Universiteit
Leiden
The Netherlands

Suicidality in Huntington's disease

Hubers, Anna Alida Maria

Citation
Hubers, A. A. M. (2016, January 21). *Suicidality in Huntington's disease*. Retrieved from https://hdl.handle.net/1887/37384

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/37384

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/37384 holds various files of this Leiden University dissertation.

Author: Hubers, Anna Alida Maria (Marloes)
Title: Suicidality in Huntington's disease
Issue Date: 2016-01-21

Chapter 3

Suicidal ideation in a European Huntington's disease population

AAM Hubers, E van Duijn, RAC Roos, D Craufurd, H Rickards, GB Landwehrmeyer, RC van der Mast, EJ Giltay; REGISTRY investigators of the European Huntington's Disease Network

J Affect Disord 2013;151(1):248-258

Abstract

Background: Previous studies indicate increased prevalences of suicidal ideation, suicide attempts, and completed suicide in Huntington's disease (HD) compared with the general population. This study investigates correlates and predictors of suicidal ideation in HD.

Methods: The study cohort consisted of 2106 HD mutation carriers, all participating in the REGISTRY study of the European Huntington's Disease Network. Of the 1937 participants without suicidal ideation at baseline, 945 had one or more follow-up measurements. Participants were assessed for suicidal ideation by the behavioural subscale of the Unified Huntington's Disease Rating Scale (UHDRS). Correlates of suicidal ideation were analysed using logistic regression analysis and predictors were analysed using Cox regression analysis.

Results: At baseline, 169 (8.0%) mutation carriers endorsed suicidal ideation. Disease duration (odds ratio [OR] = 0.96; 95% confidence interval [CI] = 0.9–1.0), anxiety (OR = 2.14; 95% CI = 1.4–3.3), aggression (OR = 2.41; 95% CI = 1.5–3.8), a previous suicide attempt (OR = 3.95; 95% CI = 2.4–6.6), and a depressed mood (OR = 13.71; 95% CI = 6.7–28.0) were independently correlated to suicidal ideation at baseline. The 4-year cumulative incidence of suicidal ideation was 9.9%. Longitudinally, the presence of a depressed mood (hazard ratio [HR] = 2.05; 95% CI = 1.1–4.0) and use of benzodiazepines (HR = 2.44; 95% CI = 1.2–5.0) at baseline were independent predictors of incident suicidal ideation, whereas a previous suicide attempt was not predictive.

Limitations: As suicidal ideation was assessed by only one item, and participants were a selection of all HD mutation carriers, the prevalence of suicidal ideation was likely underestimated.

Conclusions: Suicidal ideation in HD frequently occurs. Assessment of suicidal ideation is a priority in mutation carriers with a depressed mood and in those using benzodiazepines.

Introduction

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disease.[1] The underlying genetic defect is an unstable and expanded CAG repeat on the short arm of chromosome 4, which causes an expanded polyglutamine chain in the huntingtin protein.[2] The disease is characterised by motor abnormalities, cognitive decline, and both behavioural problems and psychiatric disorders. George Huntington first described the tendency to suicide as an important aspect of the disease in 1872.[3] Recent studies have reported that completed suicide rates among HD mutation carriers are four to eight times higher compared with the general population,[4-6] and increased prevalences of suicidal ideation and attempted suicide, of up to 20%, have been reported.[7;8]

Previous cross-sectional studies have shown that both sociodemographic characteristics such as having no offspring[9;10] or being unemployed,[11] and clinical characteristics such as the presence of a depressed mood,[7;8] aggression,[8] or having a psychiatric history[11] are associated with suicidal ideation, suicide attempts, or completed suicide in HD. Some of these studies only included a small number of participants[10] or used data obtained from family members[12]. Also, several of these studies only investigated the effect of undergoing genetic testing on suicide risk,[4;5;11] without investigating correlates or predictors of suicidal ideation during disease progression.

Despite the high suicide risk in HD, only two prospective studies have been carried out.[7;13] One study investigating both suicide attempts and completed suicide in 735 prodromal HD mutation carriers during a median follow-up of 3.5 years, reported presence of depression and a history of suicide attempts as relevant predictors.[13] However, there were only 13 incident events, which limited study power.[13] The other longitudinal study, in which 100 mutation carriers were assessed for both suicidal ideation and suicide attempts, reported 7 participants who developed suicidal ideation or attempted suicide after two years follow-up. This study also found depressed mood as a predictor of suicidal ideation and attempts in HD.[7]

The present study aimed to identify correlates and predictors of suicidal ideation in a large well-monitored European cohort of HD mutation carriers.

Method

Participants

The study cohort consisted of 2106 European HD mutation carriers participating in the REGISTRY study prior to February 2011. Our study included only monitored data of REGISTRY participants who had a Unified Huntington's Disease Rating Scale (UHDRS)[14] behavioural assessment. REGISTRY is a large prospective, observational study of the European Huntington's Disease Network (EHDN) describing the natural course of HD in many European countries.[15] More detailed information can be found at http://www.euro-hd.net/html/registry.

In the study cohort, participants from 15 European countries were included: Austria (n = 58), Belgium (n = 3), Czech Republic (n = 29), Finland (n = 23), France (n = 158), Germany (n = 493), Italy (n = 181), the Netherlands (n = 215), Norway (n = 74), Poland (n = 222), Portugal (n = 65), Spain (n = 160), Sweden (n = 18), Switzerland (n = 21) and the United Kingdom (n = 386). Full ethical approval for REGISTRY was obtained in each of the participating countries and all participants gave written informed consent after the study procedure had been fully explained. The first behavioural assessment according to the behavioural subscale of the Unified Huntington's Disease Rating Scale (UHDRS-b)[14] was taken as baseline visit. Follow-up data from mutation carriers free of suicidal ideation at baseline (n = 1937) were used in the longitudinal analyses. Of these mutation carriers, 992 participants dropped out because they had no follow-up measurements. This resulted in 945 eligible mutation carriers for follow-up assessment (Figure 1).

Instruments

Assessment of suicidal ideation

Suicidal ideation was examined using the UHDRS-b.[14] The behavioural subscale of the UHDRS assesses frequency and severity of 11 neuropsychiatric symptoms.[14] The item 'suicidal thoughts' of the UHDRS-b[14] measures frequency and severity of suicidal thoughts in the month preceding the interview. The frequency score ranges from 0 through 4: a score of 0 indicates suicidal thoughts are never present, a score of 1 indicates seldom presence, a score of 2 indicates suicidal thoughts are sometimes present, a score of 3 indicates frequent presence, and a score of 4 indicates suicidal thoughts are often present. The severity score also ranges from 0 through 4: a score of 0 indicates absence of suicidal ideation, a score of 1 indicates there are no current suicidal thoughts, but the participant considers suicide as a potential option, a score of 2 indicates presence of fleeting suicidal ideation, a score of 3 indicates the participant seriously

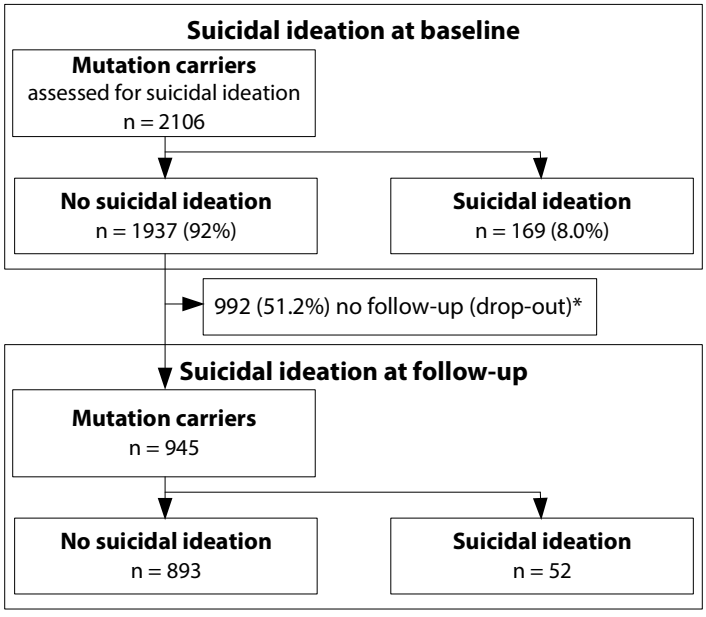


Figure 1. Flowchart of drops-outs.
* drop-outs had a significantly longer estimated duration of disease, lower Total Functioning Capacity (TFC) score and higher Unified Huntington's Disease Rating Scale (UHDRS)-motor score. No significant difference in any of the neuropsychiatric characteristics.

considered suicide but has no plan, and a severity score of 4 indicates the participant has a plan and is actively preparing.[14] The total score was computed by multiplying the frequency and severity scores (range 0–16 points).[8] Based on clinical experience, a total score > 1 point on this item was used to characterise presence of suicidal ideation, meaning that participants scoring a total score of 1 on the 'suicidal ideation' item were not considered to have suicidal ideation, since suicidal ideation is then 'not currently and seldom' present according to the participant or interviewer. When participants had fleeting suicidal thoughts, although 'seldom' (less than once per month), they scored 2 points on the 'suicidal ideation' item, and were considered to have suicidal ideation. This cut-off value also implies that participants that consider suicide as a potential option for the future, and 'seldom' think about this, were not considered to have suicidal ideation.

Assessment of neuropsychiatric characteristics

The presence of depressed mood, anxiety, apathy, irritability, and aggression was also assessed with the UHDRS-b.[14] Total scores for these separate items were computed by multiplying

their severity (range 0–4 points) and frequency (range 0–4 points) scores. Based on clinical experience, a total score > 1 point on such an item was used to characterise presence of that particular neuropsychiatric characteristic.

Assessment of sociodemographic and clinical characteristics

Data on sociodemographic and clinical characteristics were collected using detailed electronic case report forms. Participants were examined by clinicians with longstanding experience in HD.[16]

The estimated disease duration was calculated by the current age minus the estimated age of onset, calculated using the formula of Vassos et al.[17]

Global functioning was assessed with the Total Functioning Capacity (TFC)[14] with scores ranging from 0 through 13 points. Higher scores indicate better global functioning.[18] Disease stage was derived from TFC scores.[19]

A trained neurologist assessed motor functioning according to the motor subscale of the UHDRS (UHDRS-m)[14] with scores ranging from 0 through 124 points. Higher scores indicate worse motor functioning.[14] Mutation carriers were considered motor symptomatic if the total score on the UHDRS-m was > 4 points.

Medication use at baseline was determined based on the provided start and stop dates. If medication use at baseline could not be unequivocally determined, this variable was considered missing.

Statistical analyses

Data are presented as n (%), mean (± SD), or median (interquartile range [IQR]) when appropriate. Characteristics of mutation carriers with and without suicidal ideation were compared by chi-squared tests for categorical data, two-tailed t-tests for independent samples with normal distribution, or non-parametric Whitney-U tests.

The significant univariate cross-sectional correlates were included in a multivariate logistic regression analysis, while forcing sex, age, and country in the model, to yield independent correlates of suicidal ideation. The overall use of psychotropic medication was not included in the multivariate analysis because of overlap with use of the different component kinds of psychotropics.

Mutation carriers free of suicidal ideation at baseline were followed-up until they developed suicidal ideation (incident cases). If participants did not develop suicidal ideation within four years from baseline, they were censored. Incident cases were compared with mutation carriers who did not develop suicidal ideation using univariate Cox regression analysis. The significant univariate longitudinal predictors were included in a multivariate Cox regression analysis, while forcing sex, age, and country in the model, to yield the independent predictors of suicidal ideation. Additional sensitivity analyses were conducted in which missing data were imputed by either 0 or 1. Furthermore, a sensitivity analysis using only a severity score of the UHDRS suicidal ideation item > 1 point to classify participants as having suicidal ideation was carried out. In this way, participants who had no current suicidal thoughts and only considered suicide as a potential option for the future were no longer classified as having suicidal ideation, while all participants with current suicidal ideation were, irrespective of the frequency of those thoughts. A p-value < 0.05 was considered statistically significant. SPSS version 20.0 was used.

Results

The 2106 participants were both male (50.9%) and female (49.1%) with a mean (± SD) age of 50.3 (± 12.4) years. The study population included mostly motor symptomatic (98%) mutation carriers. The mean (± SD) estimated disease duration was 5.7 (± 8.1) years. The study cohort consisted of mutation carriers from all TFC stages: stage 1: n = 701 (33.3%), stage 2: n = 694 (33.0%), stage 3: n = 537 (25.5%), stage 4: n = 148 (7.0%), stage 5: n = 26 (1.2%). Psychotropics were used by 1189 (56.5%) mutation carriers: 740 (35.1%) participants used antidepressants, 709 (33.7%) antipsychotics, 348 (16.5%) benzodiazepines, and 151 (7.2%) mood stabilizers/anti-epileptics (data not shown). At baseline, 169 (8.0%) mutation carriers endorsed suicidal ideation, whereas 1937 (92.0%) did not (Figure 1). The prevalences of suicidal ideation in the three largest participating countries were 6.9% in Germany, 7.5% in the United Kingdom, and 10.4% in Poland (data not shown).

Suicidal ideation at baseline

Mutation carriers with suicidal ideation at baseline had a significantly shorter estimated disease duration and a significantly higher use of psychotropics (specifically antidepressants, benzodiazepines, and mood stabilizers/anti-epileptics) compared with mutation carriers without suicidal ideation. Furthermore, the baseline presence of a depressed mood, anxiety, apathy, irritability, aggression, and also the presence of a suicide attempt in the past were all significantly correlated with suicidal ideation (Table 1).

Table 1. Correlates of suicidal ideation in Huntington's disease mutation carriers at baseline.

	HD mutation carriers without si (n = 1937)	**HD mutation carriers with si** (n = 169)	**p-value**[a]
Sociodemographic characteristics			
Male gender	994 (51.3%)	78 (46.2%)	0.20
Age (years)	50.5 ± 12.4	48.7 ± 11.3	0.08
Clinical characteristics			
CAG repeats (number)	44.6 ± 4.4	44.4 ± 4.2	0.59
Estimated duration of disease (years)	5.9 ± 8.1	3.7 ± 8.0	0.001
TFC score	8.0 (5 – 12)	8.0 (6 – 11)	0.73
UHDRS-motor score	35.3 ± 19.7	33.1 ± 20.4	0.18
Pre-motor symptomatic	38 (2.0%)	6 (3.6%)	0.16
Psychotropic medication			
Any psychotropic medication	1080 (59.0%)	109 (68.1%)	0.03
Antidepressant use	660 (35.6%)	80 (50.0%)	<0.001
Antipsychotic use	645 (34.5%)	64 (38.8%)	0.27
Benzodiazepine use	303 (16.2%)	45 (29.0%)	<0.001
Mood stabilizer/anti-epileptic use	132 (6.9%)	19 (11.4%)	0.03
Tetrabenazine use	96 (5.0%)	10 (6.0%)	0.59
Neuropsychiatric characteristics			
Depressed mood	771 (39.8%)	159 (94.1%)	<0.001
Anxiety	641 (33.1%)	114 (67.5%)	<0.001
Apathy	881 (45.7%)	123 (73.7%)	<0.001
Irritability	775 (40.4%)	105 (63.3%)	<0.001
Aggression	395 (20.5%)	79 (47.0%)	<0.001
Suicide attempt in past	123 (6.4%)	45 (26.6%)	<0.001

Data are presented as n (%), mean (± SD) or median (interquartile range [IQR]) when appropriate. HD denotes Huntington's disease; si, suicidal ideation; TFC, total functional capacity; UHDRS, unified Huntington's disease rating scale. 117 missing values for use of psychotropic medication; 91 missing values for antidepressant use; 72 missing values for antipsychotic use; 81 missing values for benzodiazepine use; 21 missing values for mood stabilizer/anti-epileptic use; 33 missing values for tetrabenazine use; 1 missing value for presence of anxiety; 12 missing values for presence of apathy; 21 missing values for presence of irritability; 12 missing values for presence of aggression.

[a] P-values by chi-square tests for categorical data, by unpaired t-tests for independent samples with normal distribution, or non-parametric Mann–Whitney U test for continuous variables without normal distributions.

Using multivariate analyses, the estimated disease duration (odds ratio [OR] = 0.96; 95% confidence interval [CI] = 0.93-0.99), presence of depressed mood (OR = 13.71; 95% CI = 6.71–28.00), anxiety (OR = 2.14; 95% CI = 1.40–3.26), aggression (OR 2.41; 95% CI = 1.53–3.80), and previous suicide attempt (OR = 3.95; 95% CI = 2.36–6.60) were significant independent correlates of suicidal ideation (Table 2). As 190 cases were excluded from the multivariate

Table 2. Independent correlates of suicidal ideation in Huntington's disease mutation carriers at baseline.

Cross-sectional logistic regression (n = 1916)[a] *(144/1916 had suicidal ideation at baseline)*			
Baseline variable	**Odds Ratio (95% CI)**[b]	**Wald statistic**[b] **df = 1**	**p-value**[b]
Sociodemographic and clinical characteristics			
Male gender	1.16 (0.79 – 1.71)	0.56	0.46
Age (years)	1.02 (0.99 – 1.04)	2.12	0.15
Estimated duration of disease (years)	0.96 (0.93 – 0.99)	6.27	0.01
Psychotropic medication			
Antidepressant use	0.93 (0.62 – 1.40)	0.12	0.73
Benzodiazepine use	1.48 (0.93 – 2.37)	2.67	0.10
Mood stabilizers/anti-epileptic use	1.18 (0.64 – 2.18)	0.27	0.60
Neuropsychiatric characteristics			
Depressed mood	13.71 (6.71 – 28.00)	51.55	<0.001
Anxiety	2.14 (1.40 – 3.26)	12.54	<0.001
Apathy	1.42 (0.92 – 2.20)	2.47	0.12
Irritability	0.87 (0.55 – 1.37)	0.39	0.53
Aggression	2.41 (1.53 – 3.80)	14.43	<0.001
Suicide attempt in past	3.95 (2.36 – 6.60)	27.51	<0.001

Covariates cross-sectional analysis (enter model): all variables with p-value ≤ 0.05 in the univariate analysis were entered (estimated duration of disease, use of antidepressants, use of benzodiazepines, use of mood stabilizers/anti-epileptics, presence of depressed mood, presence of anxiety, presence of apathy, presence of irritability, presence of aggression, and suicide attempt in the past) and sex, age, and country were forced into the model.

[a] 190 cases excluded due to missing values.

[b] Odds ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom (df), and p-value by binary logistic regression.

analysis due to missing data, two additional sensitivity analyses were conducted in which missing data were imputed by either 0 or 1. Both of these sensitivity analyses yielded similar results, with comparable odds ratios for all correlates (data not shown).

To see whether correlates of suicidal ideation remained the same when only using the severity score of the 'suicidal ideation' item of the UHDRS-b, we carried out a multinomial regression analysis, comparing mutation carriers with a severity score of 0 on the suicidal ideation item to mutation carriers with a severity score of 1 and to mutation carriers with a severity score > 1. This sensitivity analysis confirmed most of the previous results, with higher or comparable odds ratios in the group mutation carriers with a severity score > 1 for all neuropsychiatric correlates and increasing odds ratios as the severity score rose. Only the estimated disease duration became a weaker correlate (data not shown).

Suicidal ideation at follow-up

Of the 1937 mutation carriers free of suicidal ideation at baseline, 945 were followed up for a median (IQR) period of 2.0 (1.1–3.0) years. The 992 drop-outs, had a significantly longer estimated disease duration ($p = 0.040$), lower TFC score ($p < 0.001$), and higher UHDRS-m score ($p < 0.001$). When comparing neuropsychiatric characteristics, the drop-outs did not differ significantly from the participants that were included in the follow-up analyses (data not shown).

After four years of follow-up 9.9% of the mutation carriers had developed suicidal thoughts. These mutation carriers had significantly higher hazard ratios for the use of benzodiazepines and mood stabilizers/anti-epileptics at baseline. Also, they had significantly higher hazard ratios for the presence of a depressed mood, anxiety, and apathy at baseline (Table 3).

Using multivariate Cox regression analysis, the use of benzodiazepines at baseline (hazard ratio [HR] = 2.44; 95% CI = 1.20–4.97) and the presence of a depressed mood at baseline (HR = 2.05; 95% CI = 1.06–3.96) were independent predictors of suicidal ideation at follow-up (Table 4 and Figure 2). As 57 cases were excluded from the multivariate Cox regression analysis due to missing data, again two additional sensitivity analyses were conducted imputing either 0 or 1 for the missing data. These sensitivity analyses confirmed our results, with comparable hazard ratios for all predictors (data not shown).

To see whether predictors of suicidal ideation remained the same when only using the severity score of the 'suicidal ideation' item of the UHDRS-b, we carried out a multivariate Cox regression analysis comparing mutation carriers with a severity score < 1 on the suicidal ideation item to

Table 3. Predictors of suicidal ideation at follow-up in Huntington's disease mutation carriers.

Univariate Cox regression (n = 942)[a] *(52/942 had suicidal ideation at follow-up)*			
Baseline variable	**Hazard Ratio (95% CI)[b]**	**Wald statistic[b] df = 1**	**p-value[b]**
Sociodemographic characteristics			
Male gender	0.91 (0.53 – 1.57)	0.11	0.74
Age (years)	1.00 (0.98 – 1.02)	0.01	0.95
Clinical characteristics			
CAG repeats (number)	0.98 (0.92 – 1.05)	0.25	0.62
Estimated duration of disease (years)	0.99 (0.96 – 1.03)	0.25	0.62
TFC score (points)	0.99 (0.91 – 1.07)	0.10	0.76
UHDRS-motor score (points)	1.00 (0.98 – 1.01)	0.08	0.78
Pre-motor symptomatic	1.78 (0.55 – 5.72)	0.94	0.33
Psychotropic medication			
Antidepressant use	1.72 (0.98 – 3.02)	3.59	0.06
Antipsychotic use	1.69 (0.95 – 3.01)	3.16	0.08
Benzodiazepine use	2.78 (1.48 – 5.22)	10.14	0.001
Mood stabilizer/anti-epileptic use	2.80 (1.36 – 5.76)	7.85	0.005
Tetrabenazine use	2.43 (0.59 – 10.03)	1.50	0.22
Neuropsychiatric characteristics			
Depressed mood	2.73 (1.57 – 4.76)	12.58	<0.001
Anxiety	1.99 (1.15 – 3.42)	6.11	0.01
Apathy	2.27 (1.30 – 3.96)	8.22	0.004
Irritability	1.48 (0.86 – 2.55)	1.99	0.16
Aggression	1.58 (0.85 – 2.92)	2.10	0.15
Suicide attempt in past	2.32 (0.92 – 5.84)	3.19	0.07

TFC denotes total functional capacity; UHDRS, unified Huntington's disease rating scale. 49 missing values for antidepressant use; 39 missing values for antipsychotic use; 44 missing values for benzodiazepine use; 12 missing values for mood stabilizer/anti-epileptic use; 26 missing values for tetrabenazine use; 1 missing value for presence of anxiety; 8 missing values for presence of apathy; 5 missing values for presence of irritability; 9 missing values for presence of aggression.

[a] Three cases were censored before the earliest event in the stratum.

[b] Hazard ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom (df), and p-value by univariate Cox regression analysis.

mutation carriers with a severity score > 1. This sensitivity analysis mostly confirmed previous results, with a comparable hazard ratio for the predictor depressed mood. Although the hazard ratio for benzodiazepine use decreased, it remained > 2 (data not shown).

Table 4. Independent predictors of suicidal ideation at follow-up in Huntington's disease mutation carriers.

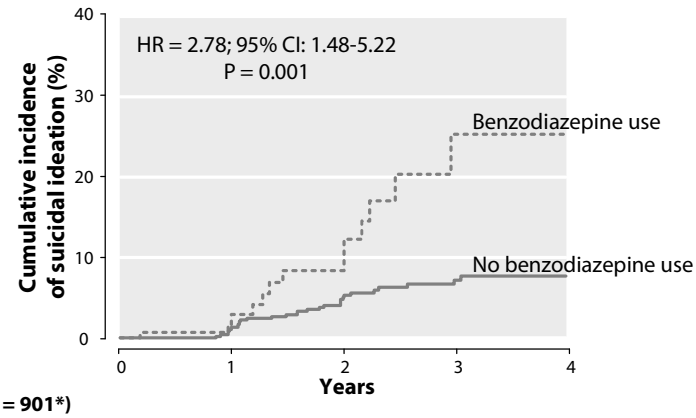
Multivariate Cox regression (n = 885)[a] *(47/885 had suicidal ideation at follow-up)*			
Baseline variable	**Hazard Ratio (95% CI)[b]**	**Wald statistic[b] df = 1**	**p-value[b]**
Sociodemographic characteristics			
Male gender	1.03 (0.57 – 1.84)	0.01	0.94
Age (years)	1.00 (0.97 – 1.02)	0.12	0.73
Psychotropic medication			
Benzodiazepine use	2.44 (1.20 – 4.97)	6.00	0.01
Mood stabilizer/anti-epileptic use	1.96 (0.88 – 4.35)	2.71	0.10
Neuropsychiatric characteristics			
Depressed mood	2.05 (1.06 – 3.96)	4.50	0.03
Anxiety	0.97 (0.50 – 1.88)	0.01	0.93
Apathy	1.67 (0.87 – 3.20)	2.35	0.13

Covariates Cox regression analysis (enter model): all variables with p-value ≤ 0.05 in the univariate Cox regression analysis were entered (use of benzodiazepines, use of mood stabilizers/anti-epileptics, presence of depressed mood, presence of anxiety, and presence of apathy) and sex, age, and country were forced into the model.
[a] Three cases were censored before the earliest event in the stratum and there were 57 cases excluded due to missing values.
[b] Hazard ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom (df), and p-value by multivariate Cox regression analysis.

A **Suicidal ideation at follow-up according to baseline depressed mood**

No. at Risk (n = 945)					
Depressed mood	359	289	152	59	29
No depressed mood	586	495	288	164	76

B **Suicidal ideation at follow-up according to baseline benzodiazepine use**



No. at Risk (n = 901*)					
Benzodiazepine use	152	124	51	14	6
No benzodiazepine use	749	620	364	193	90

*: 44 missings due to unknown benzodiazepine use

Figure 2.
Hazard ratio (HR), 95% confidence interval (CI), and p-value by univariate Cox regression analysis. Kaplan–Meier curves showing cumulativef incidence of suicidal ideation according to baseline presence of a depressed mood (Box A) and baseline benzodiazepine use (Box B).

Discussion

The results of this study demonstrate that mutation carriers with suicidal ideation at baseline, more often had a depressed mood, were more often anxious and aggressive, more often attempted suicide in the past, and had a shorter estimated disease duration compared with mutation carriers free of suicidal ideation. Longitudinally, a depressed mood and use of benzodiazepines at baseline predicted suicidal ideation at follow-up.

The presence of a depressed mood was the most important correlate and predictor of suicidal ideation. This association was previously found among both pre-motor and motor symptomatic HD mutation carriers.[7] Besides depressed mood, we also found an association between the presence of anxiety and suicidal ideation. In a previous study, the depression/anxiety factor of the UHDRS-b was found to be a correlate of suicidal ideation in HD.[8] Longitudinally, these results were confirmed as presence of depressed mood at baseline predicted suicidal ideation at follow-up, in line with two previous longitudinal studies, which reported depressed mood as a predictor of suicidal thoughts[7] and attempts.[7;13]

Moreover, aggression and a suicide attempt in the past were correlates of suicidal ideation. A previous multi-site study also found aggression as a correlate of suicidal ideation in HD.[8] Although a previous suicide attempt did not independently predict suicidal ideation at follow-up in our study, it was previously found as a predictor of suicide attempts among prodromal HD mutation carriers[13] and it is one of the strongest risk factors for completed suicide in the general population.[20] Although attempted suicide is a well-established risk factor for completed suicide, it is debatable whether or not suicidal ideation itself is a risk factor for completed suicide.[21] Therefore, future studies need to investigate and describe trajectories of suicidality in HD, and determine whether and to what extend suicidal ideation is a clinically relevant predictor of completed suicide.

Furthermore, a shorter estimated disease duration was correlated to suicidal ideation. Several authors have previously suggested that completed suicide occurs more frequently in the early stages of HD.[4;6;10;12] One study described two critical periods of suicidal ideation in HD: one when at-risk persons start to experience the first symptoms of HD, and one when patients become more dependent on others for daily functioning.[22] Both critical periods are in a relatively early course of the disease.

The use of benzodiazepines at baseline also predicted suicidal ideation at follow-up. It is known among patients with other disorders that use of benzodiazepines may lead to a

paradoxical reaction with behavioural disinhibition, especially in those with impulse control problems and pre-existing neurological disorders.[23] Since HD mutation carriers often have difficulty with impulse control already as result of disruption of frontal-subcortical circuitry,[8;24] they may indeed be at higher risk for paradoxical reactions to benzodiazepine use. Previous studies in other populations did not only show an association between impulsivity and suicidal behaviour,[25;26] but also suggested that benzodiazepine use may be associated with attempted suicide.[27;28] In our predictive study, there was no information regarding impulsivity and attempted and completed suicide during the study period, and we did not investigate which participants still used benzodiazepines at follow-up. Therefore, future research on the relationship between benzodiazepine use, impulsivity, and suicidality is necessary. Furthermore, the relationship between benzodiazepine use and suicidal ideation might be due to confounding by indication, as benzodiazepines are prescribed mainly to patients with symptoms of anxiety, which was a correlate of suicidal ideation in this study, and irritability and insomnia, which were correlates of suicidal ideation in other populations.[29;30] Also other unmeasured neuropsychiatric characteristics, like personality traits or coping styles, could be the reason for both more prevalent suicidal ideation and the use of benzodiazepines. Confounding by indication was considered the most likely explanation in a previous study that reported an association between benzodiazepine use and suicide attempts.[27]

Although there was variance in suicidal ideation prevalences among countries, baseline suicidal ideation prevalences in the three largest participating countries (Germany, United Kingdom, and Poland) were around 8.0%. It is unclear whether the variance between other countries corresponded to true differences or whether this may be explained by measurement error (country-specific over- and underestimation of the true prevalences), as assessment and expression of suicidal ideation between countries might differ depending on the cultural context and professional traditions. Since the distribution of prevalence numbers did not correspond with the distribution of prevalence numbers in the general populations of the different European countries,[31] our analyses focused on correlates and predictors of suicidal ideation irrespective of the country. It is reasonable to assume that correlates and predictors found in this study generalise to the entire European HD population, since previous research showed consistent risk factors in European countries despite important variation in country prevalences.[31]

The strength of this European cohort study is the large size and the high quality of monitored data, the use of structured electronic case report forms, the annual training of the study site raters, and the combination of cross-sectional and longitudinal analyses.

This study has several limitations that warrant discussion. Our prevalence of 8.0% is much lower than a recent study that found a prevalence of 20%.[7] However, in this study, assessment of suicidal ideation was done by psychiatrists through a detailed psychopathology interview.[7] A prevalence of 19% has been found using the UHDRS-b, but this study also categorised participants with a total score of 1 point as suicidal.[8] Another study using the severity score of the 'suicidal thoughts' item of the UHDRS-b to assess participants for suicidal ideation reported a prevalence of 17.5%.[22] However, when all mildly suicidal participants (severity score of 1) were excluded, the prevalence dropped to 10.3%,[22] which is much more in accordance with the prevalence found in our study. Although the suicidal ideation prevalence found in our study is lower than reported in previous studies, a suicidal ideation one-month prevalence of 8.0% among HD mutation carriers is still much higher compared with the one-month prevalence of 0.0% recently found among non-HD controls[7] and the twelve-month prevalence of 2.0% in the general population.[32] The lower prevalence found in our study compared with previous HD studies may be explained by the design of REGISTRY, which measured a lot of motor and cognitive symptoms, while the assessment of neuropsychiatric symptoms is rather sparse. A detailed and extensive psychopathology interview is probably more sensitive to detect suicidal ideation in HD, as was previously recommended by the authors of a multi-site HD study.[8] Additionally, psychiatrists may be better trained than neurologists in detecting subtle suicidal thoughts, as assessing suicidality is an important part of their psychiatric training. Furthermore, a selection of HD mutation carriers who were stable enough at the time of enrolment and subsequent follow-up visits participated in this study. HD patients attending REGISTRY clinics might be less disturbed and better treated; and, there was a substantial number of drop-outs, which may have caused attrition bias. This may have resulted in limited generalizability of the prevalence and incidence found in this study, as it probably is an underestimation of the prevalence and incidence in the general HD population. Another important limitation of this study is that only one item of the UDHRS-b was used to assess suicidal ideation. Finally, only predictors of suicidal ideation could emerge from this observational study and we cannot conclude whether these are causal relationships.

Because of the high prevalence of suicidal ideation in HD, it is important to regularly screen mutation carriers for the presence of suicidal ideation. In depressed HD mutation carriers assessment of suicidal ideation is a priority, especially since depressed mood is a potential treatable risk factor. Furthermore, clinicians should be aware when mutation carriers are using benzodiazepines, since use of benzodiazepines predicted suicidal ideation at follow-up.

Acknowledgments

The authors thank the NIHR Biomedical Research Centre in Manchester.

List of collaborators

Registry Steering committee: AC Bachoud-Lévi; AR Bentivoglio; I Biunno; RM Bonelli; JM Burgunder; SB Dunnett; JJ Ferreira; OJ Handley; A Heiberg; T Illmann; GB Landwehrmeyer; J Levey; Maria A. Ramos-Arroyo; JE Nielsen; S Pro Koivisto; M Päivärinta; RAC Roos; A Rojo Sebastián; SJ Tabrizi; W Vandenberghe; C VerellenDumoulin; J Zaremba; T Uhrova; J Wahlström.

Language coordinators: Katrin Barth; Leonor Correia-Guedes; Ana Maria Finisterra; Monica Bascuñana Garde; Reineke Bos; Sabrina Betz; Jenny Callaghan; Ruth Fullam; Daniel Ecker; Mette Gilling Nielsen; Olivia J Handley; Carina Hvalstedt; Christine Held; Kerstin Koppers; Matilde Laurà; Saul Martinez Horta; Asunción Martínez Descals; Tiago Mestre; Sara Minster; Daniela Monza; Lisanne Mütze; Martin Oehmen; Jenny Townhill; Michael Orth; Helene Padieu; Laurent Paterski; Nadia Peppa; Susana Pro Koivisto; Verena Roedig; Amandine Rialland; Niini Røren (formerly Heinonen); Pavla Šašinková; Yury Seliverstov; Patricia Trigo Cubillo; Marleen R van Walsem; Abigail Wright; Wildson Vieira da Silva; Marie-Noelle Witjes-Ané; Elizaveta Yudina; Daniel Zielonka; Eugeniusz Zielonka; Paola Zinzi

Austria
Graz (LKH Graz, Abteilung für Psychiatrie): Raphael M. Bonelli; Brigitte Herranhof; Anna Holl (formerly Hödl); Hans-Peter Kapfhammer; Michael Koppitz; Markus Magnet; Daniela Otti; Annamaria Painold; Karin Reisinger; Monika Scheibl; Karen Hecht; Sabine Lilek; Nicole Müller; Helmut Schöggl; Jasmin Ullah. Innsbruck (Universitätsklinik Innsbruck, Neurologie): Florian Brugger; Caroline Hepperger; Anna Hotter; Klaus Seppi; Gregor Wenning; Lisa Buratti; Eva-Maria Hametner; Christiane Holas; Eva-Maria Hametner; Anna Hussl; Werner Poewe; Eva-Maria Braunwarth; Fabienne Sprenger; Christoph Müller. Salzburg (Christian-Doppler-Klinik Salzburg, Universitätsklinikum der PMU, Universitätsklinik für Neurologie): Stefan Lilek; Daniela Sinadinosa; Anna Maria Walleczek; Raphael M. Bonelli; Gunther Ladurner; Wolfgang Staffen.

Belgium
Brussels (VUB Neurology): Anja Flamez; V Morez; Sylvie de Raedt. Leuven (Universitair Ziekenhuis Gasthuisberg,): Andrea Boogaerts; Wim Vandenberghe; Dimphna van Reijen.

Czech republic
Prague (Extrapyramidové centrum, Neurologická klinika, 1. LF UK a VFN): Jiří Klempíř; Veronika Majerová; Jan Roth.

Finland
Kuopio (Kuopion Yliopistollinen sairaala): Päivi Hartikainen. Turku-Suvituuli (Rehabilitation Centre Suvituuli): Heli Hiivola; Kirsti Martikainen; Katri Tuuha. Oulu (Dep. of Neurology): Jaakko Ignatius; Mikko Kärppä; Jaana Åman. Oulu (Dep. of Medicak Genetics): Aki Mustonen; Outi Kajula. Tampere (Terveystalo Healthcare Service Centre): Maire Santala.

France
Angers (Centre de référence des maladies neurogénétiqueCHU d'Angers): Philippe Allain; Marie-Anne Guérid; Bénédicte Gohier; Audrey Olivier; Adriana Prundean; Clarisse SchererGagou; Christophe Verny; Marie Bost.

Bordeaux (Hôpital Pellegrin): Blandine Babiloni; Sabrina Debruxelles; Charlotte Duché; Cyril Goizet; Danielle Lafoucrière; Laetitia Jameau; Umberto Spampinato. Lille (CHRU Roger Salengro): Christelle De Bruycker; Maryline Cabaret; Anne-Sophie Carette; Luc Defebvre; Eric Decorte; Arnaud Delval; Marie Delliaux; Alain Destee; Kathy Dujardin; Mireille Peter; Lucie Plomhouse; Bernard Sablonnière; Clémence Simonin; Luc Defebvre; Marie-Hélène Lemaire; Sylvie Manouvrier; Stéphanie Thibault-Tanchou; Isabelle Vuillaume. Amiens (CHU Nord): Pierre Krystkowiak; Cécile Duru; Martine Roussel; Sandrine Wannepain; Hassan Berrissoul; Marcellin Bellonet; Françoise Courtin; Béatrice Mantaux; Véronique Fasquel; Olivier Godefroy. Marseille (Hôpital La Timone): Jean-Philippe Azulay; Frédérique Fluchère; Marie Delfini; Alexandre Eusebio; Laura Mundler. Strasbourg (Hôpital Civil): Nadine Longato; Gabrielle Rudolf; Gisèle Steinmetz; Christine Tranchant; Caroline Wagner; MarieAgathe Zimmermann; Christophe Marcel. Toulouse (Hôpital Purpan/ Centre d'Investigation Clinique): Fabienne Calvas; Jérémie Pariente; Jean-François Démonet; Samia Cheriet.

Germany

Aachen (Universitätsklinikum Aachen, Neurologische Klinik): Christoph Michael Kosinski; Eva Milkereit; Daniela Probst; Kathrin Reetz; Christian Sass; Johannes Schiefer; Christiane Schlangen; Cornelius J. Werner. Berlin (Klinik und Poliklinik für Neurologie - Charité - Universitätsmedizin Berlin): Harald Gelderblom; Josef Priller; Harald Prüß; Eike Jakob Spruth. Bochum (Huntington-Zentrum (NRW) Bochum im St. JosefHospital): Jürgen Andrich; Gisa Ellrichmann; Rainer Hoffmann; Barbara Kaminski; Carsten Saft; Christiane Stamm. Dinslaken (Reha Zentrum in Dinslaken im Gesundheitszentrums Lang): Herwig Lange. Dresden (Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Neurologie): Cecile Bosredon; Antonia Maass; Simone Schmidt; Alexander Storch; Martin Wolz. Erlangen (Universitätsklinikum Erlangen, Abteilung für Molekulare Neurologie): Zacharias Kohl; Jürgen Winkler. Freiburg (Universitätsklinik Freiburg, Neurologie): Philipp Capetian; Johann Lambeck; Birgit Zucker. Hamburg (Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Neurologie): Kai Boelmans; Christos Ganos; Ines Goerendt; Ute Hidding; Jan Lewerenz; Alexander Münchau; Michael Orth; Jenny Schmalfeld; Lars Stubbe; Simone Zittel. Hannover (Neurologische Klinik mit Klinischer Neurophysiologie, Medizinische Hochschule Hannover): Gabriele Diercks; Dirk Dressler, Heike Gorzolla; Christoph Schrader; Pawel Tacik. Heiligenhafen (Psychatrium Heiligenhafen): Walburgis Heinicke. Marburg KPP (Klinik für Psychiatrie und Psychotherapie Marburg-Süd): Bernhard Longinus. Marburg Uni (Universität Marburg, Neurologie): Kathrin Bürk; Jens Carsten Möller; Ida Rissling. München (Huntington-Ambulanz im Neuro-Kopfzentrum - Klinikum rechts der Isar der Neurologischen Klinik und Poliklinik der Technischen Universität München): Mark Mühlau; Alexander Peinemann; Michael Städtler; Adolf Weindl; Juliane Winkelmann; Cornelia Ziegler. Münster (Universitätsklinikum Münster, Klinik und Poliklinik für Neurologie): Stefan Bohlen; Eva Hölzner; Herwig Lange; Ralf Reilmann; Christian Sass. Taufkirchen (Isar-Amper-Klinikum - Klinik Taufkirchen (Vils)): Matthias Dose; Gabriele Leythaeuser; Ralf Marquard; Tina Raab; Caroline Schrenk; Michele Schuierer. Ulm (Universitätsklinikum Ulm, Neurologie): Katrin Barth; Andrea Buck; Julia Connemann; Daniel Ecker; Carolin Eschenbach; Christine Held; Bernhard Landwehrmeyer; Franziska Lezius; Solveig Nepper; Anke Niess; Michael Orth; Daniela Schwenk; Sigurd Süßmuth; Sonja Trautmann; Patrick Weydt.

Italy

Bari (Clinica Neurologica - Neurophysiopatology of Pain Unit UNIVERSITA' DI BARI): Claudia Cormio; Vittorio Sciruicchio; Claudia Serpino; Marina de Tommaso. Bologna (Dipartimento di Scienze Neurologiche - Clinica Neurologica, Università di Bologna): Sabina Capellari; Pietro Cortelli; Roberto Gallassi; Roberto Poda; Giovanni Rizzo; Cesa Scaglione. Florence (Dipartimento di Scienze Neurologiche e Psichiatriche Universita' degli Studi di Firenze-Azienda Ospedaliera Universitaria Careggi): Elisabetta Bertini; Elena Ghelli; Andrea Ginestroni; Francesca Massaro; Claudia Mechi; Marco Paganini; Silvia Piacentini; Silvia Pradella; Anna Maria Romoli; Sandro Sorbi. Genoa (Dipartimento di Neuroscienze, Oftalmologia e Genetica (DiNOG)Università di Genova): Giovanni Abbruzzese; Monica Bandettini di Poggio; Emilio Di Maria; Giovanna Ferrandes; Paola Mandich; Roberta Marchese. Milan (Fondazione IRCCS Istituto Neurologico Carlo Besta): Alberto Albanese; Daniela Di Bella; Stefano Di Donato; Cinzia Gellera; Silvia Genitrini; Caterina Mariotti; Daniela Monza; Lorenzo Nanetti; Dominga Paridi; Paola Soliveri; Chiara Tomasello. Naples (Dipartimento di Scienze Neurologiche, Università di Napoli Federico II): Giuseppe De Michele; Luigi Di Maio; Elena Salvatore; Carlo Rinaldi; Fabiana Rossi; Marco Massarelli; Alessandro Roca; Sarah Ammendola; Cinzia Valeria Russo. Pozzilli (IS) (Centro di Neurogenetica e Malattie Rare IRCCS Neuromed):

Ferdinando Squitieri; Francesca Elifani; Vittorio Maglione; Alba Di Pardo; Silvia Alberti; Annamaria Griguoli; Enrico Amico; Tiziana Martino; and (Istituto Leonarda Vaccari Rome): Martina Petrollini. Rome (Istituto di Neurobiologia e Medicina Molecolare & Istituto di Scienze e Tecnologie della Cognizione /CNR; Istituto di Neurologia Università Cattolica del Sacro Cuore): Anna Rita Bentivoglio; Claudio Catalli; Raffaella Di Giacopo; Alfonso Fasano; Marina Frontali; Arianna Guidubaldi; Tamara Ialongo; Gioia Jacopini; Giovanna Loria; Carla Piano; Piccininni Chiara; Davide Quaranta; Silvia Romano; Francesco Soleti; Maria Spadaro; Paola Zinzi.

Netherlands
Enschede (Medisch Spectrum Twente): Monique S.E. van Hout; Jeroen P.P. van Vugt; A. Marit de Weert. Groningen (Polikliniek Neurologie): J.J.W. Bolwijn; M. Dekker; K.L. Leenders; HPH Kremer. Leiden (Leiden University Medical Centre (LUMC)): Reineke Bos; Eve M. Dumas; Simon J. A. van den Bogaard; Raymund A.C. Roos; Ellen P. 't Hart; Erik van Duijn.

Norway
Bergen (Haukeland University Hospital): Ellen Økland Blinkenberg. (NKS Olaviken's HD clinic): Erik Hauge; Hilde Tyvoll. Oslo University Hospital (Rikshospitalet, Dept. of Medical Genetics and Dep. of Neurology): Arvid Heiberg; Marleen R van Walsem; Jan Frich; Olaf Aaserud; Raghild Wehus. Oslo University Hospital (Ulleval, Dept of Medical Genetics): Kathrine Bjørgo; Madeleine Fannemel; Per Gørvell; Eirin Lorentzen; Susana Pro Koivisto; Lars Retterstøl; Torborg Overland; Bodil Stokke. Trondheim (St. Olavs Hospital): Inga Bjørnevoll; Sigrid Botne Sando

Poland
Gdansk (St. Adalbert Hospital, Gdansk; Medical University of Gdansk, Neurological and Psychiatric Nursing Dpt.): Artur Dziadkiewicz; Malgorzata Nowak; Piotr Robowski; Emilia Sitek; Jaroslaw Slawek; Witold Soltan; Michal Szinwelski. Katowice (Medical University of Silesia, Katowice): Magdalena Blaszcyk; Magdalena Boczarska-Jedynak; Ewelina Ciach-Wysocka; Agnieszka Gorzkowska; Barbara Jasinska-Myga; Gregorz Opala; Gabriela Kłodowska–Duda; Daniel Stompel. Krakow (Krakowska Akademia Neurologii): Krzysztof Banaszkiewicz; Dorota Boćwińska; Andrzej Szczudlik; Monika Rudzińska; Magdalena Wójcik; Małgorzata Dec; Malgorzata Krawczyk; Kamila Bojakowska-Jaremek; Elżbieta Szczygieł; Agata Stenwak; Anna Wasielewska. Poznan (Poznan University of Medical Sciences, Poland): Anna Bryl; Anna Ciesielska; Aneta Klimberg; Jerzy Marcinkowski; Justyna Sempołowicz; Daniel Zielonka; Husam Samara; Bartłomiej Wiśniewski. Warsaw-MU (Medical University of Warsaw, Neurology): Piotr Janik; Anna Gogol (formerly Kalbarczyk); Hubert Kwiecinski; Zygmunt Jamrozik; Anna Kaminska. Warsaw-IPiN (Institute of Psychiatry and Neurology Dep. of Genetics, First Dep. of Neurology): Jakub Antczak; Katarzyna Jachinska; Maryla Rakowicz; Przemyslaw Richter; Rafal Rola; Danuta Ryglewicz; Halina Sienkiewicz-Jarosz; Iwona Stępniak; Grzegorz Witkowski; Elzbieta Zdzienicka; Jacek Zaremba; Anna Sułek; Wioletta Krysa; Iwona Stępniak; Karolina ZieoraJakutowicz.

Portugal
Coimbra–(Hospital Universitário de Coimbra): Filipa Júlio; Cristina Januário. Lisbon- (Hospital de Santa Maria; Neurological Clinical Research Unit, Instituto de Medicina Molecular): Tiago Mestre; Leonor Correia-Guedes; Miguel Coelho; Tiago Mendes; Anabela Valadas; Joaquim J Ferreira. Lisbon- (Hospital Fernando da Fonseca): Ângela Timóteo; Cristina Costa. Porto- (Hospital Santo António- Centro Hospitalar do Porto): Sara Cavaco; Joana Damásio; Rui Loureiro; Marina Magalhães. Porto- (Centro Hospitalar de São João, Faculdade de Medicina da Universidade do Porto): Carlos Andrade; Miguel Gago; Carolina Garrett; Maria Rosália Guerra; Joana Lima; João Massano; Joana Meireles.

Spain
Badajoz (Hospital Infanta Cristina): Carmen Durán Herrera; Patrocinio Moreno Garcia. Granada (Hospital Universitario San Cecilio, Neurología): Francisco Barrero; Blas Morales. Burgos (Servicio de Neurología Hospital General Yagüe): Esther Cubo; Natividad Mariscal; Jesús Sánchez. Fuenlabrada (Hospital Universitario de Fuenlabrada): Fernando Alonso-Frech; Maria Rabasa Perez. Madrid-Clinico (Hospital Clínico Universitario San Carlos): María Fenollar; Rocío García-Ramos García; Purificacion Pin Quiroga; Susana Vázquez Rivera; Clara

Villanueva. Madrid RYC (Hospital Ramón y Cajal, Neurología): Javier Alegre; Mónica Bascuñana; Juan Garcia Caldentey; Marta Fatás Ventura; Guillermo García Ribas; Justo García de Yébenes; José Luis López– Sendón Moreno; Patricia Trigo Cubillo. Madrid FJD (Madrid-Fundación Jiménez Díaz): Pedro J García Ruíz; Asunción Martínez-Descals; María José Saiz Artiga; Vicenta Sánchez; Rosa Guerrero; Antonio Herranz Bárcenas. Murcia (Hospital Universitario Virgen de la Arrixaca): María Fuensanta Noguera Perea; Lorenza Fortuna; María Martirio Antequera Torres; Gema Reinante; Laura Vivancos Moreau. Barcelona-Hospital Mútua de Terrassa: Miquel Aguilar Barbera; Dolors Badenes Guia; Laura Casas Hernanz; Judit López Catena; Ana Rojo Sebastián; Pilar Quiléz Ferrer; Gemma Tome Carruesco. Barcelona-Bellvitge (Hospital Universitari de Bellvitge): Jordi Bas; Núria Busquets; Matilde Calopa. Barcelona-Merced (Hospital Mare de Deu de La Merced): Marina Dalmau Elorza; Cristóbal Díez-Aja López; Santiago Durán-Sindreu Terol; Misericordia Floriach Robert; Belén Garzón Ruíz; Ana González Casado; Isabel Haro Martínez; Celia Mareca Viladrich; Regina Pons i Càrdenas; Elvira Roca; Joan Roig Llesoy; Jesús Miguel Ruiz Idiago; Mar Ruíz Vergara; Socorro Soriano García; Antonio Villa Riballo. Oviedo (Hospital Central de Asturias): Sonia González González; Luis Menéndez Guisasola; Carlos Salvador; Esther Suaréz San Martín. Palma (Hospital Son Dureta): Mónica González; Aranzazú Gorospe; Inés Legarda; Penelope Navas Arques; María José Torres Rodríguez; Barbara Vives. Pamplona (Complejo Hospitalario de Navarra): Itziar Gaston; Maria A. Ramos-Arroyo; Maria Dolores Martinez-Jaurrieta. Sevilla ("Hospital Universitario Virgen Macarena"): Jose Manuel Garcia Moreno; José Chacón Peña; Luminita Dinca Avarvarei; Antonio Martín Bastida; Maria Fernández Recio; Luis Redondo Vergé; Violeta Sánchez Sánchez. Sevilla (Hospital Universitario Virgen del Rocío): Fátima Carrillo; María Teresa Cáceres; Pablo Mir; María José Lama Suarez. Valencia (Hospital la Fe): Maria Bosca; Juan Andres Burguera; Anabel Campos Garcia; Francisco Casterá Brugada. Zaragoza (Hospital Clinico Universitario "Lozano Blesa" de Zaragoza): Laura Martinez Martínez; Javier López del Val.

Sweden

Umeå (Umeå University Hospital): Ghada Loutfi; Carina Olofsson; Eva-Lena Stattin; Laila Westman; Birgitta Wikström. Stockholm (Karolinska University Hospital): Sven E P lhagen; Martin Paucar; Per Svenningsson; Tina Walldén RezaSoltani; Arja Höglund; Britta Sandström. Göteborg (Sahlgrenska University Hospital): Jan Wahlström; Ulrika Høsterey-Ugander; Gunnel Fredlund; Radu Constantinescu; Liselotte Neleborn-Lingefjärd. Stockholm (NeuroHealth Consulting Sweden HB): Joakim Tedroff; Mona Esmaeilzadeh; Elisabeth Winnberg. (Karolinska Univeristy Hospital): Sven Pålhagen; Per Svennigsson; Martin Paucar; Tina Waldèn Riza-Soltani. Uppsala (Uppsala University Hospital): Jimmy Sundblom; Anders Johansson; Leif Wiklund; Camilla Ekwall; Marie-Louise Göller. Lund (Lund University and Skne University Hospital, dept neurology): Asa Petersén; Jan Reimer; Hkan Widner.

Switzerland

Bern: Jean-Marc Burgunder; Yanik Stebler (Swiss HD Zentrum); Alain Kaelin; Irene Romero; Michael Schüpbach; Sabine Weber Zaugg (Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern).

United Kingdom

Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen): Zosia Miedzybrodzka; Daniela Rae; Lorna Downie; Sheila Simpson; Fiona Summers; Alexandra Ure; Roisin Jack; Kirsty Matheson. Birmingham (The Barberry Centre, Dept of Psychiatry): Shahbana Akhtar; Jenny Crooks; Adrienne Curtis; Jenny de Souza (Keylock); Hugh Rickards; Jan Wright. Bristol (Frenchay Hospital): Beverley Hayward; Kasia Sieradzan; Abigail Wright. Cambridge (Cambridge Centre for Brain Repair, Forvie Site): Roger A. Barker; Deidre O'Keefe; Anna Di Pietro; Kate Fisher; Anna Goodman; Susan Hill; Sarah Mason; Rachel Swain; Natalie Valle Guzman. Cardiff (Schools of Medicine and Biosciences, Cardiff University): Jonathan Bisson; Monica Busse; Cynthia Butcher; Jenny Callaghan; Catherine Clenaghan; Stephen Dunnett; Ruth Fullam; Olivia Handley; Sarah Hunt; Alis Hughes; Catherine Johnstone; Lesley Jones; Una Jones; Hanan Khalil; Sara Minster; Michael Owen; Kathleen Price; Linda Ellison Rose; Jenny Townhill; Anne Rosser. Edinburgh (SE Scotland Genetic Service, Western General Hospital,): Mary Porteous; Maureen Edwards; Carrie Ho (Scottish Huntington´s Association); Marie McGill; Pauline Pearson. Fife (Scottish Huntington's Association Whyteman's Brae Hospital): Peter Brockie; Jillian Foster; Nicola Johns; Sue McKenzie; Jean Rothery; Gareth Thomas; Shona Yates. Glasgow (Abercromby Center): Joanne Miller; Stuart Ritchie. Gloucester (Department of Neurology Gloucestershire Royal Hospital): Liz Burrows; Amy Fletcher; Alison Harding, Fiona Laver; Mark Silva; Aileen Thomson. Hull (Castle Hill Hospital): Liz Rowett; Deena Gallantrae; Mandy

Longthorpe; Ivana Markova; Ashok Raman; Stephanie Hamer; Sue Wild; Pam Yarduiman; Carol Chu; Alison Kraus. Leeds (Chapel Allerton Hospital, Department of Clinical Genetics): Sue Wild; Pam Yardumian; Hannah Musgrave; Liz Rowett; Jean Toscano; Stuart Jamieson; Emma Hobson. Leicester (Leicestershire Partnership NHS Trust): Carole Clayton; Heather Dipple; Julia Middleton; Dawn Freire- Patino. London (Guy's Hospital): Thomasin Andrews; Andrew Dougherty; Fred Kavalier; Charlotte Golding; Hana Laing; Alison Lashwood; Dene Robertson; Deborah Ruddy; Anna Whaite; Alastair Santhouse. London (St. Georges-Hospital): Michael Patton; Maria Peterson; Sarah Rose. London (The National Hospital for Neurology and Neurosurgery): Thomasin Andrews; Stefania Bruno; Elvina Chu; Karen Doherty; Charlotte Golding; Salman Haider; Davina Hensman; Nayana Lahiri; Monica Lewis; Marianne Novak; Aakta Patel; Nicola Robertson, Elisabeth Rosser; Sarah Tabrizi; Rachel Taylor; Thomas Warner; Edward Wild. Manchester (University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust): David Craufurd; Ruth Fullam; Liz Howard; Andrea Sollom; Julie Snowden; Jennifer Thompson; Jenny Callaghan; Mary Jones; Helen Murphy; Iris Trender-Gerhard; Dawn Rogers; Judith Bek; Emma Oughton; Liz Johnson; Marianne Hare; Natalie Arran; Nichola Verstraelen (formerly Ritchie); Lucy Partington-Jones; Susan Huson; Cheryl Stopford; Leann Westmoreland. Newcastle: Jill Davidson; Karen Morgan; Lois Savage; Baldev Singh; Suresh Komati. Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford): Andrea H Nemeth; Richard Armstrong; Ruth Valentine; Gill Siuda. Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital): David Harrison; Max Hughes; Andrew Parkinson; Beverley Soltysiak. Poole (Poole Hospital): John Burn; Caroline Coleman. Sheffield (The Royal Hallamshire Hospital– Sheffield Children's Hospital): Oliver Bandmann; Alyson Bradbury; Paul Gill; Helen Fairtlough; Kay Fillingham; Isabella Foustanos; Mbombe Kazoka; Kirsty O'Donovan; Nadia Peppa; Catherine Taylor; Katherine Tidswell; Oliver Quarrell

References

(1) Walker FO. Huntington's disease. Lancet 2007;369:218-228.

(2) Hoogeveen AT, Willemsen R, Meyer N et al. Characterization and localization of the Huntington disease gene product. Hum Mol Genet 1993;2:2069-2073.

(3) Huntington G. On Chorea. The Medical and Surgical Reporter: A Weekly Journal 1872;26:317-321.

(4) Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. Am J Med Genet 1986;24:305-311.

(5) Robins Wahlin TB, Backman L, Lundin A, Haegermark A, Winblad B, Anvret M. High suicidal ideation in persons testing for Huntington's disease. Acta Neurol Scand 2000;102:150-161.

(6) Schoenfeld M, Myers RH, Cupples LA, Berkman B, Sax DS, Clark E. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosurg Psychiatry 1984;47:1283-1287.

(7) Hubers AA, Reedeker N, Giltay EJ, Roos RA, van Duijn E, van der Mast RC. Suicidality in Huntington's disease. J Affect Disord 2012;136:550-557.

(8) Wetzel HH, Gehl CR, Dellefave-Castillo L, Schiffman JF, Shannon KM, Paulsen JS. Suicidal ideation in Huntington disease: the role of comorbidity. Psychiatry Res 2011;188:372-376.

(9) Baliko L, Csala B, Czopf J. Suicide in Hungarian Huntington's disease patients. Neuroepidemiology 2004;23:258-260.

(10) Lipe H, Schultz A, Bird TD. Risk factors for suicide in Huntingtons disease: a retrospective case controlled study. Am J Med Genet 1993;48:231-233.

(11) Almqvist EW, Bloch M, Brinkman R, Craufurd D, Hayden MR. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. Am J Hum Genet 1999;64:1293-1304.

(12) Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Suicide risk in Huntington's disease. J Med Genet 1993;30:293-295.

(13) Fiedorowicz JG, Mills JA, Ruggle A, Langbehn D, Paulsen JS. Suicidal behaviour in prodromal Huntington disease. Neurodegener Dis 2011;8:483-490.

(14) Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136-142.

(15) Orth M, Handley OJ, Schwenke C et al. Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. PLoS Curr 2010;2:RRN1184.

(16) Orth M, Handley OJ, Schwenke C et al. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. J Neurol Neurosurg Psychiatry 2011;82:1409-1412.

(17) Vassos E, Panas M, Kladi A, Vassilopoulos D. Effect of CAG repeat length on psychiatric disorders in Huntington's disease. J Psychiatr Res 2008;42:544-549.

(18) Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1-3.

(19) Shoulson I. Huntington disease: functional capacities in patients treated with neuroleptic and antidepressant drugs. Neurology 1981;31:1333-1335.

(20) Moscicki EK. Epidemiology of completed and attempted suicide: toward a framework for prevention. Clinical Neuroscience Research 2001;1:310-323.

(21) Large MM, Nielssen O. Suicidal Ideation and Later Suicide. Am J Psychiatry 2012;169:662.

(22) Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. Am J Psychiatry 2005;162:725-731.

(23) Paton C. Benzodiazepines and disinhibition: a review. Psychiatric Bulletin 2002;26:460-462.

(24) Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behaviour. Dialogues Clin Neurosci 2007;9:141-151.

(25) Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. Acta Psychiatr Scand 2006;113:180-206.

(26) Gvion Y, Apter A. Aggression, impulsivity, and suicide behaviour: a review of the literature. Arch Suicide Res 2011;15:93-112.

(27) Neutel CI, Patten SB. Risk of suicide attempts after benzodiazepine and/or antidepressant use. Ann Epidemiol 1997;7:568-574.

(28) Shih HI, Lin MC, Lin CC et al. Benzodiazepine therapy in psychiatric outpatients is associated with deliberate self-poisoning events at emergency departments-a population-based nested case-control study. Psychopharmacology (Berl) 2013;229:665-671.

(29) Conner KR, Meldrum S, Wieczorek WF, Duberstein PR, Welte JW. The association of irritability and impulsivity with suicidal ideation among 15- to 20-year-old males. Suicide Life Threat Behav 2004;34:363-373.

(30) McCall WV, Blocker JN, D'Agostino R Jr et al. Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. Sleep Med 2010;11:822-827.

(31) Bernal M, Haro JM, Bernert S et al. Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord 2007;101:27-34.

(32) Borges G, Nock MK, Haro Abad JM et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. J Clin Psychiatry 2010;71:1617-1628.