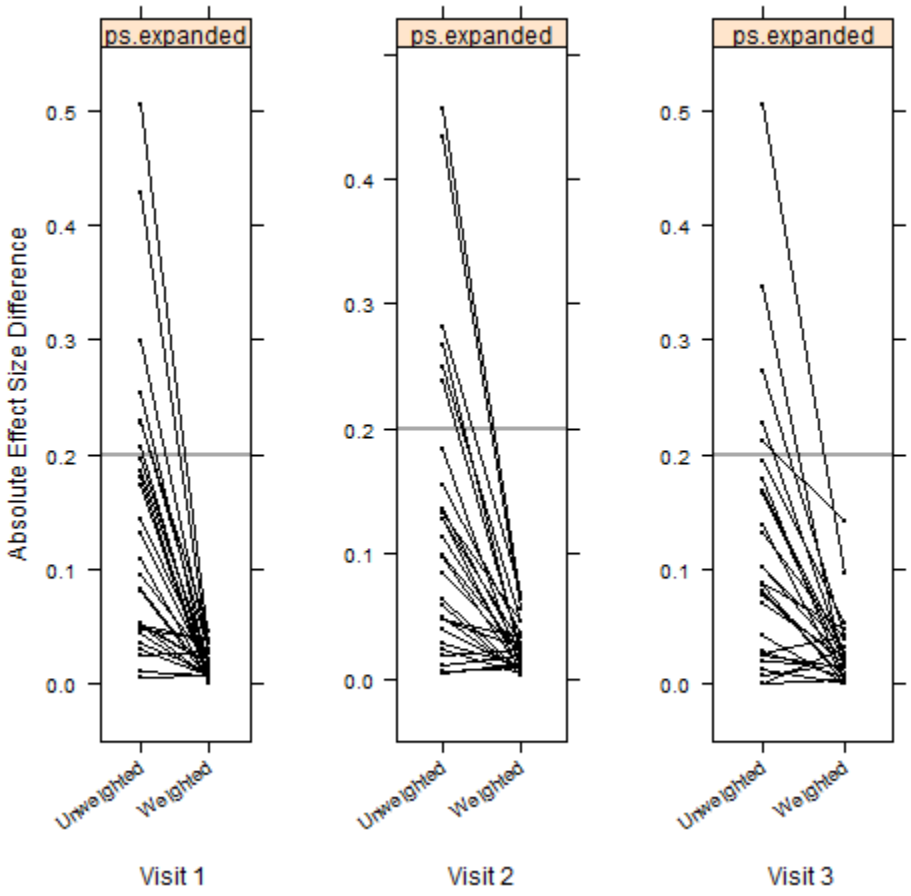


Figure E.4. Absolute ES for PS.Reduced and PS.Expanded Before and After Weighting for Indictor of Employment

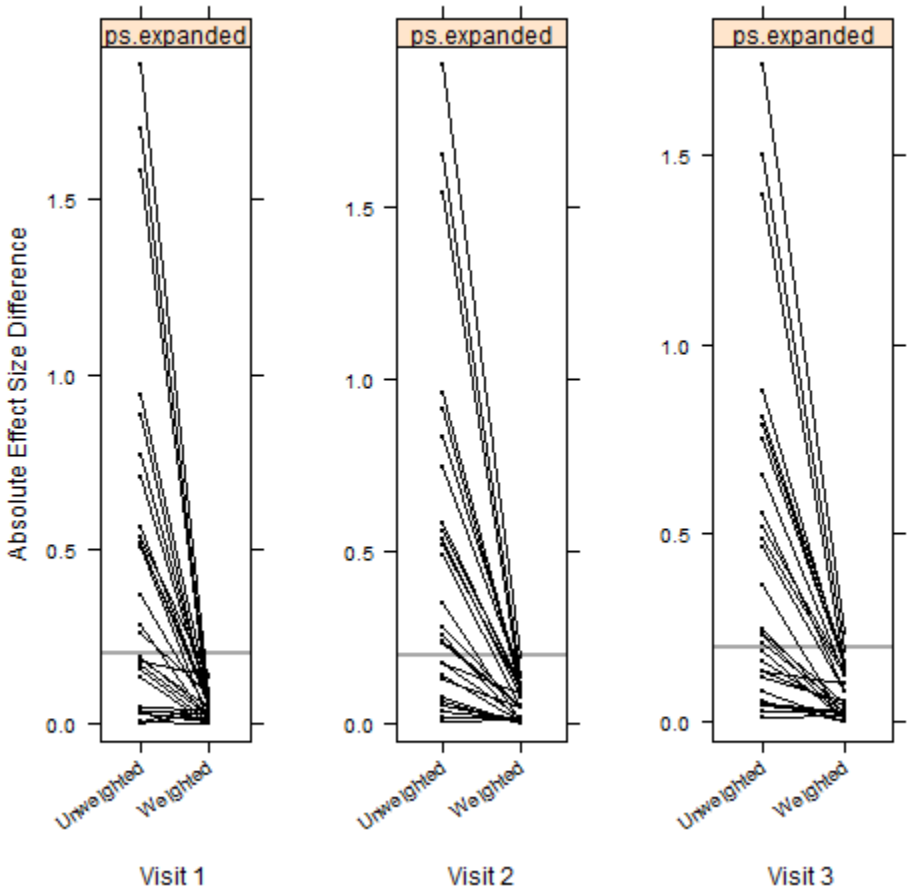


Figure E.5. Maximum Pairwise Absolute ES for PS.Expanded Before and After Weighting for Education Levels

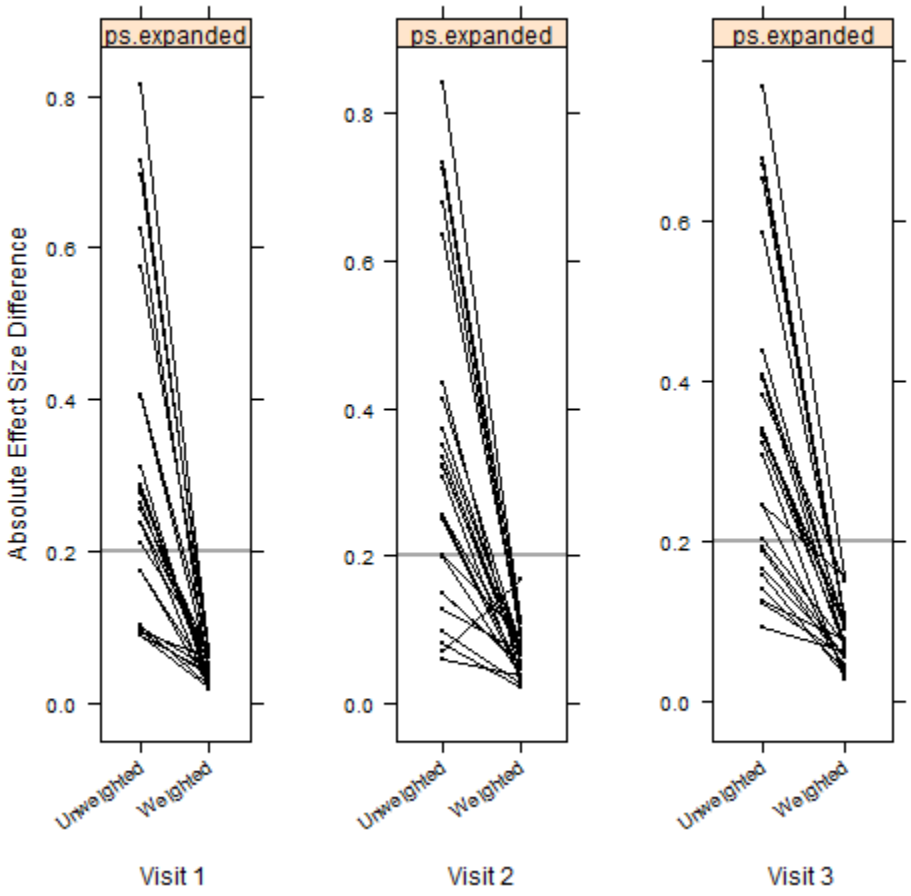


Figure E.6. Absolute ES for PS.Expanded Before and After Weighting for Indictor of Antidepressant Use

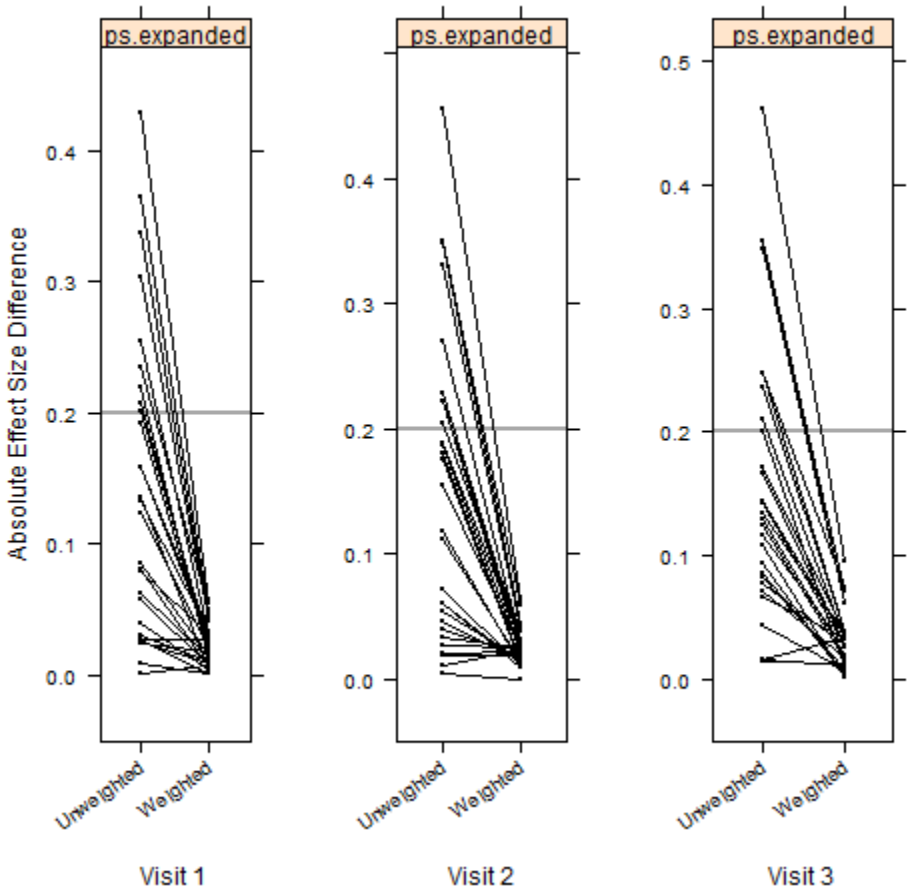
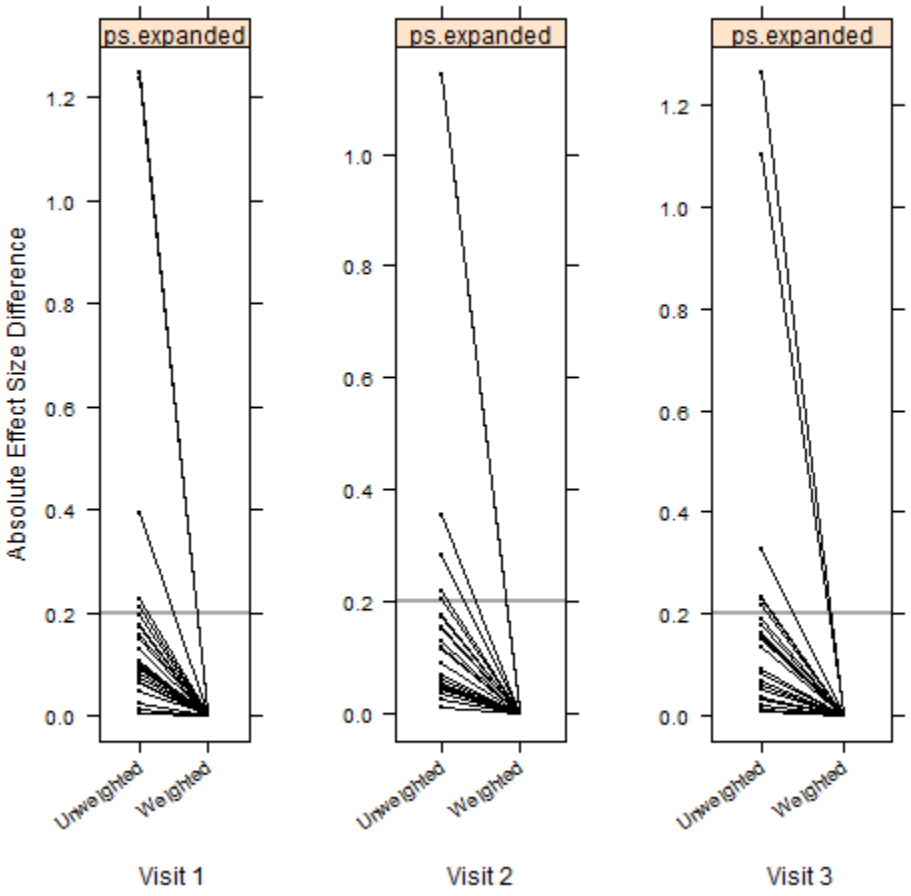


Figure E.7. Absolute ES for PS.Expanded Before and After Weighting for Indictor of Statin Use (ATT Weights)



Appendix F. Acknowledgments

The authors would like to acknowledge funding from the Cure Huntington's Disease Initiative Foundation for this work as well as grant R01DA045049 from the National Institute on Drug Abuse for helping with final publication of the findings. We would also like to thank Sara Minster, who provided helpful feedback on the data used for the study. We also are grateful to the patients and family members who participated in or are participating in the earlier REGISTRY and current Enroll-HD studies. Their involvement in these studies is critically important to improving our understanding of Huntington's disease. We thank the study investigators and administrators as well, including the European Huntington's Disease Network. Finally, we acknowledge our reviewers at the RAND Corporation, Rajeev Ramchand and Melinda Moore, Mark Kelson at Exeter University, and Simon Noble for their thoughtful and constructive feedback on this body of work.

References

[1] L.J. Beglinger, J.J. O'Rourke, C. Wang, D.R. Langbehn, K. Duff, J.S. Paulsen, Earliest functional declines in Huntington disease, Psychiatry research 178(2) (2010) 414-418.
[2] J.S. Paulsen, C. Wang, K. Duff, R. Barker, M. Nance, L. Beglinger, D. Moser, J.K. Williams, S. Simpson, D. Langbehn, Challenges assessing clinical endpoints in early Huntington disease, Movement Disorders 25(15) (2010) 2595-2603.
[3] I. Shoulson, S. Fahn, Huntington disease: clinical care and evaluation, Neurology 29(1) (1979) 1-1.
[4] D.R. Langbehn, R.R. Brinkman, D. Falush, J.S. Paulsen, M. Hayden, A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length, Clin. Genet. 65(4) (2004) 267-277.
[5] S.A. Schobel, G. Palermo, P. Auinger, J.D. Long, S. Ma, O.S. Khwaja, D. Trundell, M. Cudkowicz, S. Hersch, C. Sampaio, E.R. Dorsey, B.R. Leavitt, K.D. Kieburtz, J.J. Sevigny, D.R. Langbehn, S.J. Tabrizi, Motor, cognitive, and functional declines contribute to a single progressive factor in early HD, Neurology 89(24) (2017) 2495-2502.
[6] R.B. Cattell, The scree test for the number of factors, Multivariate behavioral research 1(2) (1966) 245-276.
[7] N. Cliff, The eigenvalues-greater-than-one rule and the reliability of components, PsyB 103(2) (1988) 276.
[8] H.F. Kaiser, The application of electronic computers to factor analysis, Educ. Psychol. Meas. 20(1) (1960) 141-151.
[9] D.J.H. Moss, A.F. Pardiñas, D. Langbehn, K. Lo, B.R. Leavitt, R. Roos, A. Durr, S. Mead, P. Holmans, L. Jones, S.J. Tabrizi, Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study, The Lancet Neurology 16(9) (2017) 701-711.