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

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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. 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) 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 for all non-genetic factors. 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.

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

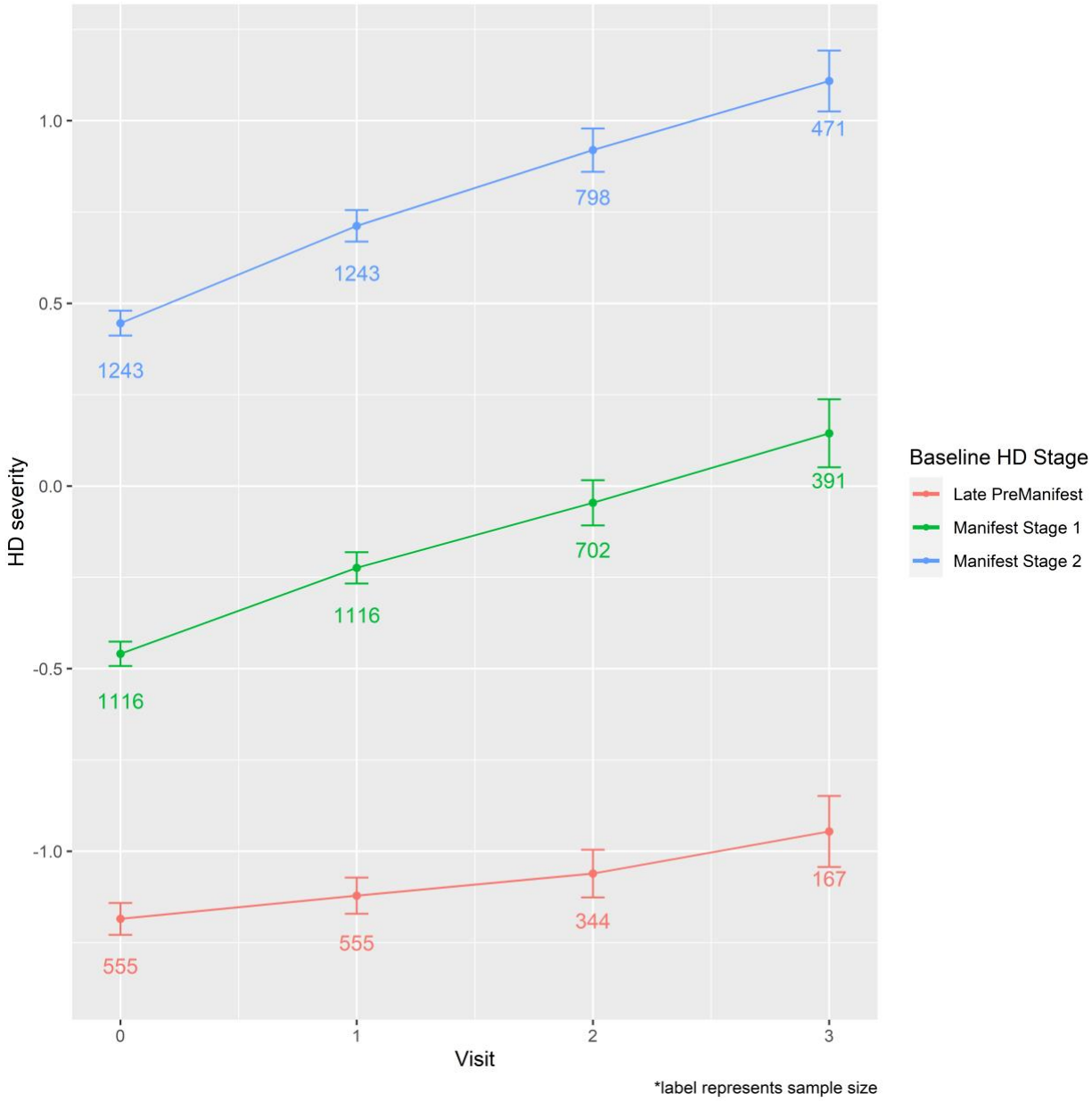
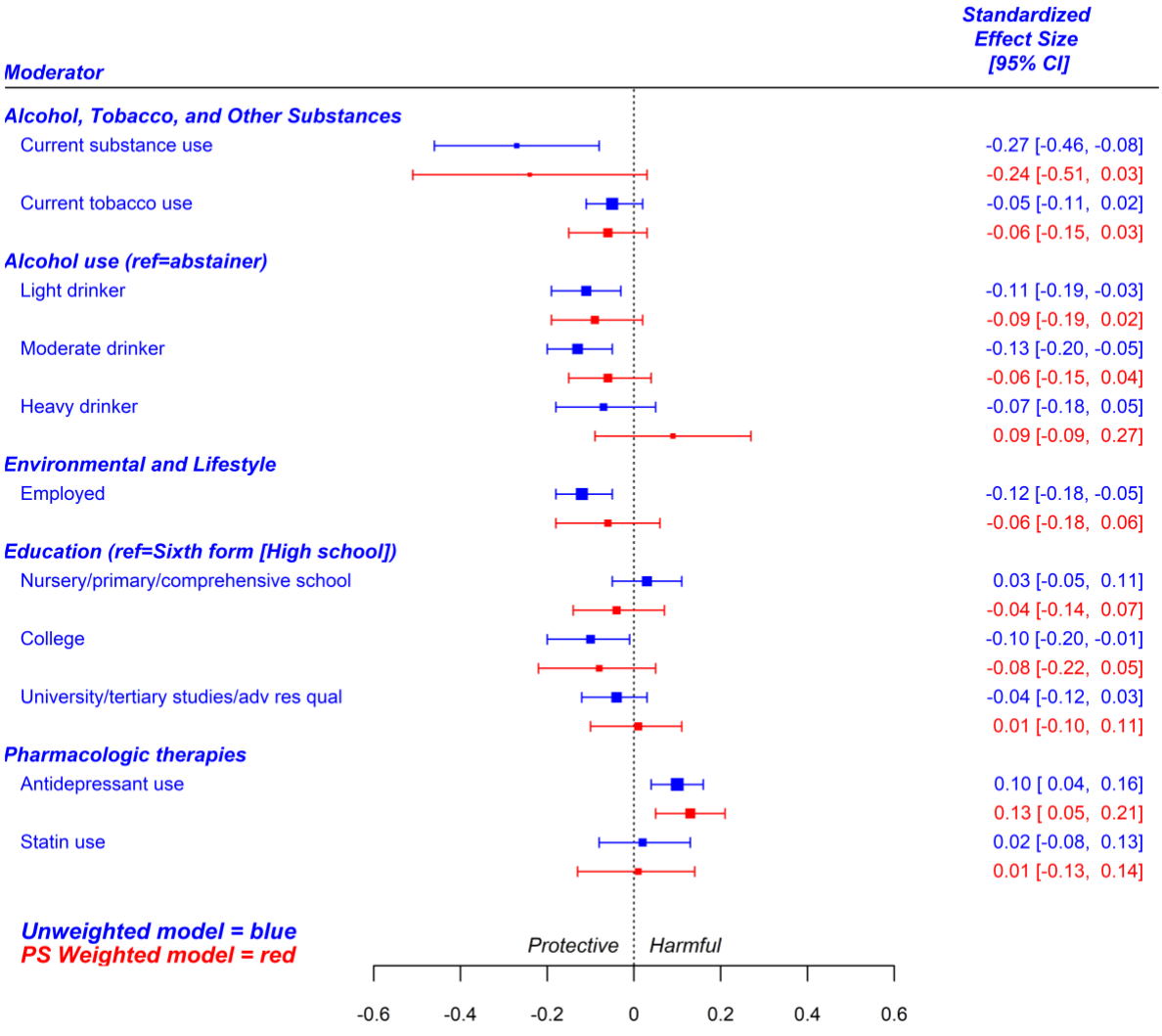


Figure 2. Doubly Robust Effect Size Estimates and 95-Percent Confidence Intervals for Each Non-Genetic Factor



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 of the HD severity composite overtime from the doubly robust outcome model

for all non-genetic factors

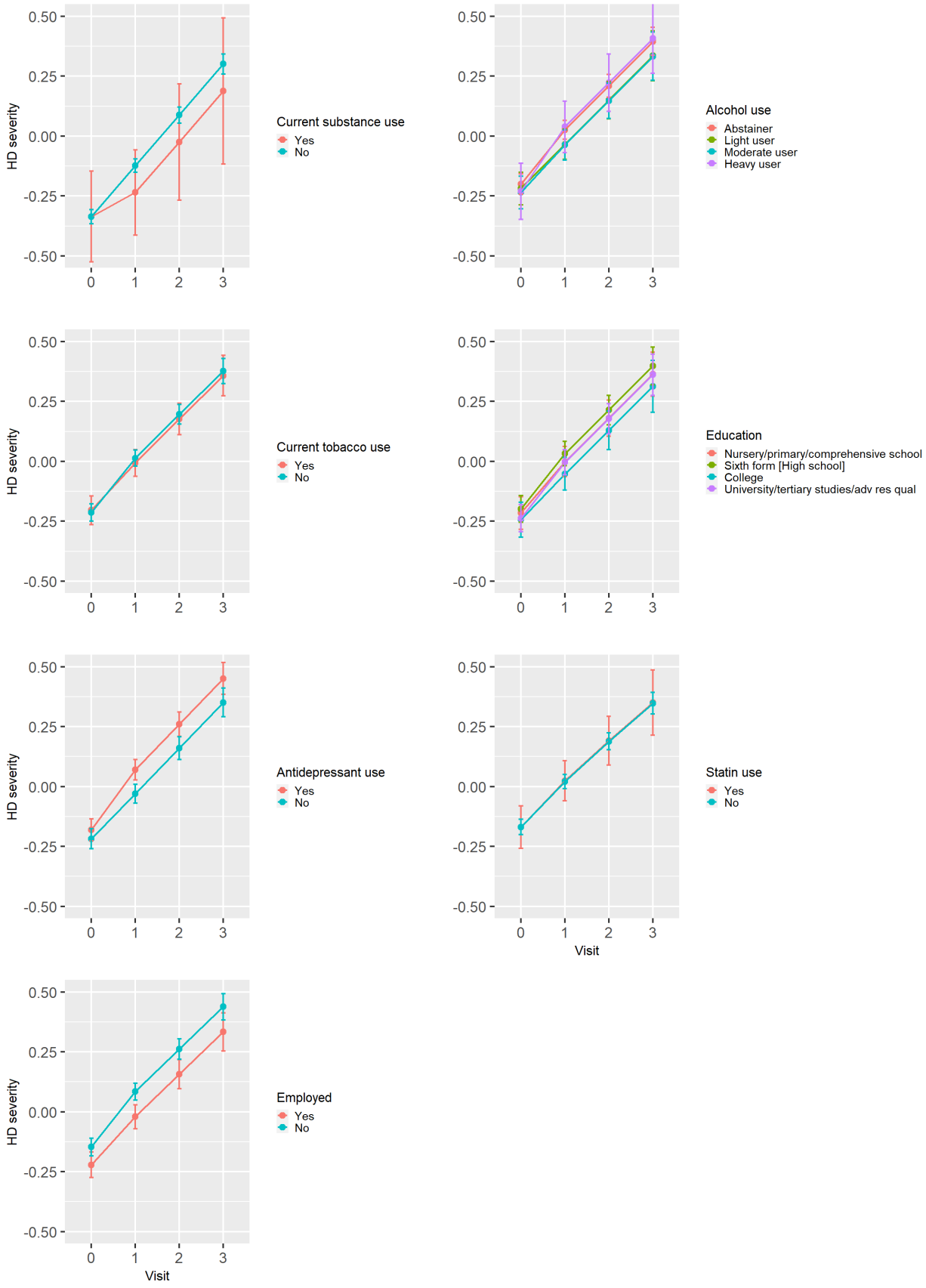

HD severity
0.50
0.25
0.00
-0.25
-0.50
0
1
2
3
Visit
Current substance use
Yes
No
Alcohol use
Abstainer
Light user
Moderate user
Heavy user
Current tobacco use
Yes
No
Education
Nursery/primary/comprehensive school
Sixth form [High school]
College
University/tertiary studies/adv res qual
Antidepressant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

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	1,116 (38%)
Stage 1	1,243 (43%)
Stage 2	555 (19%)
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)%