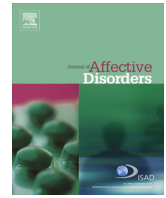




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## Research report

## Suicidal ideation in a European Huntington's disease population



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## ARTICLE INFO

## Article history:

Received 5 March 2013

Received in revised form

31 May 2013

Accepted 1 June 2013

Available online 20 July 2013

## Keywords:

Huntington's disease

Suicidal ideation

Psychopathology

Psychopharmacology

Cohort studies

## 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 analyzed using logistic regression analysis and predictors were analyzed 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.

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## 1. Introduction

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disease (Walker, 2007). 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 (Hoogeveen et al., 1993). The disease is characterized 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 (Huntington, 1872). Recent studies have reported that completed suicide rates among HD mutation carriers are four to eight times higher compared with the general population (Farrer, 1986; Robins Wahlin et al., 2000; Schoenfeld et al., 1984), and increased prevalences of suicidal ideation and attempted suicide, of up to 20%, have been reported (Hubers et al., 2012; Wetzel et al., 2011).

Previous cross-sectional studies have shown that both socio-demographic characteristics such as having no offspring (Baliko et al., 2004; Lipe et al., 1993) or being unemployed (Almqvist et al., 1999), and clinical characteristics such as the presence of a

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depressed mood (Hubers et al., 2012; Wetzel et al., 2011), aggression (Wetzel et al., 2011), or having a psychiatric history (Almqvist et al., 1999) are associated with suicidal ideation, suicide attempts, or completed suicide in HD. Some of these studies only included a small number of participants (Lipe et al., 1993) or used data obtained from family members (Di Maio et al., 1993). Also, several of these studies only investigated the effect of undergoing genetic testing on suicide risk (Almqvist et al., 1999; Farrer, 1986; Robins Wahlin et al., 2000), 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 (Fiedorowicz et al., 2011; Hubers et al., 2012). 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 (Fiedorowicz et al., 2011). However, there were only 13 incident events, which limited study power (Fiedorowicz et al., 2011). 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 for suicidal ideation and attempts in HD (Hubers et al., 2012).

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

## 2. Method

### 2.1. 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) (Huntington Study Group, 1996) 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 (Orth et al., 2010). More detailed information can be found at <http://www.euro-hd.net/html/registry>.

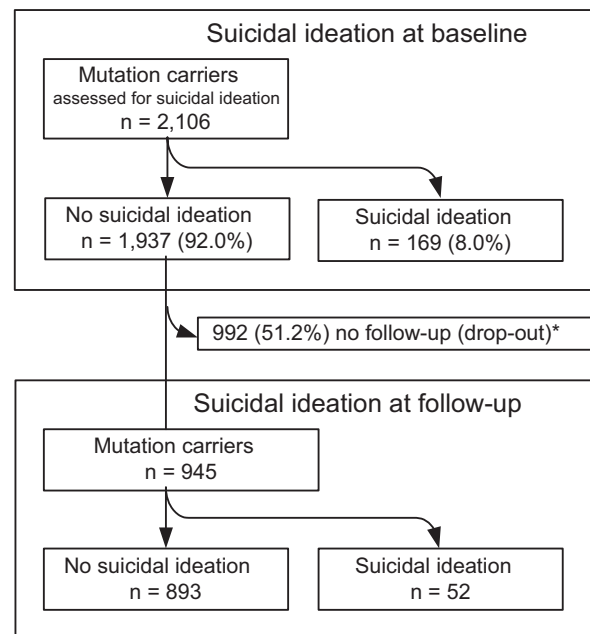
In the study cohort, participants from 15 European countries were included: Austria ( $n=58$ ), Belgium ( $n=3$ ), Czech Republic ( $n=29$ ), Finland ( $n=23$ ), France ( $n=158$ ), Germany ( $n=493$ ), Italy ( $n=181$ ), The Netherlands ( $n=215$ ), Norway ( $n=74$ ), Poland ( $n=222$ ), Portugal ( $n=65$ ), 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) (Huntington Study Group, 1996) was taken as baseline visit. Follow-up data from mutation carriers free of suicidal ideation at baseline ( $n=1,937$ ) 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 (Fig. 1).

### 2.2. Instruments

**Assessment of suicidal ideation:** Suicidal ideation was examined using the UHDRS-b (Huntington Study Group, 1996). The

behavioural subscale of the UHDRS assesses frequency and severity of 11 neuropsychiatric symptoms (Huntington Study Group, 1996). The item 'Suicidal thoughts' of the UHDRS-b (Huntington Study Group, 1996) 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 considered suicide but has no plan, and a severity score of 4 indicates the participant has a plan and is actively preparing (Huntington Study Group, 1996). The total score was computed by multiplying the frequency and severity scores (range 0–16 points) (Wetzel et al., 2011). Based on clinical experience, a total score  $> 1$  point on this item was used to characterize 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 (Huntington Study Group, 1996). 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



**Fig. 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.

was used to characterize 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 (Orth et al., 2011).

The estimated disease duration was calculated by the current age minus the estimated age of onset, calculated using the formula of Vassos et al. (2008).

Global functioning was assessed with the Total Functioning Capacity (TFC) (Huntington Study Group, 1996) with scores ranging from 0 through 13 points. Higher scores indicate better global functioning (Shoulson and Fahn, 1979). Disease stage was derived from TFC scores (Shoulson, 1981).

A trained neurologist assessed motor functioning according to the motor subscale of the UHDRS (UHDRS-m) (Huntington Study Group, 1996) with scores ranging from 0 through 124 points. Higher scores indicate worse motor functioning (Huntington Study Group, 1996). 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.

### 2.3. Statistical analyses

Data are presented as *n* (%), mean ( $\pm$  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.

### 3. Results

The 2106 participants were both male (50.9%) and female (49.1%) with a mean ( $\pm$  SD) age of 50.3 ( $\pm$  12.4) years. The study

**Table 1**

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

|   | HD mutation carriers without suicidal ideation ( <i>n</i> = 1937) | HD mutation carriers with suicidal ideation ( <i>n</i> = 169) | <i>P</i> -value <sup>a</sup> |
|---|---|---|------------------------------|
| <i>Sociodemographic characteristics</i> |   |   |                              |
| Male gender                             | 994 (51.3%)   | 78 (46.2%)  | 0.20                         |
| Age (years)                             | 50.5 $\pm$ 12.4   | 48.7 $\pm$ 11.3   | 0.08                         |
| <i>Clinical characteristics</i>         |   |   |                              |
| CAG repeats (number)                    | 44.6 $\pm$ 4.4  | 44.4 $\pm$ 4.2  | 0.59                         |
| Estimated duration of disease (years)   | 5.9 $\pm$ 8.1   | 3.7 $\pm$ 8.0   | 0.001                        |
| TFC score                               | 8.0 (5–12)  | 8.0 (6–11)  | 0.73                         |
| UHDRS-motor score                       | 35.3 $\pm$ 19.7   | 33.1 $\pm$ 20.4   | 0.18                         |
| Pre-motor symptomatic                   | 38 (2.0%)   | 6 (3.6%)  | 0.16                         |
| <i>Psychotropic medication</i>          |   |   |                              |
| 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                         |
| <i>Neuropsychiatric characteristics</i> |   |   |                              |
| 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 ( $\pm$  SD) or median (interquartile range [IQR]) when appropriate. HD denotes Huntington's disease; 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.

<sup>a</sup> *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.

population included mostly motor symptomatic (98%) mutation carriers. The mean ( $\pm$  SD) estimated disease duration was 5.7 ( $\pm$  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 (Fig. 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).

### 3.1. 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).

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 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).

### 3.2. 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 (HR=2.05; 95% CI: 1.06–3.96) at baseline were independent predictors of suicidal ideation at follow-up (Table 4) (Fig. 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 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).

## 4. 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.

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

| Baseline variable                                    | Cross-sectional logistic regression ( $n=1916$ ) <sup>a</sup> |   |                                    |                         |
|--|---|---|------------------------------------|-------------------------|
|  | No suicidal ideation at baseline ( $n=1772$ )                 | Suicidal ideation at baseline ( $n=144$ ) | Wald statistic <sup>b</sup> $df=1$ | $P$ -value <sup>b</sup> |
|  | Reference   | Odds ratio (95% CI) <sup>b</sup>          |                                    |                         |
| <i>Sociodemographic and clinical characteristics</i> |   |   |                                    |                         |
| Male gender  | 1.00  | 1.16 (0.79–1.71)                          | 0.56                               | 0.46                    |
| Age  | 1.00  | 1.02 (0.99–1.04)                          | 2.12                               | 0.15                    |
| Estimated duration of disease                        | 1.00  | 0.96 (0.93–0.99)                          | 6.27                               | 0.01                    |
| <i>Psychotropic medication</i>                       |   |   |                                    |                         |
| Antidepressant use                                   | 1.00  | 0.93 (0.62–1.40)                          | 0.12                               | 0.73                    |
| Benzodiazepine use                                   | 1.00  | 1.48 (0.93–2.37)                          | 2.67                               | 0.10                    |
| Mood stabilizers/anti-epileptic use                  | 1.00  | 1.18 (0.64–2.18)                          | 0.27                               | 0.60                    |
| <i>Neuropsychiatric characteristics</i>              |   |   |                                    |                         |
| Depressed mood                                       | 1.00  | 13.71 (6.71–28.00)                        | 51.55                              | < 0.001                 |
| Anxiety  | 1.00  | 2.14 (1.40–3.26)                          | 12.54                              | < 0.001                 |
| Apathy   | 1.00  | 1.42 (0.92–2.20)                          | 2.47                               | 0.12                    |
| Irritability   | 1.00  | 0.87 (0.55–1.37)                          | 0.39                               | 0.53                    |
| Aggression   | 1.00  | 2.41 (1.53–3.80)                          | 14.43                              | < 0.001                 |
| Suicide attempt in past                              | 1.00  | 3.95 (2.36–6.60)                          | 27.51                              | < 0.001                 |

*Covariates cross-sectional analysis (enter model):* all variables with  $P$ -value  $\leq 0.05$  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.

<sup>a</sup> 190 cases excluded due to missing values.

<sup>b</sup> Odds ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom ( $df$ ), and  $P$ -value by binary logistic regression.

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

| Baseline variable                       | Univariate Cox regression ( $n=942$ ) <sup>a</sup> |   |                                    |                      |
|---|--|---|------------------------------------|----------------------|
|   | No suicidal ideation at follow-up ( $n=890$ )      | Suicidal ideation at follow-up ( $n=52$ ) | Wald statistic <sup>b</sup> $df=1$ | P-value <sup>b</sup> |
| Reference                               |  | Hazard ratio (95% CI) <sup>b</sup>        |                                    |                      |
| <i>Sociodemographic characteristics</i> |  |   |                                    |                      |
| Male gender                             | 1.00   | 0.91 (0.53–1.57)                          | 0.11                               | 0.74                 |
| Age                                     | 1.00   | 1.00 (0.98–1.02)                          | 0.01                               | 0.95                 |
| <i>Clinical characteristics</i>         |  |   |                                    |                      |
| CAG repeats                             | 1.00   | 0.98 (0.92–1.05)                          | 0.25                               | 0.62                 |
| Estimated duration of disease           | 1.00   | 0.99 (0.96–1.03)                          | 0.25                               | 0.62                 |
| TFC score                               | 1.00   | 0.99 (0.91–1.07)                          | 0.10                               | 0.76                 |
| UHDRS-motor score                       | 1.00   | 1.00 (0.98–1.01)                          | 0.08                               | 0.78                 |
| Pre-motor symptomatic                   | 1.00   | 1.78 (0.55–5.72)                          | 0.94                               | 0.33                 |
| <i>Psychotropic medication</i>          |  |   |                                    |                      |
| Antidepressant use                      | 1.00   | 1.72 (0.98–3.02)                          | 3.59                               | 0.06                 |
| Antipsychotic use                       | 1.00   | 1.69 (0.95–3.01)                          | 3.16                               | 0.08                 |
| Benzodiazepine use                      | 1.00   | 2.78 (1.48–5.22)                          | 10.14                              | 0.001                |
| Mood stabilizer/anti-epileptic use      | 1.00   | 2.80 (1.36–5.76)                          | 7.85                               | 0.005                |
| Tetrabenazine use                       | 1.00   | 2.43 (0.59–10.03)                         | 1.50                               | 0.22                 |
| <i>Neuropsychiatric characteristics</i> |  |   |                                    |                      |
| Depressed mood                          | 1.00   | 2.73 (1.57–4.76)                          | 12.58                              | < 0.001              |
| Anxiety                                 | 1.00   | 1.99 (1.15–3.42)                          | 6.11                               | 0.01                 |
| Apathy                                  | 1.00   | 2.27 (1.30–3.96)                          | 8.22                               | 0.004                |
| Irritability                            | 1.00   | 1.48 (0.86–2.55)                          | 1.99                               | 0.16                 |
| Aggression                              | 1.00   | 1.58 (0.85–2.92)                          | 2.10                               | 0.15                 |
| Suicide attempt in past                 | 1.00   | 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.

<sup>a</sup> Three cases were censored before the earliest event in the stratum.

<sup>b</sup> Hazard ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom ( $df$ ), and P-value by univariate Cox regression analysis.

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

| Baseline variable                       | Multivariate Cox regression ( $n=885$ ) <sup>a</sup> |   |                                    |                      |
|---|--|---|------------------------------------|----------------------|
|   | No suicidal ideation at follow-up ( $n=838$ )        | Suicidal ideation at follow-up ( $n=47$ ) | Wald statistic <sup>b</sup> $df=1$ | P-value <sup>b</sup> |
| Reference                               |  | Hazard ratio (95% CI) <sup>b</sup>        |                                    |                      |
| <i>Sociodemographic characteristics</i> |  |   |                                    |                      |
| Male gender                             | 1.00   | 1.03 (0.57–1.84)                          | 0.01                               | 0.94                 |
| Age                                     | 1.00   | 1.00 (0.97–1.02)                          | 0.12                               | 0.73                 |
| <i>Psychotropic medication</i>          |  |   |                                    |                      |
| Benzodiazepine use                      | 1.00   | 2.44 (1.20–4.97)                          | 6.00                               | 0.01                 |
| Mood stabilizer/anti-epileptic use      | 1.00   | 1.96 (0.88–4.35)                          | 2.71                               | 0.10                 |
| <i>Neuropsychiatric characteristics</i> |  |   |                                    |                      |
| Depressed mood                          | 1.00   | 2.05 (1.06–3.96)                          | 4.50                               | 0.03                 |
| Anxiety                                 | 1.00   | 0.97 (0.50–1.88)                          | 0.01                               | 0.93                 |
| Apathy                                  | 1.00   | 1.67 (0.87–3.20)                          | 2.35                               | 0.13                 |

*Covariates Cox regression analysis (enter model):* all variables with  $P$ -value  $\leq 0.05$  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.

<sup>a</sup> Three cases were censored before the earliest event in the stratum and there were 57 cases excluded due to missing values.

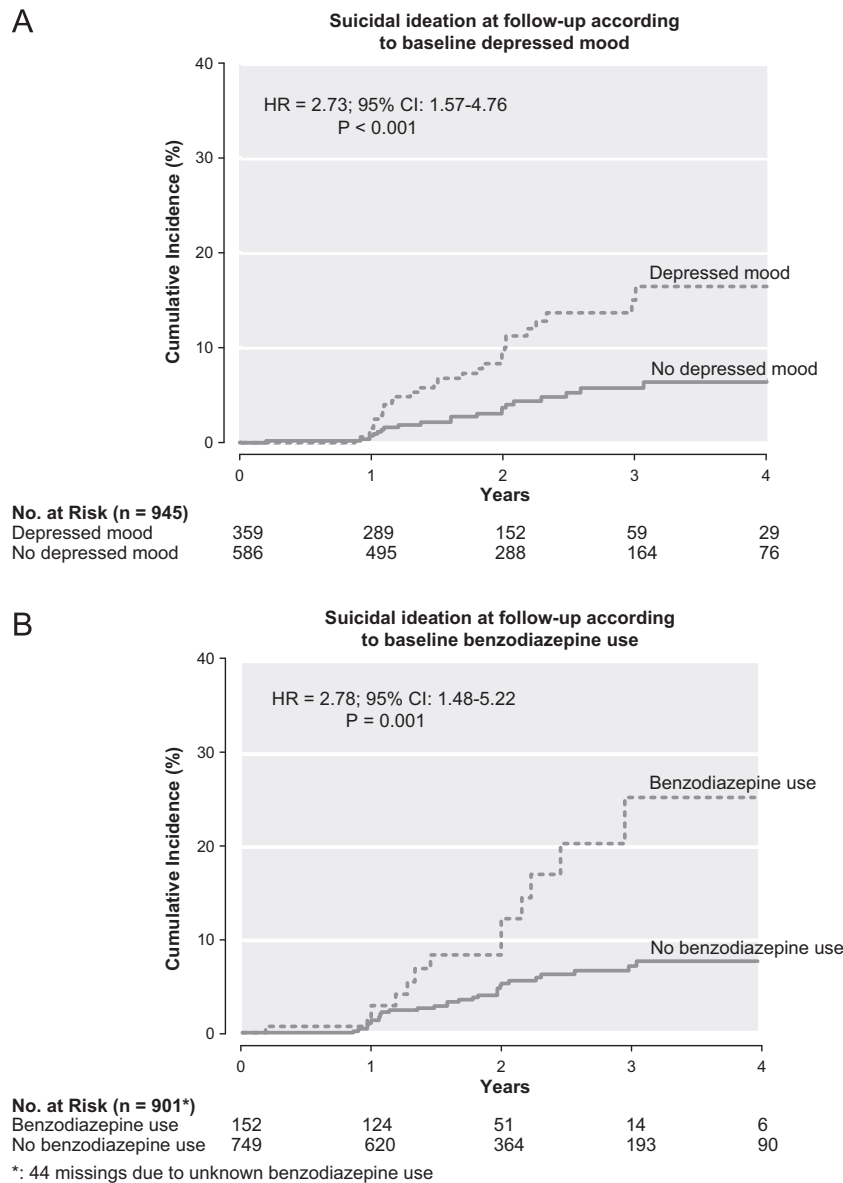
<sup>b</sup> Hazard ratio, 95% confidence interval (CI), Wald statistic, degrees of freedom ( $df$ ), and P-value by multivariate Cox regression analysis.

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 (Hubers et al., 2012). 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 (Wetzel et al., 2011). 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 for suicidal thoughts (Hubers et al., 2012) and attempts (Fiedorowicz et al., 2011; Hubers et al., 2012).

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 (Wetzel et al., 2011).



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

Although a previous suicide attempt did not independently predict suicidal ideation at follow-up in our study, it was previously found as a predictor for suicide attempts among prodromal HD mutation carriers (Fiedorowicz et al., 2011) and it is one of the strongest risk factors for completed suicide in the general population (Moscicki, 2001). 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 (Large and Nielsen, 2012). Therefore, future studies need to investigate and describe trajectories of suicidality in HD, and determine whether and to what extent suicidal ideation is a clinically relevant predictor for 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 (Di Maio et al., 1993; Farrer, 1986; Lipe et al., 1993; Schoenfeld et al., 1984). 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 (Paulsen

et al., 2005). 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 (Paton, 2002). Since HD mutation carriers often have difficulty with impulse control already as result of disruption of frontal-subcortical circuitry (Bonelli and Cummings, 2007; Wetzel et al., 2011), 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 (Brenzo et al., 2006; Gvion and Apter, 2011), but also suggested that benzodiazepine use may be associated with attempted suicide (Neutel and Patten, 1997; Shih et al., 2013). 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 (Conner et al., 2004; McCall et al., 2010). 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 (Neutel and Patten, 1997).

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 rates did not correspond with the distribution of prevalence rates in the general populations of the different European countries (Bernal et al., 2007), 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 generalize to the entire European HD population, since previous research showed consistent risk factors in European countries despite important variation in country prevalences (Bernal et al., 2007).

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% (Hubers et al., 2012). However, in this study, assessment of suicidal ideation was done by psychiatrists through a detailed psychopathology interview (Hubers et al., 2012). A prevalence of 19% has been found using the UHDRS-b, but this study also categorized participants with a total score of 1 point as suicidal (Wetzel et al., 2011). 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% (Paulsen et al., 2005). However, when all mildly suicidal participants (severity score of 1) were excluded, the prevalence dropped to 10.3% (Paulsen et al., 2005), 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 (Hubers et al., 2012) and the twelve-month prevalence of 2.0% in the general population (Borges et al., 2010). 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 (Wetzel et al., 2011). 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.

#### Role of funding source

The European Huntington's Disease Network, responsible for design and conduction of the REGISTRY study, is funded by the CHDI Foundation. There was no funding involved with regard to the analysis and interpretation of the data and preparation, review, and approval of the manuscript.

#### Conflict of interest

We report no conflicts of interest for all authors.

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Birmingham (The Barberrry Centre, Dept of Psychiatry): Shahbana Akhtar; Jenny Crooks; Adrienne Curtis; Jenny de Souza (Keylock); Hugh Rickards; Jan Wright.

Bristol (Frenchay Hospital): Beverley Hayward; Kasia Sieradzian; 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 Peppia; Catherine Taylor; Katherine Tidswell; Oliver Quarrell.

#### Acknowledgments

The authors thank the NIHR Biomedical Research Centre in Manchester.

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