

**Disease stage, but not sex, predicts depression and psychological distress in
Huntington's disease: A European population study**

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Network

Short running head: Disease stage predicts depression in HD...

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ABSTRACT

Objective

Depression and anxiety significantly affect morbidity in Huntington's disease. Mice models of Huntington's disease have identified sex differences in mood-like behaviours that vary across disease lifespan, but this interaction has not previously been explored in humans with Huntington's disease. However, among certain medical populations, evidence of sex differences in mood across various disease stages has been found, reflecting trends among the general population that women tend to experience anxiety and depression 1.5 to 2 times more than men. The current study examined whether disease stage and sex, either separately or as an interaction term, predicted anxiety and depression in Huntington's disease.

Methods

A cross-sectional study of REGISTRY data involving 453 Huntington's disease participants from 12 European countries was undertaken using the Hospital Anxiety and Depression Scale. A series of multiple regression analyses were undertaken to discover to what extent disease stage and sex predicted anxiety, depression, and general distress after controlling for a number of known predictors of mood difficulties.

Results

Disease stage, but not sex, was found to predict depressive symptoms and general distress. Neither disease stage nor sex predicted anxiety. Furthermore, an interaction term computed for disease stage and sex did not contribute to the models tested.

Conclusion

In terms of considering risks to developing depression and anxiety in the Huntington's disease population, practitioners may need to pay special attention to disease stage progression (but not sex differences) to enable early detection and treatment of depression (but not anxiety).

Key words: *Huntington disease; depression; anxiety; sex; disease stage; HADS*

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INTRODUCTION

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease characterised by impairments in movement, cognition and emotion. The onset of the disease usually occurs in mid-adulthood, with a progressive functional decline over approximately 20 years resulting in premature death[1]. Although there is no sex difference in the probability of inheriting the HD gene mutation from a parent, children who have inherited the gene from their father tend to develop symptoms earlier, due to instability of the trinucleotide cytosine-adenine-guanine (CAG) expansion found in paternal transmission[2].

Prevalence estimates of anxiety and depression in HD range considerably due to variations in assessments and disease stages measured, with 13-71% for anxiety[3], and 15-69% for depression[4, 5]. Also, the aetiology of these symptoms is complex, with contributions from the neurodegenerative process itself[6], and also from the life stresses of living with a terminal and debilitating illness[7]. Due to the familial nature of the disease, HD mutation carriers may also be at a higher risk for depression and anxiety from having to deal with challenges, perhaps from an early age, such as witnessing family members with, or dying from, the disease; caregiving duties for family members; decisions around reproductive choices; and concerns about informing others of genetic risk. Despite these additional stresses potentially increasing vulnerability to anxiety and depression, and the deleterious effects that mood difficulties have on morbidity and mortality in HD[8], evidence suggests anxiety and depression are under-treated in HD[9]. Therefore, understanding risk factors for anxiety and depression in HD is vital for adequate detection, treatment and, ideally, prevention.

One key focus for discussion regarding depression and anxiety in HD is disease stage. A model commonly used to describe functional decline in HD involves five stages, using ranges of Total Functional Capacity (TFC) scores of the United Huntington Disease Rating

Scale (UHDRS)[10], based on the following criteria: engagement in occupation; capacity to handle financial affairs; ability to manage domestic responsibilities and perform activities of daily living; and extent of care provided[11]. Thus HD patients move from relative independence in Stage 1, through to the advanced stage of the disease (Stage 5), where patients are severely impaired in their capacity to perform activities of daily living.

From the HD literature that has addressed disease stage, there are mixed results regarding critical periods for anxiety and depression, but suggest they do not necessarily follow a linear trend across disease stage[9, 12-14]. One large study revealed a significant peak in anxiety and depression symptoms at Stage 2 of the disease, while the authors of a more recent study found prevalence of moderate to severe depression to be highest among stages 4-5[9]. In order to develop the findings from previous studies, it is important to explore other variables that may impact on the risk of developing anxiety and depression, and interact with disease stage. In the current paper we focus on sex. We know that a consistent finding among the general population is that women are likely to experience anxiety and depression between 1.5 and 2 times more than men[15, 16]. Explanations for these differences have included gender biases in diagnosis and treatment of mental health problems, socio-political contexts, hormonal differences, and differences in help-seeking behaviour among men and women[17].

Despite these theoretical and empirical differences, research into sex differences in mood in HD is limited. Of the limited human studies available, there is evidence to suggest that the usual ratio of discrepancy noted between men and women does not exist in HD[9, 18]. More research regarding sex differences in anxiety and depressive-like behaviours in HD has been undertaken using various mice models[19]. Animal models of HD enable researchers to consider the aetiology of behavioural symptoms and also mechanisms underlying sex differences, as potential biological contributions can be tested in the absence

of psychosocial issues affecting human gene carriers, such as the knowledge that they have a fatal neurodegenerative condition.

Anxiety-like behaviours in mice include avoidance of open spaces, heights or light in tests such as the open field test, elevated plus maze and light/dark box test. These tests have revealed some evidence of male HD mice demonstrating more anxiety-like behaviour[20, 21]. Depression-like behaviours in rodents are measured by such paradigms as the sucrose test, whereby HD mice are considered to illustrate anhedonia when they exhibit a reduced preference for sucrose solution. The forced swimming test is another measure that may represent depressive-like behaviour through reduced swimming and climbing activity. In these tests, female mice have been shown to demonstrate more behaviours suggestive of depression [22-24]. Therefore, collectively, there is evidence of sexual dimorphism of anxiety and depressive-like behaviours in rodent models of HD, with suggestion of a potential interaction between sex differences and stage of disease progression[19], an area that has not been examined in humans.

This study therefore examines whether, in humans, disease stage *interacts* with sex to predict depression and anxiety symptoms in HD. This is important because across disease stages, men and women face different life challenges that may impact on emotional health, such as concerns about the ability to start or maintain a family, changes in social support, or peak changes in reproductive and hormonal processes (e.g. menopause)[25-27]. Furthermore, recent findings suggest complex sex effects in the clinical phenotype of HD, with women demonstrating more severe symptoms and faster rate of progression, particularly in terms of motor and functional abilities[18]. Consequently, improved understanding of any sex differences regarding the emotional component of the disease, and the interactions with disease stage, may help identify stages of critical risk for men and women in terms of mental health, and inform the design of future disease-modifying clinical trials[18]. Finally, such a

consideration would add to research that have examined these as key factors in other medical conditions, where an interaction between sex and disease-stage was found to influence mood symptoms among those in certain diseases[28, 29], but not others[30].

In the current study, we aimed to examine the influence of disease stage and sex on anxiety and depression and to test the veracity of any relationship between sex and disease stage by controlling for several known predictors of anxiety and depression. Specifically we hypothesised that: i) disease stage would not independently predict anxiety and depression symptoms; ii) there would be a sex difference in depression and anxiety, with women reporting more symptoms than men; iii) there would be an interaction effect between sex and disease stage in HD for depression and anxiety.

METHOD

Sample

Our sample comprised 453 verified HD mutation carriers, from across 12 European countries, who were REGISTRY 3 study participants. REGISTRY is a multi-national, prospective study examining the natural history of HD (<http://www.euro-hd.net/html/registry>). Ethical approval was gained locally via ethics committees for all study sites contributing to REGISTRY.

Data

We requested all available Hospital Anxiety and Depression Scale (HADS)[31] data from the European HD Network (EHDN), following approval of the research proposal by the EHDN Scientific and Bioethics Advisory Committee. As the data set included some repeat measures, we used only cross-sectional data based on participants' first visit, covering the period 27 June 2011 to 27 June 2013, which led to an initial study cohort size of $n = 496$ who had a CAG repeat of ≥ 39 . As there were only 4 participants in Stage 5, we excluded this group from the analysis. We also excluded those with juvenile HD, defined by a CAG repeat ≥ 55 on the larger allele, due to potential phenotypical differences from adult-onset HD[32]

($n=3$). A further 36 participants were excluded due to missing data (history of depression) [$n = 8$], current medication use [$n = 12$], current alcohol and cigarette intake [$n = 13$], age [$n = 1$] and education years [$n = 2$]) resulting in our total 453 (203 males, 250 females) participants, aged from 22 years to 86 years (mean age = 53.00, SD = 11.9). Participants were from the following European countries: Austria (9), Finland (2), France (116), Germany (86), Italy (10), Norway (43), Poland (88), Portugal (9), Spain (29), Sweden (12), Switzerland (2), and UK (47). The sex breakdown by disease severity stage was Stage 1 (75 males, 114 females), Stage 2 (71 males, 57 females), Stage 3 (48 males, 60 females), and Stage 4 (9 Males, 19 females).

The outcome variables (depression and anxiety) were assessed using the HADS, a 14-item self-report tool comprising two 7-item measures relating to anxiety and depression symptoms, with both scores combined to create a measure of general psychological distress. Each item is scored on a 4 point scale (0-3, with scores ranging from 0-21 on each subscale, with higher scores representing higher levels of distress). The HADS has been shown to be a reliable, sensitive and precise instrument across a wide range of populations[33] and has previously been found to have excellent screening properties for identifying clinical cases of depression in HD compared to a “gold standard” diagnostic measure of depression with the total HADS score of 13/14 (sensitivity 1.00, specificity 0.79) and for the HADS-D, a 6/7 cut-off (sensitivity 1.00, specificity 0.82)[34]. We used total scores for HADS, the HADS anxiety subscale, and the HADS depression subscale to examine symptomatology.

As one of our key predictor variables, disease stage was defined using scores from the TFC scale of the UHDRS[10, 11]: Stage 1 (11-13), Stage 2 (7-10), Stage 3 (3-6), Stage 4 (1-2) and Stage 5(0) (noting we excluded this latter group). We also included a number of other variables so we could control for several known predictors of depression and anxiety. These included: years in education, as a longer period in education has been found to be related to

lower levels of depression in later life[35]; certain medications (antidepressants, anxiolytics, mood stabilisers/anti-epileptics, neuroleptics, sleeping tablets, betablockers and tetrabenazine, the latter of which can have side-effects of anxiety and depression[36]); past use of antidepressants and anxiolytics, and history of depression (no assessment of history of anxiety is included in REGISTRY); cigarette use (number per day) and alcohol use (units per day), as these have both been found to affect depression and anxiety[37-39]; largest CAG repeat length and the Total Motor Score from the UHDRS (a composite measure of different motor tasks, including oculomotor function, dysarthria, chorea, dystonia, gait and postural stability, with higher scores indicating more motor impairment).

Statistical Analysis

A series of independent t-tests or chi-square were used to compare sex differences for the demographic variables, outcome variables, and the known predictors of depression and anxiety. Correlation statistics were used to test for the linearity of the relationship between disease progression and HADS scores. Three three-step multiple regressions were performed, with overall HADS scores, depression, and anxiety used as a dependent variable respectively, with demographic variables and known predictors of depression and anxiety entered at step 1, sex and disease stage used as the predictor variables in step 2, and used an interaction term of disease stage by sex as the predictor variables at step (step 3).

RESULTS

Descriptive Statistics

Table I reports on mean comparisons, independent t-tests and chi-squares for HADS scores, and demographic and clinical variables by sex.

Table I. *Mean comparisons, independent t-tests and chi-squares for HADS scores, and demographic and clinical variables by sex.*

	Men (n = 203)	Women (n = 250)		
	Mean (SD)	Mean (SD)	t	p =<
Total HADS Scores	11.34 (7.4)	11.83 (7.8)	-.69	.493
Depressive Symptoms	6.18 (4.8)	5.98 (4.4)	.48	.630
Anxiety Symptoms	5.16 (3.5)	5.86 (4.4)	-1.84	.067
TFC Score	8.72 (3.5)	8.78 (3.9)	-.172	.864
CAG repeat length	42.43 (2.2)	43.40 (2.6)	-4.25	.001
Total Motor Score	33.51 (21.3)	32.25 (25.1)	.570	.569
Age	55.73 (10.7)	50.80 (12.4)	4.46	.001
Years in education	12.33 (3.6)	12.00 (3.2)	1.00	.316
Nicotine Use	4.10 (8.4)	4.78 (8.7)	-.838	.402
Alcohol Units	3.3 (7.9)	0.71 (2.6)	4.86	.001
	n (%)	n (%)	X ²	p
Antidepressant	91 (44.8%)	130 (52.0%)	2.31	.129
Anxiolytic	39 (19.2%)	77 (30.8%)	7.90	.005
Betablocker	13 (6.4%)	12 (4.8%)	.55	.457
Mood stabiliser	11 (5.4%)	14 (5.6%)	.007	.933
Neuroleptic	84 (41.4%)	103 (41.2%)	.001	.969
Sleeping medication	14 (6.9%)	27 (10.8%)	2.07	.150
Tetrabenazine	23 (11.3%)	43 (17.2%)	3.10	.078
Previous history of depression	119 (58.6%)	159 (63.6%)	1.17	.279
Previous antidepressant	108 (53.2%)	159 (63.6%)	5.01	.025
Previous anxiolytic	60 (29.6%)	104 (41.6%)	7.04	.008

Group comparisons examining sex differences using independent t-tests and chi-squares (see Table I) revealed women in our sample had significantly higher CAG repeat lengths and were younger than the men. Men reported significantly more alcohol use than women, while more women were taking anxiolytics and had a history of antidepressant and anxiolytic use. No sex differences in any of the clinical symptoms were identified.

We also examined the linearity of the relationship between disease progression and HADS, and Figure 1 shows HADS scores across each of the four disease stages, demonstrating a general trend of increasing HADS scores across disease stages. There was a statistically significant correlation between increasing disease stage and total HADS score ($r = .35, p < .001$), depressive symptoms ($r = .45, p < .001$) and anxiety symptoms ($r = .15, p = .001$).

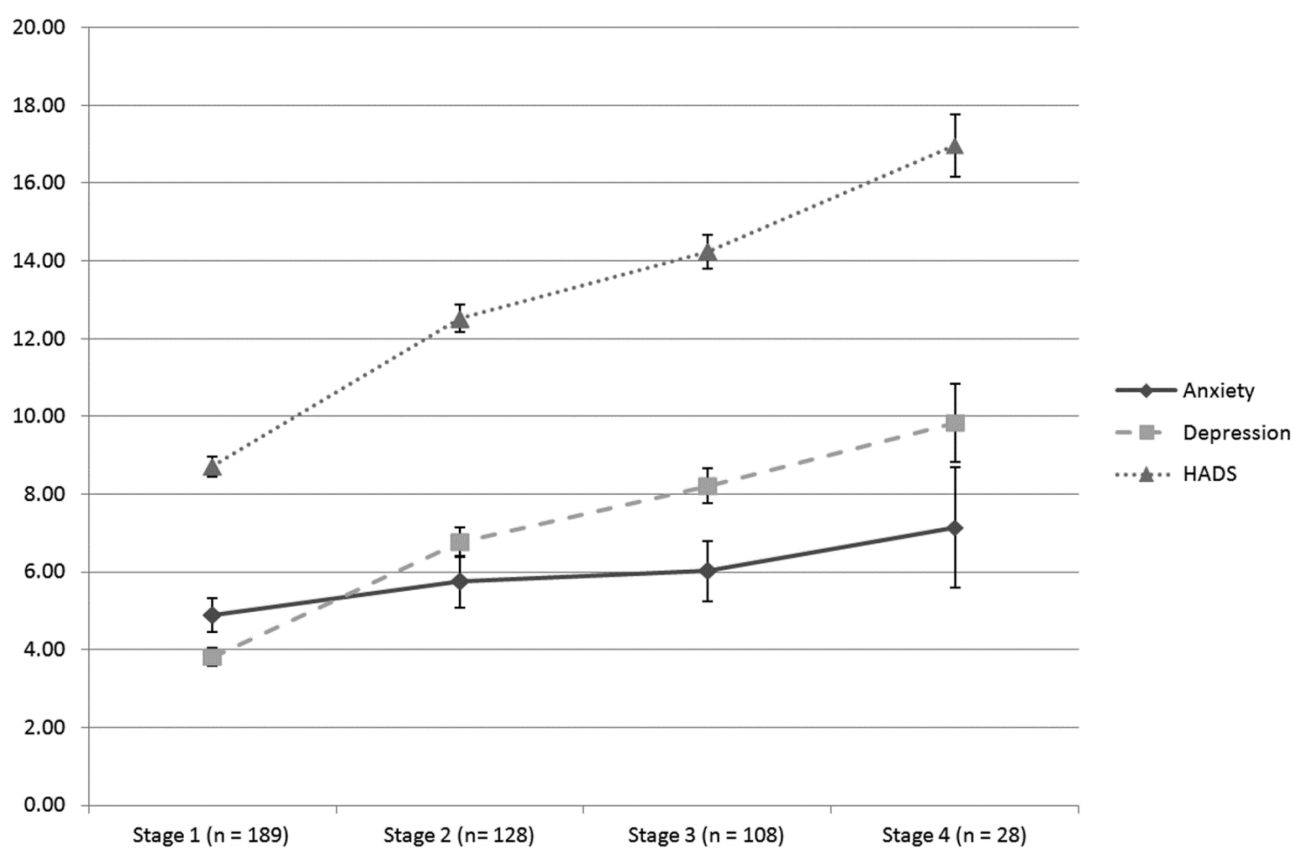


Figure 1.

Illustration of mean scores and standard errors for total HADS, anxiety subscale and depression subscale across disease stages according to TFC score ranges (n=453)

Symptomatology.

We then ran three three-step multiple regressions, with overall HADS scores, depression, and anxiety used as a dependent variable, with CAG repeat length, motor score, age, years in education, alcohol units, nicotine use, current and previous medication use and depression history used as the predictor variables in step 1, and sex and disease stage as the predictor variables in step 2. Finally, to test whether the predictive value of disease stage varied between men and women, a further step (step 3) was introduced to conduct a moderator analysis. This involved computing one new variable representing the interaction between sex and disease stage. The moderation analysis followed recommendations forming interaction variables based in the multiplication of the standardized diagnosis stage variable with the dummy-coded sex variable[40].

The variance inflation factors (VIFs) and tolerance factors for each of the single predictor variables were no larger than 3.43 and no smaller than .32, respectively. Therefore, they did not contravene the threshold values for VIF of at least 5 and tolerance statistics of less than .2 that are used to suggest collinearity between independent variables[41].

For each regression (See Table II) in step 1, the predictor variables demonstrate statistical significance in predicting each dimension (Total score, $F[16,436] = 11.23$, $r = .54$, $r^2 = .29$, $\text{adj } r^2 = .27$, $p < .001$; depression, $F[16,436] = 11.96$, $r = .55$, $r^2 = .31$, $\text{adj } r^2 = .28$, $p < .001$; anxiety, $F[16,436] = 5.65$, $r = .44$, $r^2 = .19$, $\text{adj } r^2 = .16$, $p < .001$). In this step: motor score, years in education, current anti-depressant and beta blocker use and previous treatment of depression and anxiolytic use account for unique variance in total HADS and depression scores. Previous treatment of depression and anxiolytic use account for unique variance in total HADS and anxiety scores. In step 2, the inclusion of sex and disease stage (TFC scale) led to a statistically significant change in R^2 for total HADS scores ($\Delta R = .013$, $p = .021$) and depression scores ($\Delta R = .032$, $p < .001$) but not anxiety scores ($\Delta R = .001$, $p = .830$). Disease

stage accounts for unique variance in depression and total HADS score. The statistical effect size for this is small (i.e. $\beta < .3$)[42], with variance accounting for between 1 to 3% of the variance. At step 3, for depression and total HADS scores, the interaction terms did not increase the variance explained, accounting for less than 1% of the variance. This suggests that disease stage predicts depression and total HADS scores equally for both men and women. For anxiety scores, at step 3, the interaction terms did not increase the variance explained, accounting for less than 1% of the variance.

Table II.

Multiple Regression Analysis with depression, anxiety, and total HADS scores used as Dependent Variables, and CAG repeat length, motor score, education years, nicotine and alcohol use, current and historical medication use and history of depression used at Step 1 and disease stage and gender at Step 2 used as Predictor Variables (with Step 3 interaction term not contributing to the model).

	Total HADS				Depression				Anxiety			
	B	β	t	$p = <$	B	β	t	$p = <$	B	β	t	$p = <$
Step 1												
CAG repeat length	-.206	-.067	-1.084	.279	-.058	-.032	-.520	.603	-.147	-.090	-1.366	.173
Total Motor Score	.045	.140	2.371	.018	.041	.210	3.599	.001	.005	.027	.429	.668
Age	-.061	-.095	-1.506	.133	-.020	-.053	-.843	.400	-.041	-.120	-1.773	.077
Years in education	-.239	-.107	-2.568	.011	-.152	-.114	-2.765	.006	-.087	-.073	-1.643	.101
Nicotine use	.025	.028	.657	.511	.002	.004	.088	.930	.023	.048	1.065	.288
Alcohol use	-.008	-.006	-.146	.884	.015	.020	.470	.639	-.023	-.033	-.745	.457
Antidepressant use	2.250	.148	2.084	.038	1.489	.164	2.333	.020	.762	.094	1.241	.215

Anxiolytic	-.323	-.019	-.284	.777	-.825	-.080	-1.225	.221	.502	.054	.775	.439
Betablocker	3.127	.094	2.276	.023	1.707	.086	2.103	.036	1.420	.080	1.817	.070
Mood stabiliser	1.546	.047	1.133	.258	.732	.037	.907	.365	.815	.046	1.050	.294
Neuroleptic	.793	.051	1.073	.284	.730	.079	1.671	.095	.063	.008	.151	.880
Sleeping medication	-1.186	-.045	-1.076	.283	-.916	-.058	-1.406	.161	-.270	-.019	-.431	.666
Tetrabenazine	1.261	.059	1.323	.187	.767	.060	1.361	.174	.494	.043	.912	.362
History of depression	2.908	.187	3.851	.001	1.419	.153	3.180	.002	1.489	.180	3.468	.001
Previous antidepressant	.334	.022	.295	.768	-.023	-.003	-.035	.972	.357	.044	.555	.579
Previous anxiolytic	3.988	.253	3.790	.001	2.551	.271	4.102	.001	1.438	.171	2.403	.017
Step 2												
Sex	-.488	-.032	-.741	.459	-.663	-.073	-1.729	.085				
TFC stage	1.494	.187	2.689	.007	1.366	.286	4.223	.001				

DISCUSSION

In terms of the main aims of the study, after controlling for a number of variables, we identified that disease stage, but not sex, uniquely predicted general psychological distress, and specifically depression symptomatology. Further, we found that while disease stage influenced depression, there was no impact on anxiety symptoms; therefore our results highlight a possible distinction in the course of anxiety and depression across disease stage, and that depression may be a key focus for understanding changes in psychological distress across disease stage. This finding adds a valuable addition to the literature, as it contrasts with previous studies that have found no linear relationship between depression and disease stage.

Our findings, however, show that there was no significant difference in anxiety and depression symptoms among men and women, which is inconsistent with a well-replicated finding in the general population that women are approximately twice as more likely to experience these problems. Nevertheless, our results provide further support for other studies of HD that have found either a reduced disparity in depression among women and men compared to the general population[18] or no independent effect of sex on depression when controlled for other variables in a large study using an interviewer rated measure[9]. This finding of no sex difference in depression has also been found in other neurodegenerative conditions, Parkinson's disease (PD)[30] and multiple sclerosis[43], which suggests that the finding of the current study may be illustrative of a broader trend among participants with neurodegenerative conditions and potentially the increasing disability and functional impairments with which men and women have to cope.

The current findings of no observed sex differences in distress is also inconsistent with the trend for sexual dimorphism found in mice models with HD[19]. One body of research has identified depression to be associated with altered hypothalamic–pituitary–

adrenal (HPA)-axis functioning (44-47), and these mechanisms have been proposed for sex differences in depressive behaviours in rodents[48]. As yet, sex differences in HPA-axis functioning in human HD carriers have not been explored and this would be an interesting area for future research as sex differences in response to stress have been found to alter depending on the type of stressor and duration of exposure [48]; and a multitude of chemical, environmental and psychological stressors may affect individuals with HD. A further explanation for the varying findings between humans and animals perhaps may highlight that the measurement and aetiology of depression is not equivocal, with the need to further consider psychological and social contributions to depression among humans (disparities for women, perceptions of stress, coping styles, cognitive appraisals, reduced employment opportunities and lower social status)[16, 17]. For example, the reduction of any gender differences in depression may have been due to women seeking help for depression, as was found among our sample, women were found to have been more likely to have used both anxiolytics and antidepressants in the past, therefore indicative that they may have been more likely to previously seek help for their condition[49].

The current study also found that sex did not interact with disease stage. Although a negative finding, this mirrors a similar study in PD, which also identified that disease stage predicted depression, but sex did not[30]. Given the potential similarities identified across this study and PD regarding patterns of emotional symptoms, the study of these mood processes in HD may have wider significance regarding understanding neurodegeneration and emotion more broadly.

Returning to the main findings, that disease stage predicts depressive symptomatology, the HADS has previously been found to have excellent screening properties for identifying clinical cases of depression in HD when compared with a “gold standard” diagnostic measure of depression[34]. However, in terms of assessing the importance of these

results, our findings for disease stage on general psychological distress, and specifically depression symptomatology, demonstrate a small effect size (accounting for no more than 3%). This finding regarding disease stage contrasts with previous studies that have found no linear relationship between depression and disease stage, with the majority of these previous studies having not controlled for other variables that may be associated with depression and anxiety, such as medication use[12-14]. Therefore, our findings, given the small effect size, may represent a variation in the general trend, but it also presents a relatively robust consideration of the possible influence of disease stage on general psychological distress and depression symptomatology as we have controlled for other variables. Our finding initially suggests that clinicians and researchers may want to pay more attention to disease stage as a potential marker for increased risk of developing depression, as early detection is important to ensure appropriate treatment is offered, as there is some evidence that depression may be undertreated in HD[9], with a view of discovering whether the findings may, or may not be, of clinical relevance, highlighting a change in the patient's clinical status as most important[50].

The findings also provided two considerations of note. First, examination of medication use in our sample found that women were more likely to have used both anxiolytics and antidepressants in the past. However, female participants had a higher current use of anxiolytics only, and not antidepressants. Findings from the PREDICT-HD study, involving predominantly prodromal HD carriers, revealed a sex difference in antidepressant use, with females being more commonly prescribed this medication[49]. Therefore, findings from the current study, involving a majority of those who were motor manifest, may reflect that as the disease progresses more men are subsequently prescribed antidepressant medication. Future studies may wish to consider how prescribing patterns of psychotropic medications, across men and women, change across the disease trajectory. Second, females in

this sample were found to be younger than the males, and had a higher CAG repeat length, yet had similar motor, cognitive and functional abilities. This pattern is not seen generally in HD. Both age and CAG repeat length were controlled for in the regressions analyses.

However, this factor may have influenced the scores in another way, for example, in terms of the females having lived with effects of HD for an apparent shorter period than the men, or the females having a steeper decline in functioning than the males, a suggestion consistent with the findings of Zielonka et al[18] that women with HD tend to progress faster in terms of motor and functional abilities. This might be a consideration for future research.

This study has several limitations. First, the data in this study excluded those who did not wish to participate in REGISTRY and so we cannot fully conclude that these results would be the same for those not engaged in this project. To illustrate, participants who were in stages 3 and 4 at their initial visit may not be representative of this group in general, because they may vary in the amount of help they want or need. As such, medication use and multi-disciplinary input may be higher among those recruited to REGISTRY study sites, compared to those with HD who are not engaged in the research, or may vary in their clinical presentation. Second, the validity of the HADS, though compares well to “gold standard” diagnostic measures of depression and anxiety, has been questioned, especially among participants in the later stages of the disease due to the potential self-awareness deficits, communication difficulties or motor problems influencing scores [34, 51]. An improvement to this study would have been to have used a diagnostic measure of depression and anxiety, though this data was not available in the REGISTRY battery.

In summary we found that disease stage, as measured by the TFC scale, was found to be independently associated with total and depression mean scores on the HADS. However, there was no evidence of an effect of sex, nor interaction between sex and disease stage, on anxiety and depression symptoms in HD. These findings are presented from data gained

from a large European HD sample, and can be considered robust as the study controlled for a number of other variables known to be related to depression and anxiety.

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