Suicidality in Huntington's disease

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Chapter 1

General introduction

Huntington's disease (HD) is an autosomal dominantly inherited, neurodegenerative disorder caused by an expanded cytosine-adenine-guanine (CAG) repeat within the Huntingtin gene on the short arm of chromosome 4.[1;2] The classic HD symptom triad including motor dysfunction (chorea and hypokinesia), cognitive decline and neuropsychiatric symptoms will develop when there are 36 or more CAG repeats within the HTT gene. Symptoms and signs of HD usually start to become manifest between the ages of 30 and 50,[3] with an average disease duration of 20 years.[1] Although the clinical diagnosis of HD is usually based on the manifestation of motor signs, neuropsychiatric symptoms can already occur before the onset of motor dysfuction[4-6] and are the first manifestation of the disease in 24–79% of the mutation carriers.[7] These symptoms have a substantial impact on the activities of daily living,[4;8;9] independent of the presence of motor and cognitive deficits.[8]

Psychopathology in HD

The most frequently reported neuropsychiatric symptoms in HD are depressed mood (prevalence: 33–69%),[10;11] anxiety (prevalence: 13–71%),[11;12] irritability (prevalence: 38–73%),[10;11] apathy (prevalence: 34–76%)[10;11] and obsessive-compulsive behaviours (prevalence: 10–52%).[10;11] Reported prevalence numbers vary widely depending on for example the definition and assessment method of the neuropsychiatric symptoms and disease stage of the study population.[10]

Degeneration of the striatum and impaired functioning of the frontostriatal circuits, already affected in early HD, have been proposed as important factors in the aetiology of the neuropsychiatric symptoms in HD.[10;13-17] This is supported by studies that showed a higher frequency of these symptoms in both pre-motor and motor symptomatic mutation carriers than in first-degree non-carriers.[4;5] Also environmental factors, like the psychological stress of being at risk and growing up in an HD family, most likely contribute to the neuropsychiatric symptoms.[10;14]

Prevalence of suicidal ideation, suicide attempts and completed suicide in HD

Suicide is one other common psychiatric phenomenon in HD mutation carriers, which was already described in 1872 by George Huntington. He noticed that "the tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked."[18] Also today, suicide,

after pneumonia, is considered to be one of the most frequent causes of death in HD.[3;19] Several recent studies showed that the suicide risk in HD is higher than in the general population, with up to 11% of all deaths in diagnosed motor symptomatic HD patients being due to suicide (Figure 1A).[19-38] Compared with the general population, the risk of dying by suicide was 2 to 8 times higher in HD,[19;22;23;26] with the point estimate from a meta-analysis showing a 2.9 times increased risk.[39;40] Also in persons at 50% risk of HD, an increased suicide risk has been reported,[19;22] with 4.5% of the deaths in this group due to suicide.[22]

Having a medical illness itself is a strong predictor of suicide.[40;41] Compared with other somatic medical illnesses, the standardised mortality ratio (SMR) for suicide in HD (being 2.9) is similar to multiple sclerosis (SMR = 2.4), but higher SMRs for suicide were reported for several other diseases like HIV/aids (SMR = 6.6) and lower SMRs for suicide were reported for some other diseases like malignant neoplasm (SMR = 1.8).[40] For most mental illnesses higher SMRs for suicide were found than in HD (SMRs ranging from 3.3–87).[39] In contrast, the risk of suicide in other forms of dementia is lower than or equal to that of the general population.[42]

Also, high prevalence numbers for suicidal ideation and suicide attempts (together referred to as 'suicidality') have been reported in both pre-motor and motor symptomatic HD mutation carriers. Lifetime suicide attempts were reported in 3.2–17.7% of the diagnosed motor symptomatic HD patients (Figure 1B).[14;20;23-25;27;31;37;43-46] One of the lowest numbers (4.8%) was reported in a study that considered only severe attempts which required hospitalization.[25] Also in the PREDICT-HD study, a longitudinal multi-site study investigating markers of HD prior to the onset of motor symptoms, 7.2% of the pre-motor symptomatic HD mutation carriers attempted suicide during their lives.[47] These numbers are higher than reported in the general population from 17 different countries worldwide, in which 2.7% of the individuals ever attempted suicide, with substantial variability across different countries.[48] Lifetime suicidal ideation was reported in up to 34% of the diagnosed motor symptomatic HD patients,[43;45;49] while in the worldwide general population 9.2% of the individuals reported lifetime suicidal ideation.[48] In studies with both pre-motor and motor symptomatic mutation carriers[50;51] and in studies with only motor symptomatic mutation carriers,[9;43;45;52] a high number of participants indicated suicidal ideation in the month prior to the interview, ranging from 8[43]–34%[52] (Figure 1C). The large variation in numbers can for example be explained by varying definitions and measurement instruments: the highest prevalence numbers were reported in studies where the presence of suicidal ideation was defined as a score > 0 on the suicidal ideation item of the Unified Huntington's Disease Rating Scale (UHDRS),[53] which implies that questionable thoughts of life not worth living are already considered as suicidal ideation.[45;52]

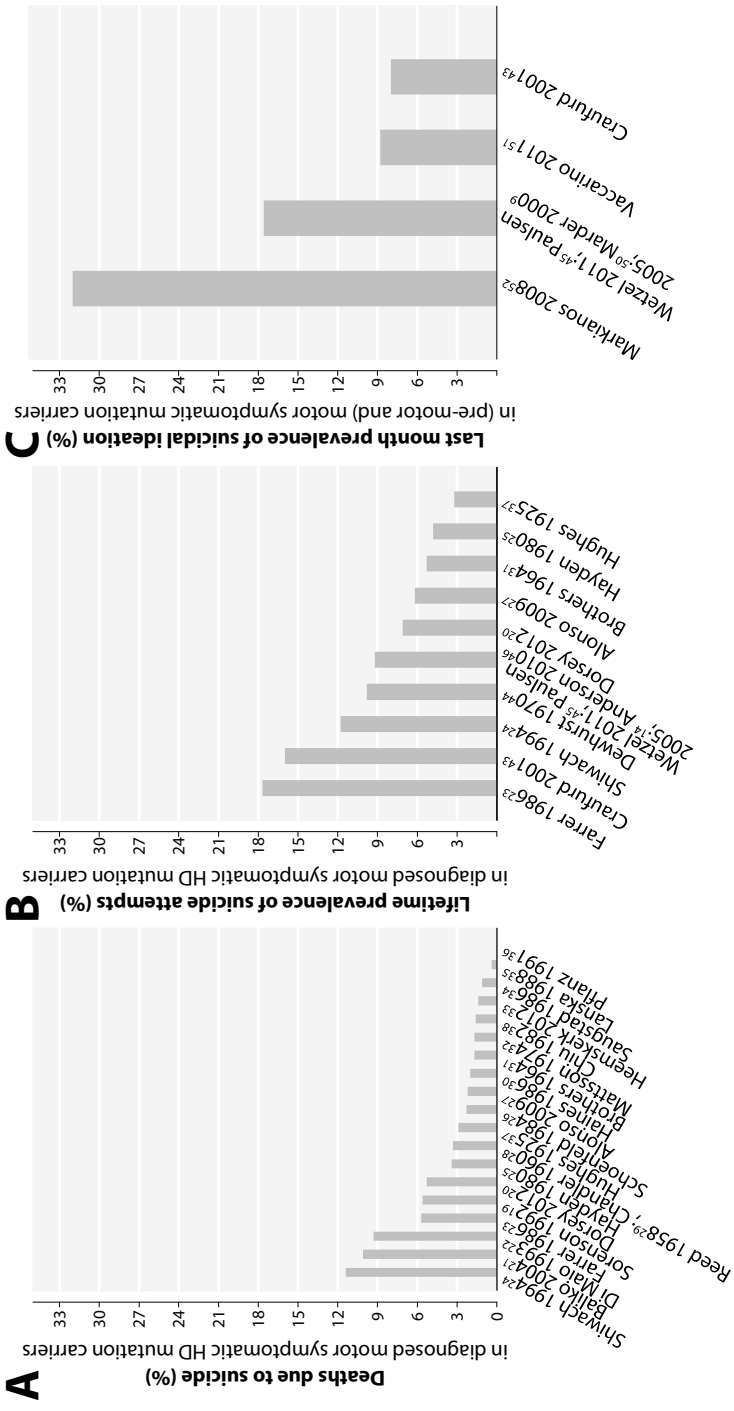

Figure 1. Bar chart showing prevalence of completed suicide (A), suicide attempts (B) and suicidal ideation (C) in HD.
When different studies reported on the same study sample, the mean of the reported prevalence numbers is presented in the bar chart.

Suicidal ideation and suicide attempts are an important field of study as suicidal patients have a lower quality of life.[54;55] However, while attempted suicide is a well-established risk factor for subsequent completed suicide, the importance of suicidal ideation in the prediction of suicide is still debatable.[56]

Suicidality and suicide in relation to predictive testing for HD

Given the increased suicide risk in both pre-motor and motor symptomatic HD mutation carriers, significant concern has been raised about the impact of predictive genetic testing,[57] especially since there is no cure for HD despite symptomatic treatment options. Predictive testing for HD using linkage analysis has been available since 1983 and in 1993, when the expanded CAG repeat in the *HTT* gene was first described,[2] direct testing of the mutation became available.[3]

Suicidality is not uncommon before predictive testing,[42;58-60] as up to 50% of the at-risk persons who requested predictive testing reported suicidal ideation[58;59] and up to 12% reported a suicide attempt before receiving the test result.[59;60] There was no difference in these prevalence numbers between at-risk participants who later turned out to carry the mutation and non-carriers.[58;59] After disclosure of the test result, the HD mutation carriers, compared with non-carriers, reported suicidal thoughts significantly more often over time,[59] with 23% of the carriers reporting suicidal ideation within 2 months after receiving the test result, compared with 2% in non-carriers.[59] Results with regard to attempted and completed suicide after predictive testing are inconsistent.[42] Some studies reported no attempted or completed suicide after predictive testing,[61-66] others reported higher rates in carriers than in non-carriers,[59;67] or comparable rates between these two groups,[68] and one other study reported suicide attempts in the non-carrier group only while there were no attempts in the carrier group.[69] A worldwide survey on catastrophic events after predictive testing[67] reported a suicide rate that was 10 times higher than that in the general population,[67;70] but showed that all of those who died by suicide after predictive testing had motor signs at the time of their suicide.[67] Despite this conflicting evidence,[42] a review on predictive testing in HD concluded that, although carriers experienced increased distress in the first period after testing, it did not result in increased serious adverse events like completed suicide.[71] Also after predictive testing for other neurodegenerative disorders, no increase in attempted or completed suicides was reported, but study groups were small.[65;66;72]

Associations of suicidality and suicide in HD

Several mechanisms for the increased occurrence of suicidality and suicide in HD could be proposed. As suicidality and suicide also occur more frequently in pre-motor symptomatic mutation carriers and persons at 50% risk of HD, it could be hypothesised that environmental factors contribute to its aetiology. In addition, its increased occurrence might be related to affected brain structures and the emotional distress of having an incurable disease with a devastating course. Another possibly important factor in the aetiology of suicidality and suicide is the psychopathology, especially depression, that is common in HD[10] and that is one of the most important risk factors for suicidality and suicide in general.[73;74] It has also been suggested that some cases of suicide in HD might be "a rational but extreme response to an intolerable situation."[23] While the aetiology of suicidality and suicide in HD remains poorly understood,[75] previous studies tried to identify particular characteristics of HD mutation carriers who were most likely to think of, attempt, or die by suicide.

Sociodemographic associations

A few studies focused on sociodemographic characteristics and reported that male HD patients were 3-4 times more likely to die by suicide than females,[22;26] while female HD mutation carriers were more likely to attempt suicide during follow-up than males.[47] Having no offspring was found as another important association of completed suicide,[76] whereas other investigated sociodemographic characteristics, like being unmarried or living alone, were not.[76] Also, no other investigated sociodemographic factors, like age or education, were significantly associated with current suicidal ideation[45] or future suicidal attempts.[47]

Clinical associations

Most studies that described associations of suicidality and suicide in HD focused on the relationship with disease stage. HD patients who died by suicide had a younger age and a shorter disease duration than those who died by other causes.[19;21-23] However, HD patients who died by suicide still had a disease duration of 9–12 years,[22;23] indicating suicide occurs most frequently in early to middle disease stages.[23] For suicidal ideation two critical periods, one in early-stage HD and the other in middle-stage HD, have been identified. The first critical period occurs when at-risk persons start to experience the first symptoms of HD and the second when patients become more dependent on others for activities of daily living.[50] Apart from disease stage, other disease progression related variables including age of onset, total motor score, and cognitive function were not significantly associated with suicidal ideation,[45] suicide attempts[47;49] or completed suicide.[21-23]

Only one study assessed the association of psychiatric symptoms with completed suicide in HD[76] and found a higher prevalence of depression in HD patients who died by suicide than in those who died by other causes.[76] Studies that focused on suicidality reported depression (or a combined factor of depression and anxiety) to be the strongest association of suicidal ideation and suicide attempts in HD.[14;45;47;49] Also, depression and a previous suicide attempt were significantly associated with future suicide attempts in a cohort of pre-motor symptomatic mutation carriers.[47] In addition, motor symptomatic HD patients with aggression[45] and obsessive and compulsive symptoms[46] were significantly more likely to report suicidal ideation. Other psychiatric symptoms that frequently occur in HD like apathy or irritability have been reported not to be associated with suicide attempts.[47;49]

Biological associations

So far, only one HD study investigated biological associations of suicidality in HD and reported no association between total cholesterol levels and suicidal ideation.[52] In non-HD populations, several studies have identified biological associations of suicidality and suicide, like inflammation[77-80] and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, in particular dexamethasone non-suppression.[81-83] While in HD populations increased inflammatory activity in the central nervous system and peripheral tissues[84-89] and hypothalamic changes and disturbed HPA axis functioning have been reported compared with controls,[90-98] associations between these biological parameters and suicidality or suicide in HD have not been investigated.

Limitations of previous studies

Many of the aforementioned studies on associations of suicidality and suicide in pre-motor and motor symptomatic HD mutation carriers were cross-sectional.[14;21-23;26;45;46;49;50] These studies for example investigated which mutation carriers were most likely to have thought of or attempted[14;49] suicide in the past. However, for clinical practice, it is particularly relevant to know which mutation carriers are most likely to currently experience suicidality and develop suicidality or die by suicide in the future. Despite the high suicide risk in HD, only one prospective cohort study with limited statistical power, which investigated predictors of suicide attempts in pre-motor symptomatic HD mutation carriers, has been carried out to date.[47]

Treatment of suicidal HD mutation carriers

Given the high frequency of suicidality and suicide in HD, adequate support and treatment strategies should be available for mutation carriers who experience suicidality or are at highest

risk of developing suicidality in the future. Currently, there are only a few case reports on the pharmacologic treatment of suicidal HD mutation carriers indicating positive effects of mirtazapine,[99] lithium[100] and lamotrigine.[101] Apart from pharmacological treatment, several psychosocial interventions are also recommended in treatment guidelines for non-HD suicidal patients. There are currently no treatment recommendations specifically for suicidal HD patients and it is unknown whether the treatment of suicidal HD patients should be different from other, non-HD, suicidal patients, given the in advance known devastating course of the disease.

Aims of this thesis

The primary aims of this thesis were to investigate the prevalence and incidence and sociodemographic, clinical, and biological associations of suicidality in HD and to explore which coping styles and support strategies can help suicidal HD mutation carriers. An additional aim was to examine whether the expression of suicidal ideation predicts subsequent completed suicide in various populations.

First, we studied the prevalence and incidence of suicidal ideation and suicide attempts in HD and both its cross-sectional and longitudinal sociodemographic and clinical associations (**Chapter 2 and 3**). The study described in chapter 2 was conducted within the PsychHD study,[5] a Dutch prospective cohort study that followed both pre-motor and motor symptomatic HD mutation carriers and controls. The study described in chapter 3 was conducted within the REGISTRY study, a large prospective cohort study of the European Huntington's Disease Network (EHDN).[102]

We also aimed to assess biological associations of suicidality within the PsychHD study. We investigated the associations between two markers of inflammation, C-reactive protein (CRP) and albumin, and several clinical characteristics, including suicidality, in HD (**Chapter 4**). Additionally, we studied whether different parameters of HPA axis activity, including dexamethasone non-suppression, were associated with the severity of depressive symptoms and suicidality in HD (**Chapter 5**).

Furthermore, in a qualitative study, we explored how HD mutation carriers coped with suicidal ideation or previous suicide attempts and we investigated ideas and wishes of HD mutation carriers regarding how relatives and healthcare professionals can help them cope with suicidality. Additionally, we explored how spouses of HD mutation carriers supported their

partners with regard to suicidality (**Chapter 6**).

Suicidal ideation, sometimes combined with attempted suicide, was the outcome in all our studies. In a meta-analysis we investigated whether the expression of suicidal ideation predicted subsequent completed suicide in various populations, including both psychiatric and non-psychiatric populations (**Chapter 7**).

The final chapter (**Chapter 8**) provides an overview of the results of this thesis and a general discussion, including directions for further research and recommendations for clinical practice.

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Chapter 2

Suicidality in Huntington's disease

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Abstract

Background: In Huntington's disease (HD) the risk of suicide is increased. Since suicidality may precede suicide, this study investigates prevalence, clinical associations and predictors of suicidality in HD.

Methods: Suicidality was investigated in 152 mutation carriers and 56 non-carriers, and was considered present if the score on the item 'suicidal ideation' of the Problem Behaviours Assessment (PBA) was >1 point. After 2 years, 100 mutation carriers who were free of suicidality at baseline were re-assessed. Associations and predictors of suicidality were analysed using multivariate logistic regression analysis.

Results: Eleven (20%) pre-motor and 20 (20%) motor symptomatic mutation carriers were considered suicidal compared to none of the non-carriers. Cross-sectionally, suicidal mutation carriers were more likely to use antidepressants (odds ratio = 5.3), were more often apathetic (OR = 2.8), more often had a depressed mood according to the PBA (OR = 5.9), and were more often diagnosed with a DSM-IV depression diagnosis (OR = 4.7). Independent associations were more frequent use of antidepressants (OR = 4.0) and presence of a depressed mood (OR = 4.2). Longitudinally, depressed mood (OR = 10.6) at baseline was the only independent predictor of suicidality at follow-up.

Limitations: Selection bias might have occurred which could have affected the suicidality prevalence and incidence.

Conclusion: It is important to screen both pre-motor and motor symptomatic HD mutation carriers for suicidality. The presence of a depressed mood is both associated with and predictive of suicidality in HD and assessment of depressed mood can help to identify individuals with increased risk for suicide.

Introduction

Huntington's disease (HD) is a neurodegenerative, autosomal dominantly inherited disease.[1] An expanded CAG repeat on the short arm of chromosome 4 causes an expanded polyglutamine chain in the huntingtin protein.[2] Motor disorders, cognitive decline and both behavioural problems and psychiatric disorders are part of the clinical presentation of HD, with progression of symptoms over time. Some of these symptoms can be treated but the disease cannot be cured.

Behavioural problems and psychiatric disorders are major constituents of the clinical spectrum of HD;[3] many patients and their relatives consider these problems to be the most distressing aspect of the disease.[4] An important clinical aspect of HD is the increased risk of suicide, as was described by George Huntington in 1872.[5] Patients with HD were shown to commit suicide four to eight times more often than the general population.[6-8] A suicide risk of 5.7 suicides per 100 deaths has been reported in HD,[6] whereas the suicide risk in the general Dutch population is about 1 suicide per 100 deaths.[9] A study investigating suicidality over the previous thirty days reported a relatively high prevalence of 19% in motor symptomatic HD mutation carriers,[10] whereas the lifetime prevalence of suicidality in a mixed population of both pre-motor and motor symptomatic HD mutation carriers was 20%.[11] In comparison, 11% of the general Dutch population, aged 18 to 64 years, ever considered suicide and 3% ever performed a suicide attempt.[12] The increased prevalence of suicidality and suicide may be related to the emotional distress of having an incurable disease as well as the psychopathology that is common in HD.

In the HD population, sociodemographic and clinical characteristics such as having no offspring,[13;14] being unemployed,[15] the presence of a depressed mood[10;11;16] and a psychiatric history[15] were found to be of importance for suicidality and suicide. However, most studies investigating suicidality or suicide in HD were retrospective,[14] or cross-sectional[10;11;13] or they focused on persons undergoing predictive testing for HD.[6;7;15] The only prospective study investigating suicidality in HD focused on suicidal behaviour in prodromal HD.[16] Some studies used survey data obtained from family members[17] or included a low number of participants.[14] Also, several studies focused on completed suicide,[13;14;17] rather than on suicidal thoughts and attempts, whereas suicidal ideation may be of particular importance because it is a strong risk factor for and antecedent of completed suicide.[18;19]

The present study aimed to assess the prevalence of suicidality, defined as the presence of suicidal ideation or suicide attempt in the month preceding the interview, in HD mutation carriers and a control group of non-carriers. Cross-sectionally, we wanted to investigate possible

sociodemographic and clinical characteristics associated with suicidality and longitudinally we analysed the possible baseline predictors of suicidality at 2-year follow-up. We hypothesised that, similar to the general population, suicidality in HD is linked to psychopathology, in particular depression.

Method

Participants

Between May 2004 and August 2006, 343 potential participants at initial 50% risk of HD were contacted through the departments of Neurology and Clinical Genetics of the Leiden University Medical Center and a nursing home specialised in the daily care of HD patients. Of these, 192 were willing and able to participate in this study. In addition, 16 participants were enrolled via the Dutch HD patients' association after posting an announcement on their internet site and in their quarterly. Finally, 152 mutation carriers (CAG repeat length ≥ 36) and 56 non-carriers were included in the cross-sectional analysis. The design of this study has been described in detail elsewhere.[20]

Two years after their initial visit, all participants were approached for a second measurement. Follow-up data from mutation carriers who were free of suicidality at baseline (n = 121) were used in the longitudinal analyses. Of them, 21 (17.4%) dropped out due to a variety of reasons. One person was deceased and one person was untraceable, whereas eight were excluded because of inability to speak, too severe symptomatology or other medical conditions. The remaining 11 persons refused to participate because they did not feel like it, or due to private circumstances. This resulted in 100 eligible mutation carriers for follow-up assessment (Figure 1).

This study was approved by the Medical Ethical Committee of the Leiden University Medical Center. Written informed consent was obtained from all participants. Because many institutionalised participants had cognitive deficiencies, special attention was paid to this important issue by contacting their physicians and asking them to thoroughly discuss study participation with these patients and their family members, before giving consent.

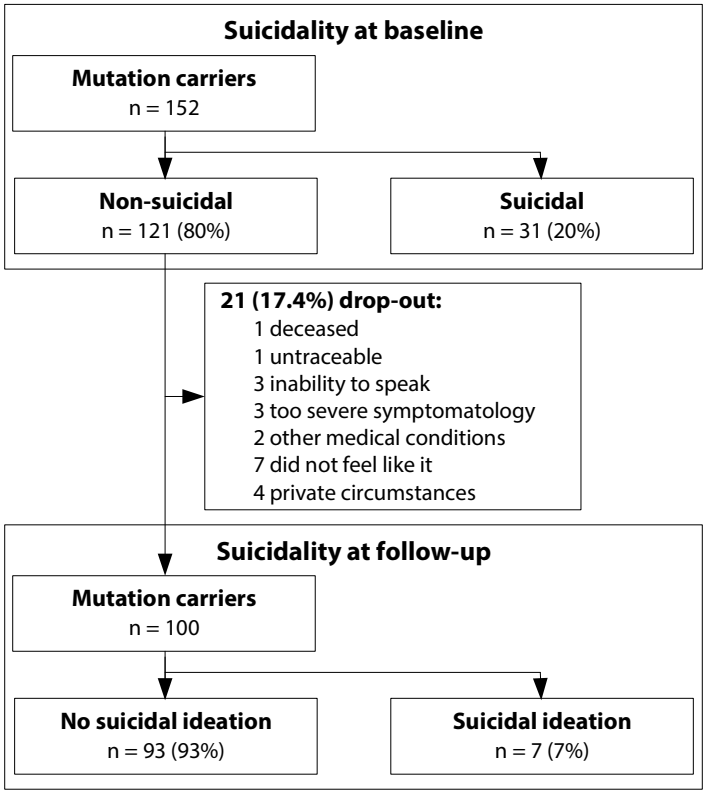


Figure 1. Flowchart of drop-outs in the present study.

Instruments

Assessment of suicidality

Suicidality was assessed using the validated Problem Behaviours Assessment (PBA).[21] The PBA is a semi-structured interview specifically designed for patients with HD, assessing the frequency and severity of 36 common behavioural problems. The interrater reliability of the PBA (Dutch translation) is 0.82 for severity scores and 0.73 for frequency scores.[22]

Severity and frequency of suicidality in the month preceding the interview were assessed with the item 'suicidal ideation' of the PBA (question 8) (Figure 2A). The total suicidality score is computed by multiplying the severity and frequency scores of this item, resulting in total scores ranging from 0 through 16. Based on clinical experience, a total (multiplied) suicidality score > 1 point was used to characterise suicidality (Figure 2B), meaning that participants

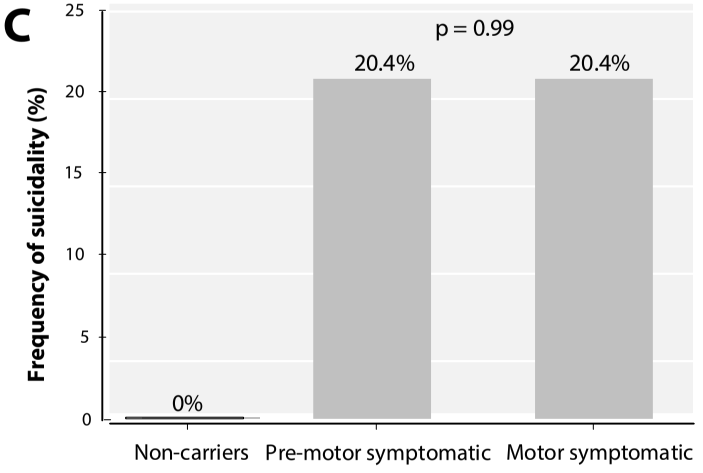
A **Frequency ratings for suicidality**

0 – **Never** or almost never
1 – **Seldom**; less than once a week
2 – **Sometimes**; at least once, up to three/four times a week
3 – **Frequently**; five, six or seven times a week
4 – **Every day**; or almost every day for most/all of the day

Severity ratings for suicidality

0 – **Absent**
1 – **Questionable**; also rate 1 if subject plans suicide at a later date when disease is more severe but obtains comfort from this as means to retain control of destiny
2 – **Mild**; sometimes very pessimistic with fleeting suicidality
3 – **Moderate**; subject has pervasive and distressing feelings of hopelessness and frequent suicidal ideation, but has not yet acted on this in any way
4 – **Severe**; subject has attempted or prepared suicide

C



B

Severity of suicidality	Frequency of suicidality				
	Absent (0)	**Seldom (1)**	**Sometimes (2)**	**Frequently (3)**	**Every day (4)**
Absent (0)	114 (75%)	0 (0%)	(0%)	0 (0%)	0 (0%)
Questionable (1)	0 (0%)	7 (4.6%)	5 (3.3%)	1 (0.7%)	5 (3.3%)
Mild (2)	0 (0%)	5 (3.3%)	4 (2.6%)	3 (2.0%)	1 (0.7%)
Moderate (3)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)	3 (2.0%)
Severe (4)	0 (0%)	1 (0.7%)	1 (0.7%)	0 (0%)	0 (0%)

Figure 2. Suicidality in the study population.

Box A shows the rating scale of suicidality according to item 8 of the Problem Behaviours Assessment, composed of severity and frequency ratings. The total suicidality score is calculated as the severity rating multiplied by the frequency rating. Participants scoring > 1 are considered suicidal. Box B shows the frequency and severity suicidality scores of all 152 mutation carriers. The shaded area indicates the suicidal mutation carriers (n = 31; 20.4%). Box C shows the frequency of suicidality in the study population according to categories of non-carriers, pre-motor symptomatic (UHDRS motor score confidence level ≤ 1) and motor symptomatic mutation carriers (UHDRS motor score confidence level > 1).

scoring a total score of 1 on the 'suicidal ideation' item were not considered suicidal, since suicidal ideation is then 'questionable and seldom' present according to the participant or interviewer. When participants were very pessimistic with fleeting suicidal thoughts, although 'seldom' (less than once a week), they scored 2 points on the 'suicidal ideation' item. These participants were categorised as being suicidal. The cut-off value also implies that participants who were not actively suicidal at the time of assessment, but 'sometimes' (at least once a week) considered suicide as an option for a later date, were categorised as being suicidal.

Sociodemographic and clinical characteristics
Information on sociodemographics and clinical characteristics, and use of psychotropics was collected using a standardised interview.

Total Functioning Capacity (TFC) subscale of the Unified Huntington's Disease Rating Scale (UHDRS) was used to assess global functioning.[23] Scores range from 0 through 13 points, with lower scores indicating poorer global functioning.[24]

Motor function was assessed by an experienced neurologist using the motor scale of the UHDRS.[23] This scale includes the rating of 15 motor symptoms on a scale from 0 (normal) to 4 (severe). The total UHDRS motor score is the sum of these 15 individual items. Total scores range from 0 through 124 points, with higher scores indicating worse motor functioning. The diagnostic Confidence Level (CL) of this UHDRS motor scale[23] was used to define mutation carriers as pre-motor symptomatic (CL score 0 or 1 point) or motor symptomatic (CL score 2 through 4 points).

Neuropsychiatric characteristics
Apathy was assessed using the Apathy Scale (AS).[25] This semi-structured interview consists of 14 questions to determine the level of apathy, with scores ranging from 0 through 3, with a maximum total score of 42 points. A cutoff score ≥ 14 points was used to indicate presence of apathy.[25;26]

The item 'depressed mood' from the PBA[21] was used to assess severity and frequency of a depressed mood in the month preceding the interview, with both severity and frequency scores ranging from 0 (normal/never) to 4 (severe/always). Based on clinical experience, a total (multiplied) depressed mood score > 1 point was used to characterise the participant as having a depressed mood, since a total score of 1 on the 'depressed mood' item is scored when the presence of a depressed mood is questionable and seldom according to the participant or interviewer.

The Dutch translation of the computerised version of the Composite International Diagnostic Interview (CIDI, Version 2.1)[27] was used to assess the presence of a psychiatric disorder according to the criteria of the Diagnostic Statistical Manual (DSM) of mental disorders, version IV.[28] The CIDI is a completely structured and standardised psychiatric diagnostic interview. The CIDI was not administered in participants scoring < 18 points on the Mini-Mental State Examination, since the CIDI cannot be reliably administered in participants with such severe cognitive dysfunction.

Cognitive characteristics

The Mini-Mental State Examination (MMSE) was used to determine global cognitive functioning. The ExCog was used as a measure for executive cognitive function. This composite variable was obtained by averaging the standardised z-scores of the cognitive subscales of the UHDRS,[23] including the Verbal Fluency Test (VFT),[29] the Symbol Digit Modalities Test (SDMT)[30] and the Stroop tests.[31]

Statistical analyses

Data are presented as n (%), mean (±SD) or median (interquartile range, IQR) when appropriate. Sociodemographic and clinical characteristics of HD mutation carriers and non-carriers were compared by chi-squared tests for categorical data, t-tests for independent samples with normal distributions, or non-parametric Whitney-U tests for continuous variables without normal distributions.

Suicidal mutation carriers were compared with non-suicidal mutation carriers using univariate logistic regression analysis. Scores on the independent variables TFC, UHDRS-motor, MMSE and ExCog were dichotomised at the median. The independent cross-sectional associations of suicidality in HD were determined by multiple forward logistic regression analysis. Variables included in this analysis had a p-value ≤ 0.10 in the univariate logistic regression and we also adjusted for sex and age (being forced into the model). The overall use of psychotropic medication was not included in the analysis because of overlap with the use of antidepressants. The presence of a formal DSM-IV diagnosis of depression according to the CIDI was not included in the original models because the CIDI could not be administered in 12 participants scoring < 18 points on the MMSE.

Non-suicidal mutation carriers at baseline, who became suicidal at follow-up, were compared with those mutation carriers who did not become suicidal at follow-up using univariate logistic regression analyses. Since only 7 mutation carriers had incident suicidality at the 2-year follow-up that resulted in low power, the multivariate cross-sectional model was the only one tested

using the longitudinal data in which the significant associations of suicidality in the cross-sectional model (use of antidepressants and presence of a depressed mood according to the PBA) and sex and age were entered. A p-value < 0.05 was considered statistically significant. SPSS version 16.0 was used.

Results

Mutations carriers versus non-carriers

Compared with the 56 non-carriers, the 152 mutation carriers were significantly older and more often had a depressed mood according to the PBA, although there was no significant difference in the presence of a formal DSM-IV diagnosis of depression. Mutation carriers also had worse cognitive scores on all cognitive tests compared with non-carriers (data not shown). Suicidality was only present in mutation carriers (Figure 2C).

Comparison of Huntington's disease mutation carriers with and without suicidality

At baseline, 31 mutation carriers (20%) were considered suicidal according to the PBA, whereas 121 mutation carriers (80%) were not (Table 1, Figure 2B, C). There was no significant difference in the prevalence of suicidality between pre-motor symptomatic (CL ≤ 1) and motor symptomatic (CL ≥ 2) mutation carriers (Figure 2C). Also, there was no significant difference in presence of suicidality between participants who received their genetic test result in the year preceding the interview and those who received their genetic test result more than a year prior to the interview (data not shown).

Univariate analyses showed a significantly higher use of psychotropics (specifically antidepressants) in suicidal mutation carriers compared with non-suicidal mutation carriers. Suicidal mutation carriers were more often apathetic, more often had a depressed mood according to the PBA, and were more often diagnosed with a formal DSM-IV diagnosis of depression. There was no significant difference between the two groups in cognitive functioning (Table 1).

Table 1. Sociodemographic and clinical characteristics as associations of suicidality in Huntington's disease mutation carriers.[a]

	Non-suicidal (n = 121)	**Suicidal** (n = 31)	**Odds Ratio**[b]	**95% CI**[b]	**p-value**[b]
Sociodemographic characteristics					
Male gender (n, %)	55 (46%)	14 (45%)	0.99	0.45 – 2.18	0.98
Age (years ± SD)	47.9 ± 11.5	47.2 ± 13.2	1.00	0.96 – 1.03	0.79
Married or with partner (n, %)	89 (74%)	22 (71%)	0.88	0.37 – 2.11	0.77
Children (n, %)	95 (80%)	19 (68%)	0.53	0.22 – 1.33	0.18
Institutionalised (n, %)	10 (8%)	4 (13%)	1.64	0.48 – 5.65	0.43
Clinical characteristics					
CAG repeats (number ± SD)	44.1 ± 3.2	43.9 ± 2.9	0.98	0.86 – 1.11	0.70
Estimated duration of disease[c] (years ± SD)	2.6 ± 11.4	1.5 ± 13.5	0.99	0.96 – 1.03	0.64
TFC score[d] ≤ 10.5 points (n, %)	57 (47%)	19 (61%)	1.78	0.79 – 3.98	0.16
UHDRS-motor[e] ≥ 15 points (n, %)	62 (51%)	16 (52%)	1.02	0.46 – 2.24	0.97
Pre-motor symptomatic disease stage[f] (n, %)	43 (36%)	11 (36%)	1.00	0.44 – 2.28	0.99
Use of psychotropic medication (n, %)	42 (35%)	20 (65%)	3.42	1.50 – 7.81	0.004
Use of antidepressants (n, %)	25 (21%)	18 (58%)	5.32	2.30 – 12.3	<0.001
Use of benzodiazepines (n, %)	25 (21%)	11 (36%)	2.11	0.90 – 4.98	0.09
Use of antipsychotics (n, %)	13 (11%)	5 (16%)	1.60	0.52 – 4.88	0.41

Neuropsychiatric characteristics					
Apathy Scale score[g] ≥ 14 points (n, %)	33 (27%)	16 (52%)	2.84	1.27 – 6.40	0.01
Depressed mood to PBA[h] score > 1 point (n, %)	50 (41%)	25 (81%)	5.92	2.26 – 15.5	<0.001
Any psychiatric disorder to CIDI[i] (n, %)	13/113 (12%)	6/27 (22%)	2.20	0.75 – 6.44	0.15
Depressive disorder to CIDI[i] (n, %)	4/113 (4%)	4/27 (15%)	4.74	1.10 – 20.3	0.04
Cognitive characteristics					
MMSE[j] score ≤ 27 points (n, %)	63 (52%)	19 (61%)	1.46	0.65 – 3.26	0.36
ExCog[k] ≤ 0.04 (n, %)	62 (51%)	14 (45%)	0.78	0.36 – 1.73	0.55

[a] Cross-sectional analysis using univariate logistic regression.
[b] Odds ratio, 95% CI and p-value by binary logistic regression.
[c] Estimated duration of disease is calculated by the current age minus the estimated age of onset (calculated using the formula of Vassos et al).[34] Estimated duration of disease can be negative.
[d] TFC score: Total Functional Capacity score, scores ranging from 0 t0 13 points; higher scores indicating better total functioning.
[e] UHDRS-motor: Unified Huntington's Disease Rating Scale motor section, scores ranging from 0 through 124 points; higher scores indicating more motor disorders.
[f] Pre-motor symptomatic mutation carriers are defined as HD mutation carriers with a UHDRS confidence level ≤ 1 point. HD mutation carriers with a UHDRS confidence level > 1 point are considered to be motor symptomatic.
[g] Apathy Scale score: scores ranging from 0 through 42 points; higher scores indicating more apathy.
[h] Depressed mood score of the Problem Behaviours Assessment (question 1), consisting of the severity and frequency score for depressed mood. Scores ranging from 0 through 16 points.
[i] CIDI: Composite International Diagnostic Interview to assess the presence of a depressive disorder and a psychiatric disorder in the last month. Could not be completed in 12 participants because of a MMSE score < 18 points.
[j] MMSE score: Mini-Mental State Examination, scores ranging from 0 through 30 points; higher scores indicating better mental state.
[k] ExCog: executive cognition; higher scores indicating better cognitive function.

Using multivariate analyses, the use of antidepressants (odds ratio (OR) = 3.96; 95% confidence interval (CI) = 1.59–9.87) and the presence of a depressed mood according to the PBA (OR = 4.17; 95% CI = 1.52–11.5) were independently associated with suicidality (Table 2).

In addition, sensitivity analyses were conducted to evaluate the robustness of the model. All participants scoring 1 (non-suicidal) or 2 (suicidal) on the suicidality item were excluded from the analysis. This sensitivity analysis confirmed our findings with higher OR on the covariates, whereas the TFC score (OR = 2.88; 95% CI = 1.04–7.95) and use of benzodiazepines (OR = 3.14; 95% CI = 1.18–8.37) also showed a significant difference between the suicidal and non-suicidal groups (data not shown). In the multivariate model, the presence of a depressed mood and use of antidepressants remained the only independent associations of suicidality (data not shown).

Next, the DSM-IV diagnosis of depression was forced into the cross-sectional multivariate model. The presence of a depressed mood and use of antidepressants remained the independent associations of suicidality (data not shown).

Table 1 shows that 8 participants had a formal DSM-IV diagnosis of depression (4 in the non-suicidal and 4 in the suicidal group). After exclusion of these 8 participants, the presence of a depressed mood according to the PBA and use of antidepressants again remained the only independent associations of suicidality (data not shown).

Predictors of suicidality at follow-up

Of the 121 participants free of suicidality at baseline (all had a suicidality score of 0), 100 were available for re-assessment after 2 years. The 21 drop-outs (17.4%) showed no significant differences on any of the baseline variables compared with the 100 participants that were followed up (data not shown). Seven (7%) of these 100 participants were suicidal at follow-up. Four of these 7 mutation carriers scored ≥ 4 on the suicidality item at follow-up, indicating moderate to severe suicidality. At baseline, these suicidal mutation carriers more often had a depressed mood according to the PBA (OR = 10.4; 95% CI = 1.20–90.2) and a formal DSM-IV psychiatric diagnosis (OR = 6.58; 95% CI = 1.27–34.2), although not particularly of depression (data not shown). Assessment of the CIDI at baseline was not possible in 5 of the 100 participants who were followed up because of severe cognitive impairment.

Using multivariate analysis in which sex, age, use of antidepressants and depressed mood were entered, depressed mood (OR = 10.6; 95% CI = 1.17–97.0) was the only significant independent predictor of suicidality (Table 2).

Table 2. Independent associations and predictors of suicidality in Huntington's disease mutation carriers.

Cross-sectional analysis (n = 152) *(31/152 were suicidal at baseline)*			
Baseline variable	**Odds Ratio**[a]	**95% CI**[a]	**p-value**[a]
Male gender	0.82	0.34 – 1.99	0.66
Age (years)	0.99	0.96 – 1.03	0.67
Use of antidepressants	3.96	1.59 – 9.87	0.003
Depressed mood[b]	4.17	1.52 – 11.5	0.006
Longitudinal analysis (n = 100) *(7/100 were suicidal at follow-up)*			
Baseline variable	**Odds Ratio**[a]	**95% CI**[a]	**p-value**[a]
Male gender	0.16	0.02 – 1.54	0.11
Age (years)	1.01	0.94 – 1.09	0.71
Use of antidepressants	1.33	0.21 – 8.48	0.76
Depressed mood[b]	10.6	1.17 – 97.0	0.04

Covariates cross-sectional analysis (forward model): use of antidepressants, use of benzodiazepines, Apathy Scale score, and depressed mood according to the PBA. Adjustment for sex and age.
Entered longitudinal analysis (enter model): sex, age, use of antidepressants, and depressed mood according to the PBA.
[a] Odds ratio, 95% CI and p-value by binary logistic regression.
[b] Depressed mood score of the Problem Behaviours Assessment (question 1), consisting of the severity and frequency score for depressed mood. Scores ranging from 0 through 16 points.

Discussion

The results of this study confirm that suicidality frequently occurred in this HD study group with a prevalence of 20% in mutation carriers compared with 0% in non-carriers. No difference was found in suicidality prevalence between pre-motor symptomatic and motor symptomatic mutation carriers. Cross-sectionally, suicidal mutation carriers were more likely to be depressed than non-suicidal mutation carriers, as shown by the higher use of antidepressants, the higher prevalence of apathy, possibly being a symptom of depression, the increased prevalence of a depressed mood according to the PBA and a more frequent formal DSM-IV diagnosis of depression. Longitudinally, these results were confirmed since the presence of a depressed mood was the only predictor of suicidality.

The prevalence of 20% suicidality among mutation carriers as found in our study is in accordance with a recent multi-site HD study reporting a suicidality month prevalence of 19% among motor symptomatic HD carriers, while the suicidality prevalence among pre-motor symptomatic mutation carriers was not investigated.[10] A large European cross-sectional study (Registry) also reported a suicidality prevalence of 19.9% among pre-motor and motor symptomatic mutation carriers.[11] However, the Registry study reported lifetime prevalence of suicidal ideation or suicidal attempts, assessed as present or absent, whereas our study focused on suicidality prevalence in the previous month, assessed by a score ranging from 0 through 16. This lifetime prevalence in the Registry study may be an underestimation of the true suicidality prevalence in HD due to recall bias in that study, and because the presence of suicidality was not investigated in a detailed psychopathology interview but in a general questionnaire on medical history.

Remarkably, both in pre-motor symptomatic and motor symptomatic mutation carriers the baseline suicidality prevalence was 20%. This is in line with previous studies that suggested two critical periods of suicide risk in HD. This first critical period for suicidality occurs when genetically at-risk individuals are in the period immediately before diagnosis when they start to experience symptoms of HD,[8;17;32] while they only have non-specific neurological signs and not yet unequivocal signs of HD.[32] Suicidal pre-motor symptomatic mutation carriers in our study population belong to this first critical period of suicidality. A similar suicidality prevalence was found among motor symptomatic mutation carriers, who belonged to the second critical period for suicide risk occurring when patients with unequivocal motor symptoms of HD become more dependent on others for daily activities, as assessed by the TFC.[32] In contrast to others,[32] we found no relationship between TFC and suicidality. Various phenomena may contribute to the equal suicidality prevalence in both pre-motor and motor symptomatic mutation carriers

in the present study. First, before motor symptoms even appear, psychopathology (in particular depression) often arises.[22;33] This may contribute to the relatively high prevalence of suicidality in pre-motor symptomatic mutation carriers since the presence of a depressed mood seems to be the most important predictor of suicidality. Furthermore, the emotional distress of having an incurable disease with a devastating course might also contribute to the relatively high suicidality prevalence already in pre-motor symptomatic mutation carriers. Moreover, diminished support from and increased mortality rates among affected family members could also lead to complicated grief, depression and suicidality.

The most important correlate and predictor of suicidality in HD mutation carriers was the presence of a depressed mood according to the PBA, despite that not all these participants had a formal DSM-IV diagnosis of depression. Cross-sectionally, an association between a depression subscale and suicidality was found in the Registry study and the multi-site HD study, whereas in these studies motor and cognitive subscores of the UHDRS were not associated with suicidality.[10;11] Longitudinally, depressed mood was found to be predictive of suicidal attempts and completed suicide in prodromal HD.[16] Both our cross-sectional and longitudinal findings are in line with these latter results.

Besides having a depressed mood, suicidal mutation carriers were cross-sectionally more likely to use antidepressants. The percentage of participants using antidepressants was much higher than the percentage of participants officially diagnosed with a DSM-IV diagnosis of depression. However, antidepressants may already be prescribed before a patient meets the official criteria of a DSM-IV diagnosis of depression, or because of a depression in remission. Furthermore, in HD antidepressants are also prescribed for anxiety and irritability.[3] Since use of antidepressants was only associated with suicidality in the cross-sectional analysis, it is unlikely that the use of antidepressants causes suicidality.

The strengths of this study are the combination of cross-sectional and longitudinal analyses, the use of a comparison group (consisting of first-degree non-carriers at risk for HD), and the use of specific and validated measurement tools in a standardised interview.

Some limitations also warrant discussion. First, the study population available for follow-up was relatively small since HD is a rare disease; the use of larger databases will improve reliability. Despite the relatively small number of participants, all analyses consistently indicated a strong relationship of suicidality with depressed mood. Further, many of the variables included in this study were dichotomised because of their skewed distributions, which adversely affected the statistical power. Third, variables previously found to be associated with suicidality in HD, like

pessimism, hopelessness,[7] aggression,[10] unemployment[15] and a history of suicide attempt,[16] were not included in our analyses. Finally, selection bias might have occurred since suicidal and/or depressed participants might have been more likely to refuse participation, which may have caused an underestimation of the true suicidality prevalence and incidence in HD.

Given the elevated suicidality prevalence in the HD population, it is important to regularly screen both pre-motor and motor symptomatic HD mutation carriers for suicidal ideation during clinical assessment. We found that the presence of a depressed mood was the main risk factor for suicidality in HD. Assessment of suicidal ideation is a priority in those with a depressed mood, and strategies of support and treatment should certainly be available for this subgroup of patients.

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Chapter 3

Suicidal ideation in a European Huntington's disease population

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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

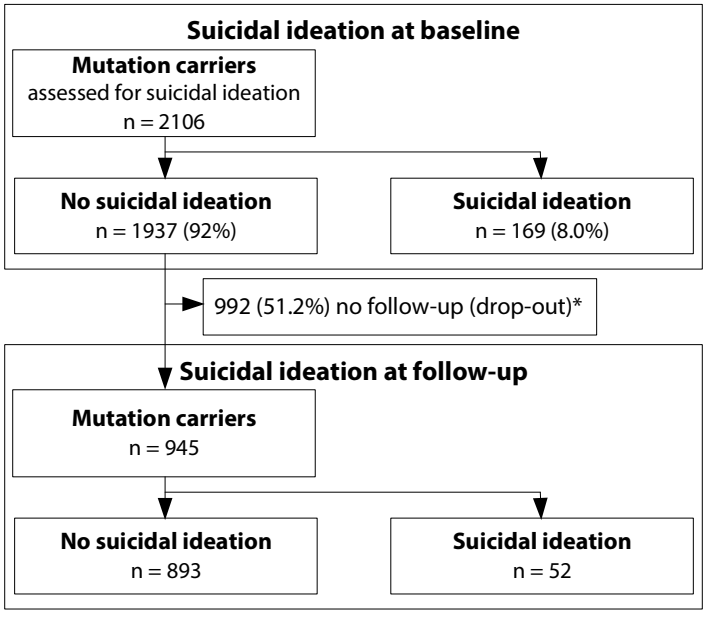


Figure 1. Flowchart of drops-outs.
* drop-outs had a significantly longer estimated duration of disease, lower Total Functioning Capacity (TFC) score and higher Unified Huntington's Disease Rating Scale (UHDRS)-motor score. No significant difference in any of the neuropsychiatric characteristics.

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.

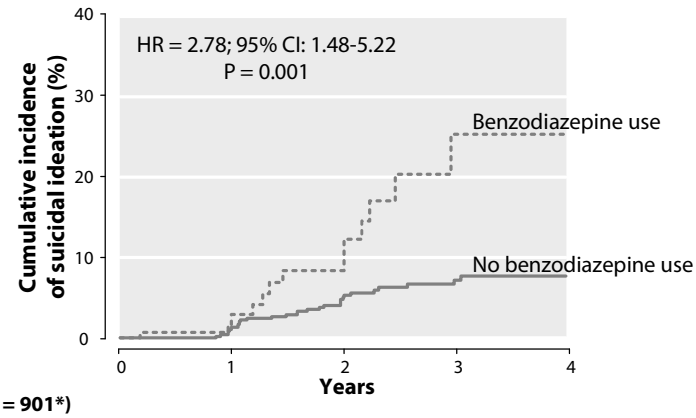
Multivariate Cox regression (n = 885)[a] *(47/885 had suicidal ideation at follow-up)*			
Baseline variable	**Hazard Ratio (95% CI)[b]**	**Wald statistic[b] df = 1**	**p-value[b]**
Sociodemographic characteristics			
Male gender	1.03 (0.57 – 1.84)	0.01	0.94
Age (years)	1.00 (0.97 – 1.02)	0.12	0.73
Psychotropic 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.

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Chapter 4

Acute-phase proteins in relation to neuropsychiatric symptoms and use of psychotropic medication in Huntington's disease

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Abstract

Activation of the innate immune system has been postulated in the pathogenesis of Huntington's disease (HD). We studied serum concentrations of C-reactive protein (CRP) and albumin as positive and negative acute-phase proteins in HD. Multivariate linear and logistic regression was used to study the association between acute-phase protein levels in relation to clinical, neuropsychiatric, cognitive, and psychotropic use characteristics in a cohort consisting of 122 HD mutation carriers and 42 controls at first biomarker measurement, and 85 HD mutation carriers and 32 controls at second biomarker measurement. Significant associations were found between acute-phase protein levels and Total Functioning Capacity (TFC) score, severity of apathy, cognitive impairment, and the use of antipsychotics. Interestingly, all significant results with neuropsychiatric symptoms disappeared after additional adjusting for antipsychotic use. High sensitivity CRP levels were highest and albumin levels were lowest in mutation carriers who continuously used antipsychotics during follow-up versus those who had never used antipsychotics (mean difference for CRP 1.4 SE mg/L; $p = 0.04$; mean difference for albumin 3 SE g/L; $p < 0.001$). The associations found between acute-phase proteins and TFC score, apathy, and cognitive impairment could mainly be attributed to the use of antipsychotics. This study provides evidence that HD mutation carriers who use antipsychotics are prone to develop an acute-phase response.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, characterised by motor abnormalities, cognitive dysfunction, and neuropsychiatric symptoms[1] including depressed mood,[2] apathy,[3;4] and irritability.[5] Although the mean age of onset is 40 years, there is a wide range in age at onset, severity, and symptomatology of HD. HD is caused by an expanded trinucleotide cytosine-adenine-guanine (CAG) repeat on chromosome 4 coding for the mutant huntingtin protein.[6] Although the genetic defect has been elucidated, its role in the pathogenesis of HD remains unclear.

There is increasing evidence that the immune system may be involved in the pathogenesis of HD. Increased activation of components of the innate and adaptive immune systems has been found in the central nervous system (CNS)[7-9] and peripheral tissues of HD patients.[10] In particular, increased concentrations of tumor necrosis factor (TNF)-α and interleukin (IL)-6, have been found in plasma of HD mutation carriers when compared to controls.[11] Physiologically, TNF-α and IL-6 are pro-inflammatory cytokines which are released in the bloodstream as part of the acute-phase response.[12;13] C-reactive protein (CRP) synthesis is upregulated in the liver under regulation of IL-6,[14] whereas the synthesis of other proteins such as albumin is down-regulated. Since in the acute-phase response CRP levels increase, CRP can be thought of as a positive acute-phase protein and since albumin levels decrease, albumin can be thought of as a negative acute-phase protein.

Previously, CRP levels have been reported to be significantly increased in HD mutation carriers in advanced disease stage when compared to controls.[15] Levels of CRP were significantly higher in a group of 13 HD mutation carriers when compared to 10 healthy controls. Also, levels of CRP were higher in HD mutation carriers with more advanced disease.[16] A large set of markers for inflammation and innate immunity was measured in a recent study that included two cohorts comprising 81 HD mutation carriers and 40 controls, but none of the more than 20 plasma constituents were significantly different between the groups.[17] Nevertheless, post-hoc tests revealed significantly lower CRP levels in HD mutation carriers with early disease versus controls, whereas premanifest HD had similar levels compared with controls.

In various other populations, there are reports indicating an association between CRP[18-20] and albumin[21-24] levels on the one hand, and both cognitive dysfunction and neuropsychiatric symptoms on the other hand. In a systematic review assessing the association between CRP level and stroke, cognitive disorders, and depression,[18] raised CRP concentrations were associated with cognitive decline and increased risk of dementia. Low albumin levels were

associated with cognitive dysfunction in two large population-based studies of the non-demented elderly.[21;22] In a large longitudinal study with 73,131 participants from the general population, a positive association was found between CRP levels and depressive symptoms.[19] Also, a meta-analysis showed a positive correlation between CRP levels and depression (d = 0.15; 95% confidence interval [CI] 0.10–0.21).[20] Low albumin levels were found in depressed patients compared to healthy controls.[23;24] Cross-sectionally, a significant association was found between CRP levels and apathy in elderly individuals.[25] Longitudinally, however, higher CRP levels were not associated with an increased risk of apathy in individuals aged 85 years and over.[26]

Antipsychotics are frequently prescribed for symptomatic treatment of chorea and neuropsychiatric symptoms in HD.[27] It has become apparent that the use of antipsychotics may adversely affect CRP levels.[23;28;29] In addition, weight gain is a well-known side-effect of treatment with atypical antipsychotics,[30] which is associated with an increase of IL-6 and other proteins associated with low-grade inflammation.[31] The effects of antipsychotics on levels of albumin have not been thoroughly studied, although serum albumin was decreased in a group of schizophrenic patients when compared with healthy controls. However, no significant effect of the use of antipsychotics was demonstrated.[32]

This study aims to investigate CRP levels as a positive acute-phase protein and albumin levels as a negative acute-phase protein in relation to clinical, neuropsychiatric, and cognitive characteristics in a cohort of HD mutation carriers. For this, we took into account factors that might have confounded or otherwise influenced these associations, in particular the use of antipsychotics. Our hypothesis was that, with disease progression, inflammatory activity would increase leading to higher CRP levels and lower albumin levels, associated with a higher prevalence of cognitive impairment and neuropsychiatric symptoms.

Experimental procedures

Population

Between May 2004 and August 2006, 152 HD mutation carriers and 56 controls were recruited for participation. Sources for recruitment were the outpatient departments of Neurology and Clinical Genetics of the Leiden University Medical Center (LUMC) and a regional nursing home specialised in care for HD patients. Besides HD mutation carriers, verified first-degree non-carriers participated in the study as controls. The study design is described in detail elsewhere.[33] A second measurement was conducted two years after the baseline visit (including 128

mutation carriers and 42 controls) and a third measurement two years thereafter (including 94 HD mutation carriers and 32 controls). Blood samples suitable for the determination of high sensitivity CRP (hsCRP) and albumin levels were available at the second and the third measurement. Since 6 participants did not give blood at the first biomarker measurement (defined as t1) they were excluded from the analyses, which resulted in 122 mutation carriers at t1. At the second biomarker measurement (defined as t2), 9 participants did not give blood, which resulted in 85 mutation carriers at t2.

Sample withdrawal and biochemical analyses

At t1 and t2 EDTA blood was withdrawn between the years 2008 and 2012 and subsequently stored at -80 ºC within 2 h. Blood samples were stored until measurement of hsCRP and albumin levels in the fall of 2012. hsCRP was determined in EDTA plasma with an IFCC standardised method (Cat. no. 04628918190) on a COBAS INTEGRA 800 analyser from Roche Diagnostics, according to the instructions of the manufacturer. The expected reference range for hsCRP in adult males and females is < 5 mg/L. Between-run coefficients of variation (CVs) during the study period (12 runs) were 5.8% at 4.09 mg/L, and 5.7% at 12.81 mg/L. Albumin in EDTA plasma was determined with an IFCC standardised method (Cat. no. 11970909216) on Modular P systems from Roche Diagnostics, using a BCG-based colorimetric assay with endpoint detection. This method has been standardised against the CRM 470 reference preparation. The reference range for serum albumin in adult males and females is 34–48 g/L. CVs during the study period (7 runs) were 2.94% at 37.5 g/L and 1.01% at 55.0 g/L.

Sociodemographic and clinical characteristics

Information on sociodemographic and clinical characteristics, including the potential confounders like current smoking, high alcohol consumption (defined as drinking more than 14 standardised units of alcohol a week), body weight and height, and medication use, was collected using a standardised interview. Use of antipsychotics was divided in different categories: typical antipsychotics, atypical antipsychotics, and tiapride. Tiapride was considered a separate category as it was used by many participants and cannot be classified unambiguously within one of the other categories. The estimated duration of disease was calculated by the current age minus the estimated age of onset according to the equation of Vassos.[34] The Total Functional Capacity (TFC) scale of the Unified Huntington's Disease Rating Scale (UHDRS)[35] was used to assess global daily functioning and disease stage.[36] Total scores range from 0 through 13 points, with higher scores indicating better global functioning.[37]

Motor functioning was assessed by a trained neurologist using the motor scale of the UHDRS.[35] Total scores range from 0 through 124, with higher scores indicating worse motor functioning.

The diagnostic Confidence Level (CL) of the UHDRS motor scale was used to define mutation carriers as pre-motor symptomatic (CL 0 or 1 point) or motor symptomatic (CL 2 through 4 points).

Neuropsychiatric characteristics

Neuropsychiatric characteristics were assessed by the Dutch version of the Problem Behaviours Assessment (PBA),[38] a semi-structured interview, assessing the frequency and severity of 36 potential behavioural problems in HD. The inter-rater reliability of the Dutch version of the PBA is 0.82 for severity scores and 0.73 for frequency scores.[39] In this study we used symptom factors that were previously estimated by factor analysis of the PBA, which resulted in three factors: apathy (range 0–64), irritability (range 0–80), and depression (range 0–80).[39] Additionally, suicidality was assessed with the PBA[38] by multiplying the severity and frequency score of the item 'suicidal ideation'. As done before, a total score > 1 point on this item was used to characterise the presence of suicidality.[40]

Cognitive characteristics

The Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning. Total scores range from 0 through 30 points, with higher scores indicating better global cognitive functioning.[41] The cognitive scales of the UHDRS,[35] including the Verbal Fluency Test (VFT),[42] the Symbol Digit Modalities Test (SDMT),[43] and the Stroop tests,[44] were used to assess executive cognitive functioning. For all cognitive scales, higher scores indicate better executive functioning. The ExCog, a composite variable obtained by averaging the standardised z-scores of the other executive cognitive subscales, was used as a measure for executive cognitive functioning.

Statistical analyses

Data are presented as n (%), mean (± standard deviation [SD]), mean (95% CI), or median (interquartile range [IQR]) when appropriate.

Because of their positively skewed distribution, hsCRP levels were log transformed before being used in statistical analyses. Characteristics of HD mutation carriers and controls at t1 were compared by chi-squared tests for categorical data, t-tests for independent samples with normal distributions, or non-parametric Whitney-U tests for continuous variables without normal distributions.

Associations between hsCRP and albumin levels and clinical, neuropsychiatric, and cognitive characteristics were determined by linear regression analysis for continuous outcomes and

logistic regression analysis for dichotomous outcomes. Apart from the crude model, we adjusted in the first multivariate models for the potential confounders sex, age, body mass index (BMI), smoking, and alcohol consumption at t1. Since previous literature indicated that the use of antipsychotics may affect CRP levels,[23;28;29] a second model was built, including the variables from the adjusted model and the use of antipsychotics. Furthermore, analysis of covariance (ANCOVA) was used to compare acute-phase protein levels between participants who did not use antipsychotics, participants who started using antipsychotics during the study period, and participants who continuously used antipsychotics, with adjustment for sex, age, BMI, smoking, and alcohol consumption at t1. In an additional model comparing acute-phase protein levels at t2 between the different groups, we additionally adjusted for acute-phase protein levels at t1. As a sensitivity analysis, this ANCOVA was repeated without participants whose hsCRP level was above 10 mg/L, due to their possible association with acute infectious diseases. Since almost all participants who used antipsychotics were in later disease stages and disease stage may also be related to the acute-phase response, we performed a sensitivity analysis which only included the participants with a disease stage > 2 (TFC score < 7) at t1. As previous research showed that the effect of antipsychotic use on CRP levels is different for different kinds of antipsychotics,[28] we performed a mixed model analysis (i.e., multilevel regression analysis) with adjustment for age, sex, BMI, smoking, and alcohol consumption at t1, to evaluate associations between the different categories of antipsychotics and acute-phase protein levels.

A p-value < 0.05 was considered statistically significant. P-values presented were not corrected for multiple comparisons, since we interpreted the overall pattern of diminishing effect sizes and p-values after additional adjustment for the use of antipsychotics in multivariable models. SPSS version 20.0 was used.

Results

Characteristics of mutation carriers versus controls

At t1, mutation carriers more often used psychotropic medication, had higher scores on the apathy, irritability, and depression factors of the PBA and worse scores on all cognitive tests, compared with controls (Table 1). When comparing acute-phase proteins, the hsCRP level of the mutation carriers at t1 was non-significantly higher in mutation carriers compared with controls (Table 1). At t2, the hsCRP level of mutation carriers was significantly higher compared with controls (mean = 1.94; 95% CI = 1.50–2.51 versus 0.99; 95% CI = 0.64–1.52, respectively; p = 0.002) (data not shown). There was a significant trend of increasing hsCRP levels across

Table 1. Characteristics of HD mutation carriers and controls at first biomarker measurement (t1).

	Mutation carriers (n = 122)	**Controls** (n = 42)	**p-value**[a]
Sociodemographic characteristics			
Male gender	54 (44%)	19 (45%)	0.91
Age (years)	49.2 ± 11.5	41.0 ± 11.2	<0.001
BMI (kg/m^2)	25.6 ± 5.1	25.1 ± 4.3	0.62
Smoking	30 (26%)	12 (29%)	0.73
High alcohol consumption	11 (9%)	1 (2%)	0.30
Biological characteristics			
Albumin (mean in g/L, 95% CI)	47.1 (46.5 – 47.7)	48.5 (47.6 – 49.5)	0.01
hsCRP[b] (mean in mg/L, 95% CI)	1.49 (1.20 – 1.86)	1.23 (0.85 – 1.79)	0.39
Clinical characteristics			
CAG repeats (number)	44.1 ± 3.2	21.6 ± 4.2	<0.001
Estimated disease duration (years)	3.8 ± 11.4	NA	NA
TFC score	8 (3 – 13)	13 (13 – 13)	<0.001
UHDRS motor score	19 (5 – 48)	NA	NA
Pre-motor symptomatic	33 (28%)	NA	NA
Antidepressant use	44 (36%)	1 (2%)	<0.001
Benzodiazepine use	25 (21%)	0 (0%)	0.001
Antipsychotic use	35 (29%)	0 (0%)	<0.001
Neuropsychiatric characteristics			
PBA apathy factor score	2 (0 – 18)	0 (0 – 0)	<0.001
PBA irritability factor score	4 (0 – 15)	0 (0 – 2)	<0.001
PBA depression factor score	4 (0 – 12)	0 (0 – 6)	0.04
PBA suicidality	14 (12%)	1 (2%)	0.08

Table continued on the next page.

Table 1 (continued). Characteristics of HD mutation carriers and controls at first biomarker measurement (t1).

	Mutation carriers (n = 122)	**Controls** (n = 42)	**p-value**[a]
Cognitive characteristics			
MMSE score	28 (24 – 29)	29 (29 – 30)	<0.001
SDMT score	35 (12 – 50)	53 (47 – 58)	<0.001
VFT score	20 (10 – 30)	29 (25 – 37)	<0.001
Stroop colour score	50 (33 – 71)	76 (69 – 87)	<0.001
Stroop word score	71 (41 – 98)	99 (99 – 100)	<0.001
Stroop interference score	29 (16 – 40)	44 (39 – 47)	<0.001
ExCog	-0.20 ± 0.9	0.68 ± 0.3	<0.001

Data are presented as n (%), mean (± SD), or median (interquartile range [IQR]), unless otherwise specified. BMI denotes Body Mass Index; hsCRP, high sensitivity C-reactive protein; CI, confidence interval; NA, applicable; TFC, total functional capacity; UHDRS, Unified Huntington's Disease Rating Scale; PBA, Problem Behaviour Assessment; MMSE, Mini Mental State Examination; SDMT, Symbol-Digit Modalities Test; VFT, Verbal Fluency Test.

[a] P-values by chi-squared test for categorical data, by t-test for independent samples with normal distributions, or non-parametric Whitney-U tests for independent samples without normal distributions.

[b] Because of its skewed distribution, hsCRP was log transformed before the analyses.

increasing disease stages at t1 and t2 (Suppl. Table 1). The albumin level of the mutation carriers was significantly lower compared with controls, both at t1 (Table 1) and t2 (mean = 46.4; 95% CI = 45.8–47.1 versus 47.6; 95% CI = 46.5–48.7, respectively; p = 0.03) (data not shown). However, after correction for potential confounders (sex, age, BMI, smoking, and alcohol consumption) only the hsCRP level at t2 remained significantly different between mutation carriers and controls. There was a significant trend of decreasing albumin levels across increasing disease stages at t1 and t2 (Suppl. Table 1).

Associations between acute-phase proteins and clinical characteristics at t1

Serum hsCRP level was significantly associated with TFC score, apathy score (Table 2), benzodiazepine use, and antipsychotic use (Table 3). Using multivariate linear regression analyses, with adjustment for potential confounders, the hsCRP level remained significantly associated with apathy score, Stroop interference test, and ExCog (Table 2). However, after additional adjustment for use of antipsychotics, all these associations lost their statistical significance (Tables 2 and 3).

Table 2. Cross-sectional relationships between acute-phase proteins and continuous clinical, neuropsychiatric, and cognitive characteristics in 122 HD mutation carriers at first biomarker measurement (t1).

	Crude		Model 1[a]		Model 2[a]	
	hsCRP[b]	**Albumin**	**hsCRP[b]**	**Albumin**	**hsCRP[b]**	**Albumin**
Clinical characteristics						
CAG repeats	0.01	0.11	0.17	-0.04	0.15	0.00
Estimated disease duration	0.12	-0.27**	0.10	-0.04	0.09	-0.01
TFC score[b]	-0.19*	0.38***	-0.15	0.28**	-0.07	0.16
UHDRS motor score[b]	0.12	-0.24**	0.14	-0.14	0.09	-0.05
Neuropsychiatric characteristics						
PBA apathy factor score[b]	0.21*	-0.29***	0.22*	-0.24*	0.15	-0.12
PBA irritability factor score[b]	0.06	-0.05	0.02	-0.10	0.02	-0.11
PBA depression factor score[b]	0.09	0.04	0.08	0.02	0.07	0.04
Cognitive characteristics						
SDMT score[b]	-0.13	0.31***	-0.16	0.20*	-0.08	0.06
VFT score[b]	-0.12	0.24**	-0.17	0.18	-0.11	0.07
Stroop Word Test score[b]	-0.14	0.27**	-0.19	0.18*	-0.12	0.08
Stroop Colour Test score[b]	-0.13	0.32***	-0.18	0.24*	-0.10	0.11
Stroop Interference Test score[b]	-0.13	0.32***	-0.22*	0.24*	-0.14	0.10
ExCog	-0.14	0.30**	-0.20*	0.22*	-0.12	0.09

Data are standardised betas. Analyses performed by linear multivariate regression analyses. Model 1: adjusted for sex, age, BMI, smoking, and alcohol consumption at t1; Model 2: additional adjustment for use of antipsychotics at t1. Explanations of abbreviations and symbols see legend table 3.

Table 3. Cross-sectional relationships between acute-phase proteins and dichotomous clinical, neuropsychiatric, and cognitive characteristics in 122 HD mutation carriers at first biomarker measurement (t1).

	Crude		Model 1[a]		Model 2[a]	
	hsCRP[b]	**Albumin**	**hsCRP[b]**	**Albumin**	**hsCRP[b]**	**Albumin**
Clinical characteristics						
Pre-motor symptomatic	1.20	0.92	1.31	0.97	1.18	1.05
Antidepressant use	1.15	0.88*	0.88	0.92	0.74	0.98
Benzodiazepine use	1.47*	0.75***	1.21	0.79*	1.08	0.84
Antipsychotic use	1.64**	0.72***	1.54	0.77**	n/a	n/a
Neuropsychiatric characteristics						
PBA suicidality	1.05	0.83*	0.92	0.83	0.80	0.86
Cognitive characteristics						
MMSE score	0.79	1.18**	0.71	1.19*	0.78	1.13

Data are odds ratios. Analyses performed by logistic multivariate regression analyses. Model 1: adjusted for sex, age, BMI, smoking, and alcohol consumption at t1; Model 2: additional adjustment for use of antipsychotics at t1.
hsCRP denotes high sensitivity C-reactive protein; TFC, total functional capacity; UHDRS, Unified Huntington's Disease Rating Scale; PBA, Problem Behaviour Assessment; SDMT, Symbol-Digit Modalities Test; VFT, Verbal Fluency Test; BMI, Body Mass Index. MMSE, Mini Mental State Examination.
*$p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[a] n = 115 mutation carriers because of missing values.
[b] Because of its skewed distribution, hsCRP, TFC score, UHDRS motor score, PBA factor scores, SDMT score, VFT score, and Stroop scores were log transformed before the analyses.

Serum albumin level was independently associated with TFC score, apathy score, SDMT score, the Stroop test scores, ExCog (Table 2), MMSE score, use of benzodiazepines, and use of antipsychotics (Table 3). Likewise, after additional adjustment for use of antipsychotics, all these associations lost their statistical significance (Tables 2 and 3).

Associations between acute-phase proteins and clinical characteristics at t2
When analysing cross-sectional associations between hsCRP and albumin levels on the one hand and clinical, neuropsychiatric, and cognitive characteristics on the other hand at t2, similar associations were found as at t1. Once more, significant associations disappeared after additionally adjusting for antipsychotic use (data not shown).

Use of antipsychotics and acute-phase proteins
When comparing mutation carriers who started using antipsychotics during the study period with mutation carriers who did not use antipsychotics during the study period, the hsCRP level of starters at t1 was not significantly different from non-users. At t2, however, the hsCRP level of starters had increased and was higher compared with non-users, although statistical significance disappeared after adjustment for the hsCRP level at t1 (Figure 1 and Suppl. Table 2). Compared with non-users, mutation carriers who continuously used antipsychotics had significantly higher hsCRP levels at both measurements and also had a larger increase in hsCRP level between the two measurements (Figure 1 and Suppl. Table 2).

Likewise, serum albumin levels of antipsychotic starters tended to decline, but the comparison with non-users was not significant at both measurements (Figure 1 and Suppl. Table 2). Albumin levels of continuous users were significantly lower compared with non-users at both t1 and t2, even after adjustment for the albumin level at t1 (Figure 1 and Suppl. Table 2).

After excluding participants with an hsCRP level above 10 mg/L, differences in hsCRP and albumin levels between non-users and starters and between non-users and continuous users at t1 persisted. At t2, continuous users had significantly more often hsCRP levels above 10 mg/L than non-users (21.1% versus 4.1%, respectively; $p = 0.03$). hsCRP levels remained higher and albumin levels lower in starters and continuous users compared with non-users, although the absolute differences substantially attenuated.

When repeating the analysis only in participants with a disease stage > 2, the differences that were found between continuous users and non-users at both t1 and t2 were comparable to those in the original analysis, while this was not the case for the differences between starters and non-users.

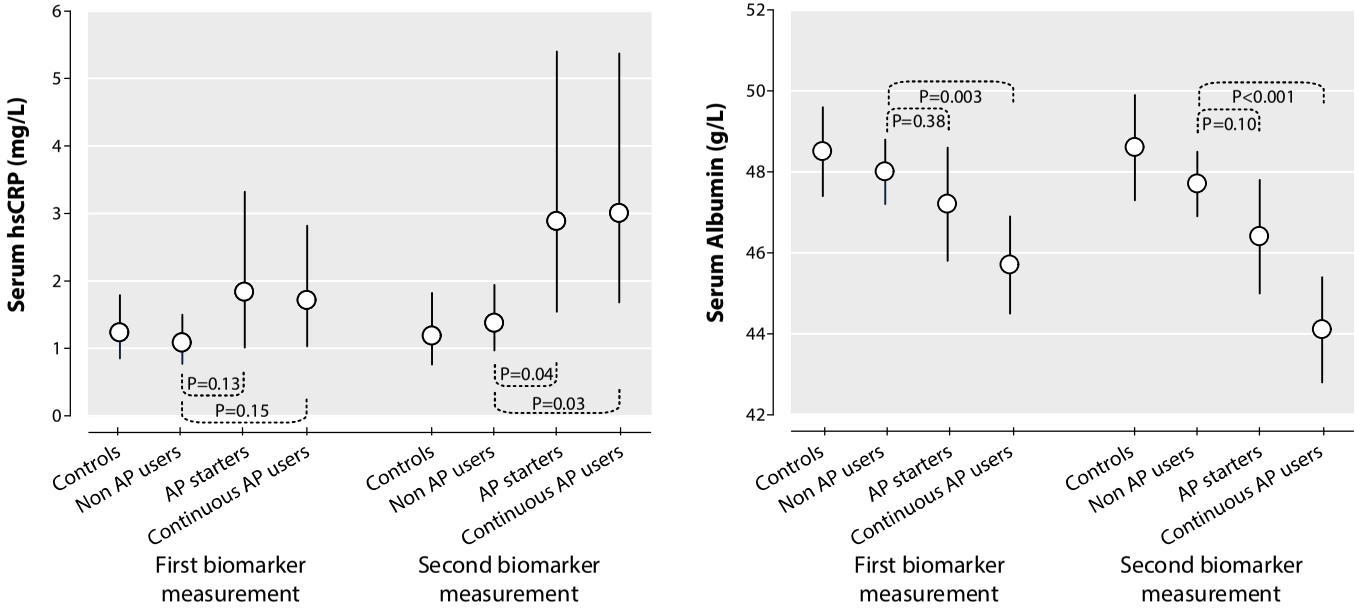

Figure 1.
High sensitivity C-reactive protein (hsCRP) and albumin levels in controls and mutation carriers. For hsCRP levels the adjusted, backtransformed geometric mean values and for albumin the adjusted mean values are presented. Error bars represent the 95% confidence intervals. Mutation carriers were categorised according to antipsychotic (AP) usage into those: (1) who did not use AP at either time points; (2) who started the use of AP; and (3) who continuously used AP at both time points. Data were analysed using analyses of covariance (ANCOVA) adjusting for sex, age, body mass index, smoking, and alcohol use at first biomarker measurement.

Using linear mixed models analyses, with adjustment for potential confounders, all three categories of antipsychotics were positively associated with hsCRP levels. Effect estimates indicated a rather similar effect sizes for typical antipsychotics (n = 32; ß = 0.42), atypical antipsychotics (n = 26; ß = 0.25), and tiapride (n = 28; ß = 0.30). Likewise, inverse associations were found with albumin: typical antipsychotics (n = 32; ß = -0.47), atypical antipsychotic (n = 26; ß = -0.53), and tiapride (n = 28; ß = -0.36) (data not shown).

Discussion

We found strong associations between the use of antipsychotics and an elevated acute-phase response in HD. Other associations between hsCRP and albumin levels on the one hand and TFC score, apathy, and cognitive impairment on the other hand, disappeared when adjusting for the use of antipsychotics. Also, mutation carriers who continuously used antipsychotics had significantly higher hsCRP levels and lower albumin levels compared with mutation carriers who did not use antipsychotics during the study period.

Increases in CRP levels have previously been found in HD mutation carriers when compared to controls and one study also found a correlation between disease stage and CRP levels.[15;16] In contrast, we only found a significant increasing trend of CRP across increasing disease stages but no differences in CRP levels between the whole group of HD mutation carriers and controls. The relatively low number of HD mutation carriers in more advanced disease stages in our cohort may have accounted for this finding. This idea is in line with the finding of a study reporting that premanifest and early-stage HD mutation carriers, who are in lower disease stages, had similar or lower CRP levels respectively, when compared with controls.[17]

Previous publications offer several mechanisms that could explain our finding of an elevated acute-phase reaction in mutation carriers who used antipsychotics. First, the use of antipsychotics may cause symptoms associated with the metabolic syndrome which in turn induces an acute-phase response. Atypical antipsychotics are strongly associated with the development of metabolic syndrome, which is characterised by abdominal obesity, dyslipidaemia, hypertension, and insulin resistance. Obesity,[45] dyslipidaemia,[31] and insulin resistance[46] may induce low-grade inflammation reflected in increased CRP levels. In rats, it has been shown that treatment with olanzapine induces weight gain and increased adipose tissue. In addition, the adipose tissue of olanzapine-treated rats had become infiltrated with macrophages and there was a 2-fold increase in the expression of the TNF-α, both indicative of low-grade inflammation.[47] Second, the use of antipsychotics may directly induce low-grade

inflammation through their hepatic impact since antipsychotics are eliminated predominantly by hepatic metabolism. In the CATIE trial,[28] increased CRP levels were indicative of having more signs of the metabolic syndrome but were also independently associated with the use of atypical antipsychotics, in particular olanzapine. In a smaller open-label study, with 111 patients randomised to haloperidol, olanzapine, and risperidone, patients on haloperidol showed the strongest increase in CRP levels after three months of treatment.[29]

Since the effects in our study were largely unaffected by adjustment for BMI, we assume that the use of antipsychotics directly induced an acute-phase response. Atypical antipsychotics are most often implicated in induction of inflammation but in our mixed-model analyses, we did not find a differential role for atypical antipsychotics, typical antipsychotics, and tiapride. Therefore these groups were combined.

Immune activation in HD is widespread[48] and is known to positively correlate with disease stage. IL-6, a cytokine that plays a main role in the innate immune response, was shown to be up-regulated both centrally and peripherally in HD.[11] One of its functions is to initiate the acute-phase response, thus subsequently increasing the synthesis of CRP while decreasing albumin levels. Neuroinflammation leads to neuronal degeneration through several mechanisms, and neuronal degeneration in the striatum is one of the key histopathological features of HD that is associated with movement abnormalities, cognitive and several neuropsychiatric symptoms. Our findings may therefore also be explained by reverse causation meaning that neuroinflammation has caused movement abnormalities and neuropsychiatric symptoms, which in turn has led to the prescription of antipsychotics.

Although influenced by the use of antipsychotics, we did find associations between levels of acute-phase proteins and several clinical variables. We found an association for TFC, apathy, and cognitive impairment. Previous studies in non-HD populations also found associations between levels of acute-phase proteins and both apathy[25] and cognitive impairment.[18;21;22] In contrast to our study, these studies did not investigate the role of antipsychotics in these associations. In our study, the elevated acute-phase reaction was strongly associated with the use of antipsychotics and all associations between acute-phase proteins and clinical variables disappeared when adjusting for antipsychotics. As previously argued, we hypothesise that the use of antipsychotics induced an acute-phase response which in turn was associated with several neuropsychiatric symptoms and cognitive impairment. But associations between acute-phase proteins on the one hand and TFC, apathy, and cognitive impairment on the other hand, may have been confounded by the use of antipsychotics. Alternatively, confounding by indication may explain our results.

To our knowledge, this is the first study investigating the role of the acute-phase response in the occurrence of neuropsychiatric symptoms and cognitive dysfunction in HD. Strengths of this study are the use of a comparison group (consisting of first-degree non-carriers), the use of validated measurement tools in a standardised interview, and the adjustment for potential confounders, including antipsychotic use, in the analyses. There are several limitations that warrant discussion. Since inflammation is associated with the neurodegenerative process in HD, relationships found in this study might not be generalised to other disorders and the general population. Given the observational rather than experimental nature of our study, it is impossible to make causal inferences about our findings.

Future research on the role of antipsychotic use on the acute-phase reaction is necessary, both in HD and in other populations. We found strong evidence for a role of antipsychotics in inducing an acute-phase response in HD mutation carriers. Although we could not make inferences regarding the direction of causation, HD mutation carriers who receive antipsychotics may be prone to the development of low-grade inflammation, which may subsequently increase their risk of cardiovascular morbidity, lower functioning capacity, apathy, and cognitive dysfunction.

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Supplementary Table 1. Levels of hsCRP and albumin at different disease stages according to TFC score at t1 and t2.

Disease stage according to TFC score[a]	Stage I	Stage II	Stage III	Stage IV	Stage V	p-value for trend
t1						
No. of mutation carriers	52	19	25	10	16	
Albumin (g/L)	48.2 ± 2.8	47.0 ± 2.3	47.1 ± 2.9	46.0 ± 3.3	44.2 ± 4.2	<0.001
hsCRP (mg/L)	2.3 ± 3.3	2.4 ± 2.9	4.2 ± 5.2	3.2 ± 1.8	5.5 ± 6.1	0.02
Antipsychotic use	1 (2%)	4 (21%)	13 (52%)	7 (70%)	10 (63%)	<0.001
t2						
No. of mutation carriers	33	16	22	7	7	
Albumin (g/L)	47.5 ± 3.7	46.9 ± 2.5	46.5 ± 2.5	43.2 ± 0.8	43.2 ± 3.8	<0.001
hsCRP (mg/L)	2.4 ± 2.7	5.4 ± 12.3	4.1 ± 4.9	3.3 ± 2.1	17.6 ± 25.8	0.01
Antipsychotic use	0 (0%)	5 (31%)	15 (68%)	7 (100%)	7 (100%)	<0.001

Data are numbers, means ± standard deviation (SD), or numbers (percentages) where appropriate.
hsCRP denotes high sensitivity C-reactive protein; TFC, total functional capacity.
[a] Stage I: TFC > 10, Stage II: 6 < TFC < 11, Stage III: 2 < TFC < 7, Stage IV: 0 < TFC < 3, Stage V: TFC = 0.
P-value for trend computed by linear regression analysis or chi-squared test, linear by linear term.

Supplementary Table 2. Levels of acute-phase proteins in mutation carriers according to antipsychotic use.

	Mutation carriers not using AP (n = 51; reference)	**Mutation carriers who started AP** (n = 15)	**p-value**	**Mutation carriers who continuously used AP** (n = 23)	**p-value**
High sensitivity C-reactive protein (mg/L)[a]					
First biomarker measurement					
- Crude	1.10 (0.76 – 1.58)	1.67 (0.79 – 3.50)	0.28	1.93 (1.27 – 2.93)	0.04
- Model 1[b]	1.08 (0.77 – 1.50)	1.83 (1.01 – 3.32)	0.13	1.71 (1.03 – 2.82)	0.15
Second biomarker measurement					
- Crude[c]	1.40 (0.99 – 1.98)	2.57 (1.29 – 5.12)	0.10	3.61 (2.02 – 6.46)	0.005
- Model 1[d]	1.37 (0.97 – 1.94)	2.88 (1.54 – 5.40)	0.04	3.00 (1.68 – 5.37)	0.03
- Model 2[e]	1.47 (1.07 – 2.01)	2.31 (1.29 – 4.15)	0.18	2.82 (1.67 – 4.77)	0.04
Albumin (g/L)					
First biomarker measurement					
- Crude	48.1 (47.4 – 48.8)	47.2 (45.3 – 49.1)	0.27	45.3 (44.1 – 46.5)	<0.001
- Model 1[b]	48.0 (47.2 – 48.8)	47.2 (45.8 – 48.7)	0.38	45.7 (44.5 – 46.9)	0.003
Second biomarker measurement					
- Crude[c]	47.6 (46.9 – 48.3)	46.4 (45.0 – 47.9)	0.10	44.0 (42.6 – 45.4)	<0.001
- Model 1[d]	47.7 (46.9 – 48.5)	46.4 (45.0 – 47.8)	0.10	44.1 (42.8 – 45.4)	<0.001
- Model 2[e]	47.4 (46.8 – 48.0)	47.0 (45.8 – 48.2)	0.55	44.7 (43.6 – 45.7)	<0.001

AP denotes antipsychotics. Data are presented as adjusted (geometric) mean values (with 95% confidence interval [CI]). P-values by t-tests for crude models and by analyses of covariance (ANCOVA) for model 1 and model 2.
Model 1: adjusted for sex, age, body mass index, smoking, and alcohol use at t1; Model 2: additional adjustment for acute-phase protein level (hsCRP/albumin) at t1.
[a] Because of its positively skewed distribution, high sensitivity C-reactive protein was log transformed before the analyses.
[b] 2 missings for non-users; [c] 2 missings for non-users, 4 for continuous users; [d] 4 missings for non-users, 4 for continuous users; [e] 4 missings for non-users, 1 for starters and 4 for continuous users.

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Chapter 5

Hypothalamic-pituitary-adrenal axis functioning in Huntington's disease and its association with depressive symptoms and suicidality

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Abstract

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been reported in Huntington's disease (HD). In non-HD populations, alterations in HPA axis activity have been associated with depression and suicidality. The present study aims to compare HPA axis activity between HD mutation carriers and controls, and examine its association with depressive symptoms and suicidality. To this end, salivary cortisol concentrations at seven time points, as well as depressive symptoms and suicidality, were assessed in 49 pre-motor, 102 motor symptomatic mutation carriers and 55 controls, at baseline and follow-up combined. Differences in parameters of HPA axis activity between these three groups, and their associations with depressive symptoms and suicidality in HD mutation carriers, were analysed using multilevel regression analyses. There were no differences in parameters of HPA axis activity between mutation carriers and controls, whereas pre-motor symptomatic mutation carriers had a significantly higher area under the curve to the increase (AUC_i) compared to motor symptomatic mutation carriers. In the entire HD cohort, HPA axis activity was not associated with depressive symptoms or suicidality. After stratifying mutation carriers into pre-motor, early and advanced disease stages, β values differed between these groups. Remarkably, a higher AUC_i was significantly associated with depressive symptoms in pre-motor and early disease stage mutation carriers, with a reverse non-significant association in advanced disease stage mutation carriers. The lower AUC_i in motor symptomatic mutation carriers and the varying associations with depressive symptoms and suicidality in pre-motor, early and advanced disease stages could possibly be explained by exhaustion of the HPA axis after prolonged stress-induced HPA axis hyperactivity and deserves further longitudinal study.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disease caused by a CAG expansion in the HTT gene on chromosome 4. The disease is characterised by motor symptoms, cognitive decline, behavioural symptoms and psychiatric disorders.[1]

Depression is a common psychiatric disorder in HD,[2] which can precede the onset of motor abnormalities.[3] The prevalence of a depressed mood is reported to range from 33% to 69%, depending on the disease stage and assessment method used.[2] The presence of a depressed mood in HD is an important predictor of suicidal ideation[4;5] and suicidal behaviour.[5,6] Previous studies showed that completed suicide rates among HD mutation carriers are four- to eight-fold higher compared to the general population,[7,8] with increased suicidality prevalences (including both suicidal ideation and attempts) of up to 20% in the previous month in both pre-motor and motor symptomatic mutation carriers.[5] Although some of the psychiatric symptoms in HD might be attributed to environmental factors, pathophysiological mechanisms may also be involved, such as dysfunction in the caudate nucleus,[2;9] which is one of the brain structures with prominent cell loss in HD.[1]

In non-HD populations, the presence of depression and suicidality has also been associated with disturbed functioning of the hypothalamic-pituitary-adrenal (HPA) axis. Although several studies indicated hyperactivity of the HPA axis in depressed patients or in those developing depression compared to non-depressed controls,[10-15] other studies have reported normal[16;17] or even lower HPA axis activity in depressed patients or those developing depression compared to non-depressed controls.[18-20] These inconsistent results might partly be explained by the existence of a non-linear association between HPA axis activity and depression, which implies that both hyper- and hypoactivity of the HPA axis can be associated with depression.[21]

Also, an association between dysfunction of the HPA axis (most commonly dexamethasone non-suppression) and completed suicide has repeatedly been described, mainly in depressed patients.[22-24] A meta-analysis showed that non-suppressors of the dexamethasone suppression test (DST) are 4.7 times more likely to commit suicide than suppressors.[25] Evidence for a relationship between HPA axis functioning and suicidal ideation or attempted suicide is less consistent[22,24,26] (i.e. some studies reported hyperactivity of the HPA axis in those with suicidal ideation or attempts, whereas others found no association or reported a reverse association).[22;24;26-28]

Hypothalamic changes and hyperactivity of the HPA axis have been reported in HD mouse

models and in HD mutation carriers compared to controls.[29-38] Both alterations have been reported in early disease stages[30;34;37] and elevated salivary cortisol concentrations were found in pre-motor symptomatic HD mutation carriers compared to diagnosed HD patients.[39;40] Elevated cortisol concentrations in an early stage of HD could indicate that psychiatric symptoms in this stage are related to a perturbed HPA axis[30] and it has been suggested that HPA axis alterations may contribute to depressive symptoms in HD.[41] A recent study reported higher salivary morning cortisol concentrations in early disease stage mutation carriers with mild to severe depressive symptoms compared to non-depressed early disease stage mutation carriers,[40] whereas other studies found no significant relationship between HPA axis activity and depression scores,[30;42] the presence of a major depressive disorder (MDD) or dysthymia,[38] or a history of MDD.[31] So far, studies investigating the relationship between HPA axis functioning and psychiatric symptoms in HD were limited to the presence of depression and did not investigate suicidality. Furthermore, these studies were small (≤ 56 mutation carriers) and reported contradicting results.

In a previous cross-sectional study conducted by our group,[39] in contrast to earlier studies, no significant differences were found in overall parameters of HPA axis activity between HD mutation carriers and controls. For the present study, additional follow-up data was collected, and we aimed to compare HPA axis functioning, as measured by salivary cortisol concentrations at different time points during the day, between HD mutation carriers and controls at both baseline and follow-up measurements combined. We hypothesised that HPA axis activity would be elevated in both pre-motor and motor symptomatic mutation carriers compared to controls. We also aimed to assess the change in parameters of HPA axis activity between baseline and follow-up and expected to find a decrease in HPA axis functioning with disease progression. In addition, we aimed to investigate whether elevated HPA axis activity was associated with severity of depressive symptoms and suicidality within the cohort of HD mutation carriers and we expected to find higher depressive symptom and suicidality scores in mutation carriers with elevated parameters of HPA axis activity.

Materials and methods

Participants

Between May 2004 and August 2006, 152 HD mutation carriers were recruited for participation through the outpatient departments of Neurology and Clinical Genetics of the Leiden University Medical Center (LUMC) and a regional nursing home specialised in care for HD patients. In addition, 56 relatives, who initially had a 50% risk for the mutation but tested negative for the

HD mutation, were recruited as a control group. The study design and recruitment procedure have been described in detail elsewhere.[43]

A second measurement was made between 2006 and 2008; in this period, 128 mutation carriers and 42 non-carriers continued to participate. A third measurement was made between 2009 and 2011, which included 94 mutation carriers and 32 non-carriers. Biomarker measurements, including cortisol measurements at seven different time points during two consecutive days to assess HPA axis functioning, were made at the second and third measurements. Because several participants refused saliva collection or insufficient saliva was collected, only 97 mutation carriers and 33 controls could participate at the first cortisol measurement (2006–2008; baseline for this substudy) and 55 mutation carriers and 22 controls could participate at the second cortisol measurement (2009–2011; follow-up) (Figure 1).

Data from the first cortisol measurement were also used in a previous study investigating HPA axis functioning in HD compared to controls;[39] however, this latter study was limited to cross-sectional analyses with baseline data only. After the analyses for the previous study, additional data on baseline HPA axis activity were acquired in 13 mutation carriers and five controls and follow-up data on HPA axis activity were acquired in 55 mutation carriers and 22 controls. Also, the previous study did not investigate the change in parameters of HPA axis activity between baseline and follow-up and did not investigate the association between HPA axis functioning on the one hand and depressive symptoms and suicidality on the other. In addition, for the present study, all salivary cortisol samples used in the previous article were re-assayed using an improved re-standardised cortisol in saliva assay that guarantees accurate values in the 5–50 nmol/l range. Correlation coefficients between cortisol concentrations at the different times throughout the day, as determined by the former and the improved assay, ranged from 0.96 to 1.00. This improved assay was also used to assess the newly collected salivary cortisol samples.

The study was approved by the Medical Ethical Committee of the LUMC and all participants provided their written informed consent.

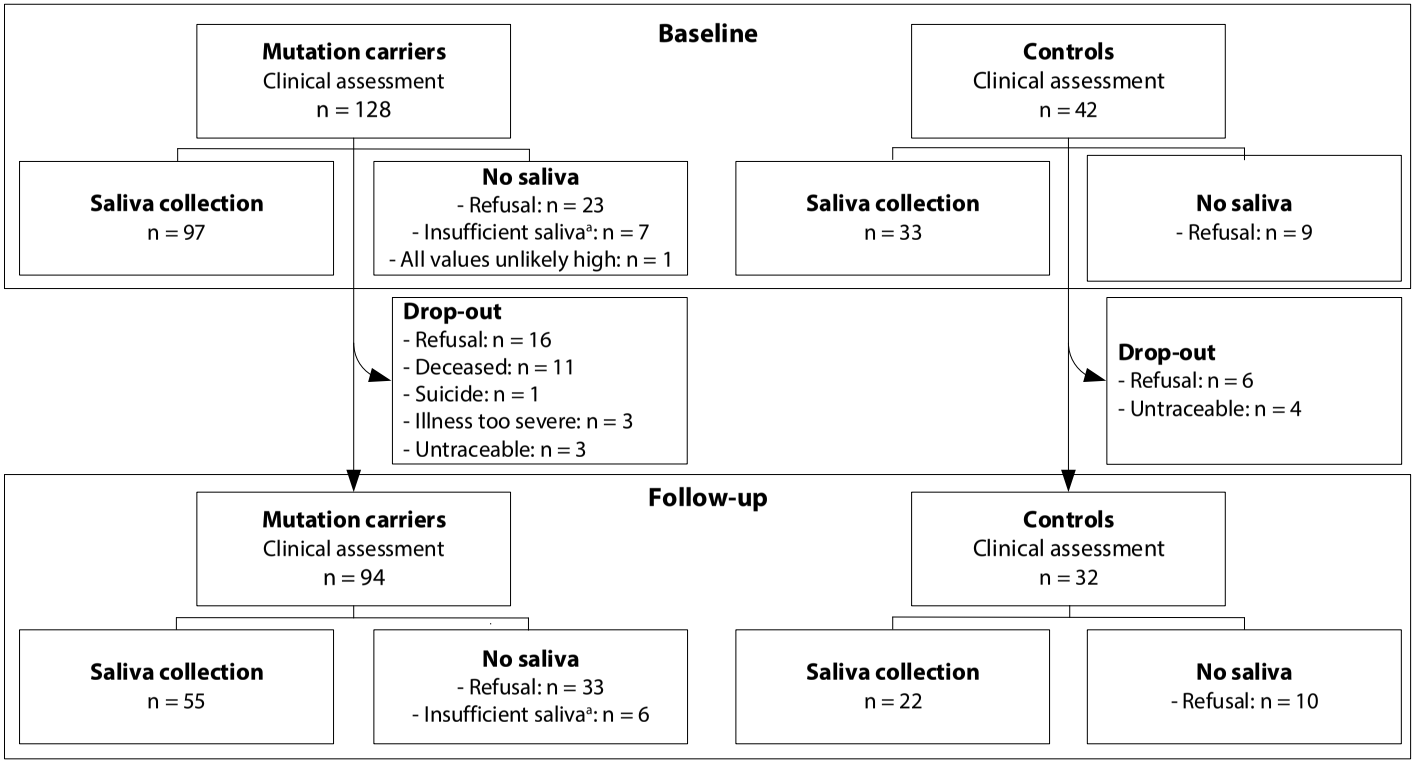

Figure 1. Flowchart of the study participants.

[a] Participants with > 4 missing cortisol concentrations (as a result of insufficient saliva collection) were excluded from the analyses.

Assessment of HPA axis functioning

HPA axis functioning was assessed by measuring cortisol concentrations in saliva samples. All participants received an oral and written instruction that asked them to collect saliva on two consecutive days. Instructions provided by the manufacturer were used. The participants had to place cotton wads from a saliva collection tube (Salivettes, catalogue no. 1.1534, Sarstedt AG & Co., Nümbrecht, Germany) in their mouth and chew until the cotton was saturated. To avoid contamination of the saliva with food or blood, participants were asked to refrain from eating, drinking or brushing their teeth before sampling. The participants were free to wake up on the basis of their own time schedule.

The day curve of cortisol concentrations was assessed by collecting the saliva on six different times throughout the day: at the time of awakening, 30 min after awakening, 45 min after awakening, 60 min after awakening, and at 22.00 and 23.00 h. In addition, the saliva cortisol concentrations after the DST were measured at the time of awakening on day two. Participants were also asked to record the date and time of collection. We assumed cortisol concentrations ≥ 100 nmol/l to be physiologically unlikely (e.g. as a result of bleeding gums) and these values were excluded. One or more cortisol values were excluded for this reason in two control participants (3.6%), two pre-motor symptomatic (4.1%) and five motor symptomatic mutation carriers (4.9%). When one to four cortisol values were missing, $\log_e$-transformed cortisol concentrations were imputed using multiple imputation (five times), in which other known characteristics of the participant were used: the remaining $\log_e$-transformed cortisol concentrations, time of awakening at day 1, time of awakening at day 2, season, sex, age, smoking, high alcohol use, body mass index (BMI), $\log_e$-transformed Total Functional Capacity (TFC) score, $\log_e$-transformed depressive symptom score, $\log_e$-transformed suicidality score, use of psychotropics, and time of measurement (baseline/follow-up). In total, from both baseline and follow-up combined, 63 of the 1449 (4.3%) cortisol values were imputed.

Two indicators of the cortisol awakening response (CAR), the area under the curve to the ground (AUC_g) and the area under the curve to the increase (AUC_i), were calculated using the first four time points, according to the trapezoid formula.[44] The mean evening cortisol was assessed by the mean of the two evening measurements on day 1, at 22.00 and 23.00 h. Physiologically, the DST results in a decrease in the morning cortisol concentration because of the inhibition of ACTH secretion. On the evening of day 1, the participants were instructed to orally take a low-dose dexamethasone tablet (0.5 mg). The dexamethasone suppression rate was determined by the cortisol concentration at time of awakening on day 1/the cortisol concentration at time of awakening on day 2 (post DST).

After collecting all seven saliva samples, participants returned their samples through the regular postal service. Upon arrival, saliva was harvested by centrifuging the Salivettes during 5 min at 10°C and 3309 g. Saliva was stored at -80 °C until analysis. Determination of cortisol in saliva was performed with a competitive electrochemoluminescent immunoassay using a Modular Analytics E170 immunoassay analyser (Roche Diagnostics, Mannheim, Germany). For the determination, a cortisol reagent (catalogue number 11875116 122/lot number 00168267) and calibrator (catalogue number 11875124 122/lot number 00169356: expiration date December 2013) were used.

The functional sensitivity for salivary cortisol is < 8.5 nmol/l, with a lower limit of detection of 0.5 nmol/l (source: Roche Diagnostics product insert). The internal quality control was monitored using home-made controls of saliva pools manufactured in an ISO-certified production facility (ISO 13485:2003). During the measurements, the mean ± SD was 8.04 ± 0.57 nmol/l for pool 1/20111281 (inter-run coefficient of variation [CV] = 7.11%; n = 28) and 20.70 ± 0.97 nmol/l (inter-run CV = 4.69%; n = 28) for pool 2/20111282.

Sociodemographic and clinical characteristics

Information on sociodemographic and clinical characteristics (e.g. height and weight, current smoking, high alcohol consumption [defined as drinking > 14 standardised units of alcohol a week] and medication use) was collected using a standardised interview. The estimated duration of disease was calculated by the current age minus the estimated age of onset according to the equation of Vassos et al.[45] Global daily functioning and disease stage[46] were assessed by the TFC scale[47] of the Unified Huntington's Disease Rating Scale (UHDRS),[48] and motor functioning was assessed by a trained neurologist using the motor scale of the UHDRS.[48] The confidence level (CL) of the UHDRS motor scale[48] was used to characterise mutation carriers as pre-motor (CL 0–1 points) or motor symptomatic (CL 2-4 points).

Assessment of depressive symptoms and suicidality

Depressive symptoms and suicidality were assessed using the Dutch version of the Problem Behaviours Assessment (PBA). The PBA is a semi-structured interview designed to assess the frequency and severity of 36 common behavioural symptoms in HD.[49;50] Total scores for the separate items of the PBA are computed by multiplying severity (range 0–4 points) and frequency (range 0–4 points) scores (range 0–16 points). Depressive symptoms in the previous month were assessed using the depressive symptoms cluster that was previously reported.[50] This depression subscale (range 0-80 points) consists of five items: 'depressed mood', 'depressive cognitions', 'anxiety', 'tension', and 'suicidal ideation'.[50] In addition, the 'suicidal ideation' item of the PBA (range 0–16 points) was used to assess the presence of suicidal ideation and suicide

attempts in the month preceding the interview.

Statistical analysis

Because of their positively skewed distributions, parameters of HPA axis activity, depressive symptom scores and suicidality scores were $\log_e$-transformed before being analysed. Data are presented as n (%), mean (± SD) or geometric back-transformed mean (i.e. back-transforming the mean of logarithmic values) (95% confidence intervals [CI]) when appropriate.

Sociodemographic and clinical characteristics of controls and pre-motor and motor symptomatic mutation carriers at baseline were compared using chi-squared tests for categorical data and one-way between-groups analysis of variance (ANOVA) for continuous data. Post-hoc comparisons were made using a chi-squared test for categorical data and Tukey's honestly significant difference test for continuous data.

Parameters of HPA axis activity of controls and pre-motor and motor symptomatic mutation carriers, both at baseline and follow-up combined, were compared using multilevel regression analyses (i.e. linear mixed models), with additional adjustment for potential confounders (sex, age, and time of measurement [baseline/follow-up]). An unstructured covariance matrix was used to account for the repeated measurements within a participant. Additionally, changes in the parameters of HPA axis activity between baseline and follow-up were compared between controls and pre-motor and motor symptomatic mutation carriers, using ANOVA. Analysis of covariance (ANCOVA) was used to adjust for sex and age.

The associations between continuous parameters of HPA axis activity on the one hand, and continuous depressive symptom and suicidality scores on the other, in HD mutation carriers at both baseline and follow-up combined were analysed using multilevel regression analyses with an unstructured covariance matrix. Analyses were adjusted for the potential confounders sex, age, season, smoking and time of measurement (baseline/follow-up). Because a previous study reported a relationship between HPA axis functioning and depression only in early symptomatic HD mutation carriers,[40] we stratified the mutation carriers into pre-motor symptomatic, early disease stage (motor symptomatic and disease stage 1 or 2)[46] and advanced disease stage (motor symptomatic and disease stage 3–5)[46] and repeated the analyses to explore whether the associations varied between these different disease stages.

In additional sensitivity analyses, BMI and alcohol use were added to the models of the original analyses. Also, analyses were restricted to those who woke up at, or before, 09.00 h and to those who reported the time of saliva collection and did not violate the prescribed time for

saliva collection by more than 5 min. For the DST, we considered participants with more than 60 min between time of awakening on day 1 and time of awakening on day 2 as time protocol violators.

For illustrative purposes only, scores on the outcome measures (depressive symptom and suicidality scores) were categorised into quartiles of parameters of HPA axis activity in the tables and figures, whereas statistical tests were solely based on the appropriate continuous data. $P < 0.05$ (two-tailed) was considered statistically significant. SPSS, version 20.0 (IBM Corp., Armonk, NY, USA) was used for the analyses.

Results

Baseline characteristics of pre-motor and motor symptomatic mutation carriers versus controls
At baseline, the study population consisted of 33 controls, 30 pre-motor symptomatic mutation carriers and 67 motor symptomatic mutation carriers (Table 1). Motor symptomatic mutation carriers were significantly older compared to pre-motor symptomatic mutation carriers and controls, and also had lower TFC scores. In addition, the use of psychotropic medication showed a significant difference between the three groups. Depressive symptom scores were higher in both pre-motor and motor symptomatic HD mutation carriers compared to controls. Also, suicidality scores in pre-motor and motor symptomatic mutation carriers were higher compared to controls; however, these differences were not significant (Table 1).

Table 1. Sociodemographic and clinical characteristics of controls and pre-motor and motor symptomatic Huntington's disease mutation carriers at baseline.

	Controls (n = 33)	**Pre-motor symptomatic** (n = 30)	**Motor symptomatic** (n = 67)	**p-value**[a]
Sociodemographic characteristics				
Male gender	16 (48.5)	13 (43.3)	33 (49.3)	0.86
Age (years)	43.7 ± 11.2[A]	43.4 ± 10.9[A]	52.7 ± 10.1[B]	<0.001
Body mass index (kg/m^2)	25.5 ± 4.45	25.9 ± 6.08	25.7 ± 4.64	0.95
Smoking (yes/no)	7 (21.2)	8 (26.7)	15 (23.8)	0.88
High alcohol consumption	0 (0)	4 (13.3)	6 (9.0)	0.12
Clinical characteristics				
CAG repeats (number)	21.5 ± 4.56[A]	42.1 ± 2.33[B]	44.4 ± 3.12[C]	<0.001
Estimated disease duration (years)	NA	-6.67 ± 9.14[A]	8.28 ± 8.20[B]	<0.001
Motor score (points)[b]	NA	3.27 (2.28 – 4.34)[A]	30.4 (24.7 – 37.0)[B]	<0.001
Total Functional Capacity score (points)[b]	12.8 (12.6 – 13.0)[A]	11.6 (10.7 – 12.5)[A]	6.17 (5.08 – 7.34)[B]	<0.001
Use of psychotropics	1 (3.0)[A]	6 (20.0)[B]	42 (62.7)[C]	<0.001
Neuropsychiatric characteristics				
PBA depressive symptom score (points)[b]	3.13 (1.67 – 4.78)[A]	7.23 (3.91 – 11.3)	7.19 (4.91 – 9.81)[B]	0.04
PBA suicidality[b]	0.10 (0.00 – 0.31)	0.34 (0.00 – 0.74)	0.65 (0.17 – 1.14)	0.22

Data are presented as n (%), mean ± SD, or geometric mean values (i.e. back-transforming the mean of logarithmic values) (95% confidence interval). PBA denotees Problem Behaviours Assessment; NA, not applicable.

[a] P-values determined using a chi-squared test for categorical data and one-way between-groups ANOVA (or t-test when comparing only two groups) for continuous data. Post-hoc comparisons were made using a chi-squared test for categorical data and a Tukey's honestly significant difference test for continuous variables. Values in the same row with different superscript letters (uppercase) are significantly different (p-value < 0.05).

[b] Because of its skewed distribution, these variables were $\log_e$-transformed before the analyses.

Parameters of HPA axis activity in HD mutation carriers versus controls

Comparison of the parameters of HPA axis activity between controls and pre-motor symptomatic and motor symptomatic mutation carriers, at both baseline and follow-up combined, showed that the only significant difference was a higher AUC_i in pre-motor symptomatic mutation carriers compared to motor symptomatic mutation carriers (Table 2a); this difference remained significant after adjustment for sex and age. Although the AUC_g was also higher in pre-motor symptomatic mutation carriers compared to motor symptomatic mutation carriers and controls, this difference was not significant. Also, the mean evening cortisol and the cortisol suppression ratio showed no significant difference between controls and pre-motor and motor symptomatic mutation carriers, in both the crude and adjusted models (Figure 2 and Table 2a).

The largest change in parameters of HPA axis activity from baseline to follow-up was observed for the AUC_i (> 9% decrease in all groups). However, the changes in parameters of HPA axis activity between baseline and follow-up showed no significant difference between controls and pre-motor and motor symptomatic mutation carriers, in both the crude and adjusted comparisons for all parameters (Table 2b).

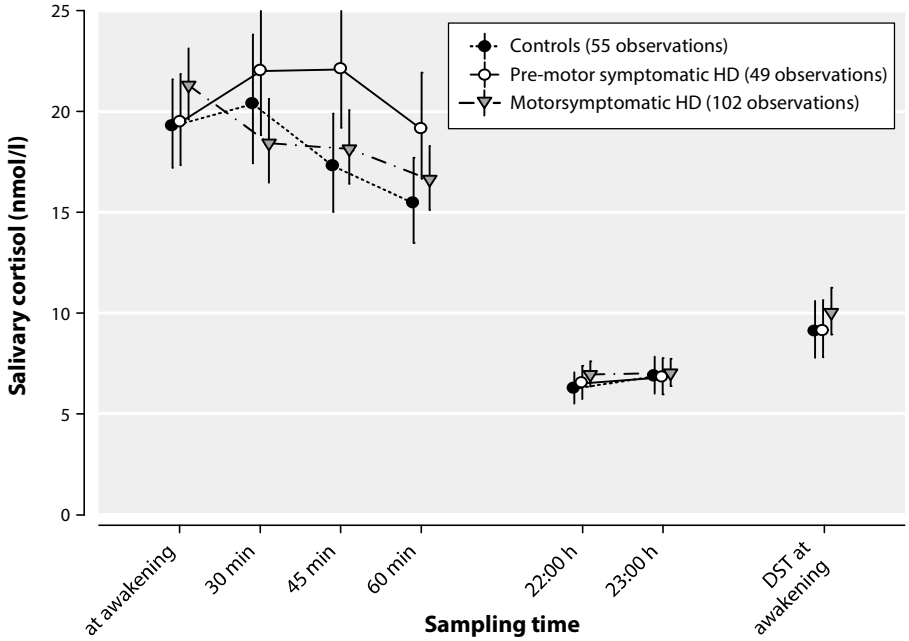

Figure 2.

Geometric mean cortisol concentrations (i.e. back-transforming the mean of logarithmic values) (95% confidence interval) at the different sampling times for controls and pre-motor and motor symptomatic HD mutation carriers at both baseline and follow-up combined. For one observation, a motor assessment was missing, which resulted in 55 control and 151 mutation carrier observations.

Table 2a. Parameters of hypothalamic-pituitary-adrenal (HPA) axis activity of controls and pre-motor and motor symptomatic Huntington's disease mutation carriers, at baseline and follow-up combined.

	Controls (observations = 55)[a]	**Pre-motor symptomatic** (observations = 49)[a]	**Motor symptomatic** (observations = 102)[a]	**p-value**[b]	**Adjusted p-value**[c]
Parameters of HPA axis activity[d]					
AUC to the ground (nmol/l)	1149 (1028; 1284)	1306 (1168; 1461)	1181 (1091; 1279)	0.22	0.20
AUC to the increase (nmol/l)	-17.6 (-138; 104)	123 (-2.57; 250)[A]	-139 (-233; -43.7)[B]	0.004	0.002
Mean evening (nmol/l)	6.62 (5.88; 7.47)	6.88 (6.11; 7.75)	7.09 (6.52; 7.72)	0.65	0.76
Cortisol suppression ratio	2.12 (1.85; 2.43)	2.17 (1.88; 2.50)	2.08 (1.87; 2.31)	0.85	0.95

Table 2b. Change in parameters of hypothalamic-pituitary-adrenal (HPA) axis activity of controls and pre-motor and motor symptomatic Huntington's disease mutation carriers, from baseline to follow-up.

	Controls (n = 21)	**Pre-motor symptomatic** (n = 20)	**Motor symptomatic** (n = 32)	**p-value**[e]	**Adjusted p-value**[f]
Delta measurements (values t2–t1)					
Delta AUC to the ground (nmol/l)	-2.63 (-210; 205)	-21.9 (-383; 340)	7.72 (-111; 126)	0.97	0.96
Delta AUC to the increase (nmol/l)	-155 (-300; -11.1)	-11.3 (-333; 310)	-41.3 (-215; 132)	0.59	0.54
Delta mean evening cortisol (nmol/l)	-1.14 (-3.65; 1.36)	0.35 (-1.46; 2.15)	0.08 (-0.65; 0.80)	0.40	0.48
Delta cortisol suppression ratio	2.64 (-2.58; 7.86)	-0.14 (-0.70; 0.41)	-0.01 (-0.44; 0.41)	0.25	0.11

AUC denotes area under the curve. Data are presented as geometric mean values (i.e. back-transforming the mean of logarithmic values) (95% CI) in table 2a and as mean (95% CI) in table 2b. Values in the same row with different superscript letters (uppercase) are significantly different (p-value < 0.05).

[a] For one observation, a motor assessment was missing which resulted in 55 control and 151 mutation carrier observations in these analyses.

[b] P-values by multilevel regression analyses.

[c] P-values adjusted for sex, age, and measurement (baseline/follow-up) calculated with multilevel regression analyses.

[d] Because of its skewed distribution, these measures were $\log_e$-transformed before the analyses.

[e] P-values by analysis of variance (ANOVA).

[f] P-values adjusted for sex and age calculated with analysis of covariance (ANCOVA).

Associations between parameters of HPA axis activity and depressive symptoms and suicidality
Analyses of the associations between parameters of HPA axis activity and PBA depressive symptom score (Table 3) showed that the strongest but non-significant association was with the AUC_i. No associations were found between the AUC_g, mean evening cortisol and cortisol suppression ratio (CSR) on the one hand and depressive symptom score on the other. After adjustment for potential confounders, the β values remained similar or became smaller compared to those in the crude model (Figure 3 and Table 3).

Analyses of the associations between parameters of HPA axis activity and suicidality showed that the AUC_g, AUC_i, mean evening cortisol and the CSR were not associated with suicidality score, either in the crude or in the adjusted model (Figure 3 and Table 3).

Associations in pre-motor symptomatic, early and advanced disease stages
When exploring associations separately in pre-motor symptomatic (49 observations), early disease stage (48 observations) and advanced disease stage (53 observations) mutation carriers, both the crude and adjusted β values differed for all parameters of HPA axis activity between the three groups (data not shown). For the depressive symptom score, the difference between the adjusted β values was largest for the AUC_i. A higher AUC_i was associated with depressive symptoms in both pre-motor symptomatic ($\beta_{adjusted}$ = 0.27, 95% CI = 0.04 to 0.51) and early disease stage mutation carriers ($\beta_{adjusted}$ = 0.44, 95% CI = 0.21 to 0.67), whereas a reverse association was found in advanced disease stage mutation carriers ($\beta_{adjusted}$ = -0.09, 95% CI = -0.38 to 0.21). Regarding suicidality, the difference between adjusted β values was largest for the CSR. A lower CSR was associated with suicidality in the pre-motor symptomatic group ($\beta_{adjusted}$ = -0.19, 95% CI = -0.43 to 0.06). This association was weaker in the early disease stage group ($\beta_{adjusted}$ = -0.04, 95% CI = -0.36 to 0.28) and was reversed in the advanced disease stage group ($\beta_{adjusted}$ = 0.15, 95% CI = -0.23 to 0.53).

Sensitivity analyses
For both the depressive symptom and suicidality analyses in the entire group of HD mutation carriers, additional adjustments for BMI and alcohol use resulted in comparable or smaller β values compared to the original adjusted models, which differed no more than 0.05 points from those of the original analyses. Also, when restricting the analyses to those mutation carriers who woke up at, or before, 09.00 h, the crude and adjusted β values for both depressive symptoms and suicidality differed no more than 0.05 points from those of the original analyses. When time protocol violators were excluded from the analyses, the crude and adjusted β values for both depressive symptoms and suicidality differed no more than 0.04 points from those of the original analyses (data not shown).

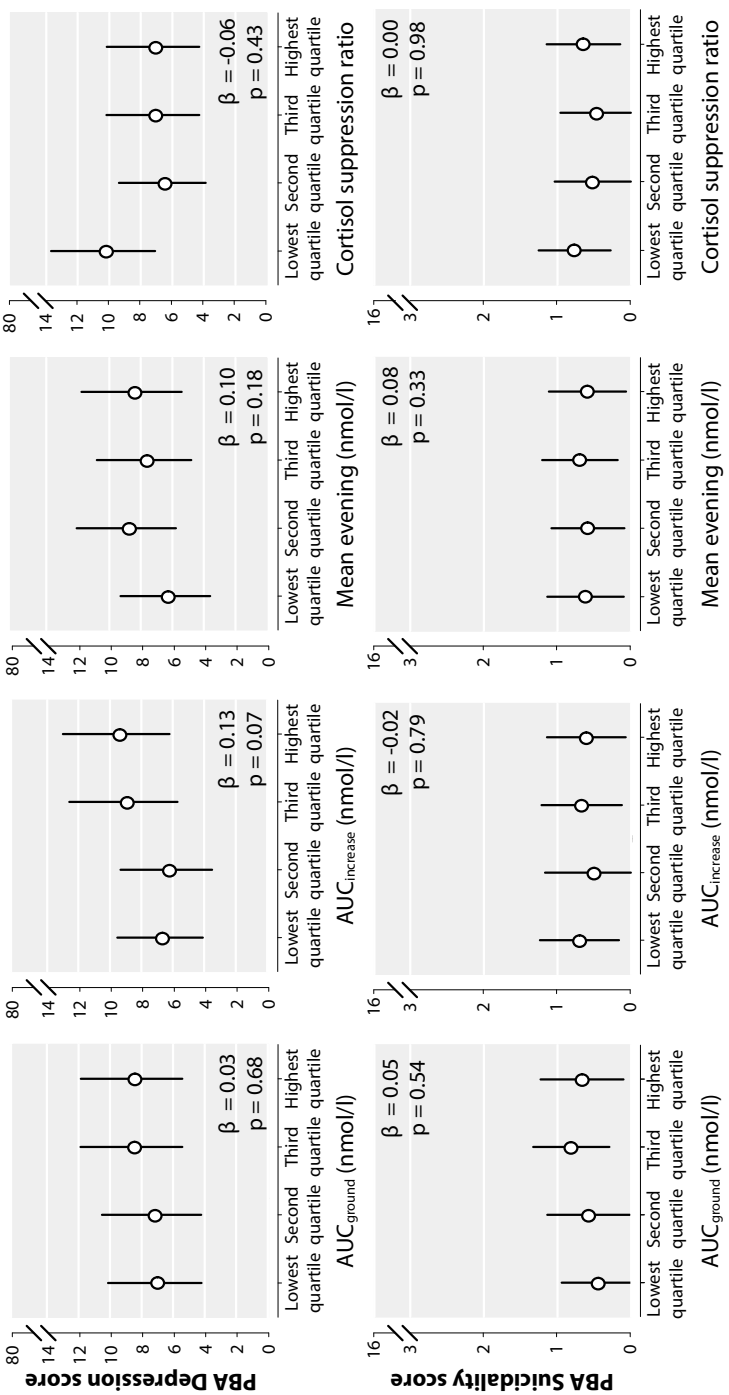

Figure 3.
Geometric mean Problem Behaviours Assessment (PBA) depressive symptom and suicidality scores (i.e. back-transforming the mean of logarithmic values) (95% confidence interval) are given in different hypothalamic-pituitary-adrenal (HPA) axis parameter quartiles for illustrative purposes only. Unadjusted β values and p-values by multilevel regression analyses (log_e-transformed parameters of HPA axis activity as continuous determinant, log_e-transformed depressive symptom or suicidality score as continuous outcome). Results are based on 151 observations (one missing observation on the PBA), with both baseline and follow-up combined. AUC denotes area under the curve.

Table 3. Associations between parameters of hypothalamic-pituitary-adrenal (HPA) axis activity on the one hand, and depressive symptom and suicidality score on the other, at both baseline and follow-up combined.

	Lowest quartile HPA axis parameter	Second quartile HPA axis parameter	Third quartile HPA axis parameter	Highest quartile HPA axis parameter	β (95% CI)	p-value	Adjusted β (95% CI)[a]	Adjusted p-value[a]
AUC_g[b]	(Observ. = 39)	(Observ. = 37)	(Observ. = 37)	(Observ. = 38)				
Range	337; 960	961; 1217	1218; 1567	1568; 5014				
Depression score	6.90 (4.20 – 10.1)	7.08 (4.22 – 10.5)	8.37 (5.42 – 11.9)	8.35 (5.41 – 11.8)	0.03 (-0.12; 0.18)	0.68	0.00 (-0.15; 0.16)	0.97
Suicidality score	0.43 (0.00 – 0.95)	0.56 (0.02 – 1.14)	0.80 (0.30 – 1.33)	0.65 (0.10 – 1.23)	0.05 (-0.11; 0.20)	0.54	0.06 (-0.11; 0.22)	0.49
AUC_i[b]	(Observ. = 38)	(Observ. = 39)	(Observ. = 37)	(Observ. = 37)				
Range	-2136; -281	-280; -63.8	-63.7; 253	254; 1384				
Depression score	6.59 (4.10; 9.52)	6.15 (3.50 – 9.32)	8.82 (5.69 – 12.6)	9.30 (6.20 – 13.0)	0.13 (-0.01; 0.27)	0.07	0.14 (-0.01; 0.28)	0.06
Suicidality score	0.69 (0.17 – 1.24)	0.49 (0.00 – 1.17)	0.66 (0.13 – 1.22)	0.59 (0.07 – 1.14)	-0.02 (-0.17; 0.13)	0.79	-0.01 (-0.17; 0.15)	0.91
Mean evening[b]	(Observ. = 37)	(Observ. = 38)	(Observ. = 38)	(Observ. = 38)				
Range	2.94; 5.29	5.30; 6.55	6.56; 8.63	8.64; 27.1				
Depression score	6.19 (3.60 – 9.29)	8.65 (5.77 – 12.1)	7.53 (4.79 – 10.8)	8.31 (5.41 – 11.8)	0.10 (-0.05; 0.26)	0.18	0.05 (-0.13; 0.22)	0.60
Suicidality score	0.61 (0.10 – 1.14)	0.58 (0.09 – 1.08)	0.68 (0.18 – 1.21)	0.58 (0.07 – 1.12)	0.08 (-0.08; 0.23)	0.33	0.03 (-0.15; 0.22)	0.71
CSR[b]	(Observ. = 38)	(Observ. = 38)	(Observ. = 38)	(Observ. = 37)				
Range	0.42; 1.60	1.61; 2.07	2.08; 2.85	2.86; 7.77				
Depression score	10.1 (7.10 – 13.7)	6.40 (3.89 – 9.38)	6.98 (4.28 – 10.2)	6.97 (4.29 – 10.2)	-0.06 (-0.20; 0.09)	0.43	-0.06 (-0.20; 0.09)	0.43
Suicidality score	0.76 (0.26 – 1.30)	0.56 (0.07 – 1.06)	0.39 (0.00 – 0.90)	0.72 (0.18 – 1.29)	0.00 (-0.17; 0.17)	0.98	0.02 (-0.15; 0.18)	0.83

AUC_g denotes area under the curve to the ground; AUC_i, area under the curve to the increase; CSR, cortisol suppression ratio; observ., observations.
Geometric mean Problem Behaviours Assessment (PBA) depressive symptom and suicidality scores (i.e. back-transforming the mean of logarithmic values) (95%

confidence interval [CI]) are given in different HPA axis parameter quartiles for illustrative purposes only. β values (95% CI) and p-values by multilevel regression analyses (log_e-transformed parameters of HPA axis activity as continuous determinant, log_e-transformed depressive symptom or suicidality score as continuous outcome).
Crude analyses: 151 observations (one missing on the PBA), adjusted analyses: 147 observations (four additional missings on smoking status).
[a] Adjusted for: sex, age, season, smoking, measurement (baseline/follow-up).
[b] Because of their skewed distribution, the PBA depressive symptom score, PBA suicidality score, and parameters of HPA axis activity were log_e-transformed before the analyses.

Discussion

The present study examined HPA axis activity in HD and revealed a significantly higher AUC_i in pre-motor symptomatic mutation carriers compared to motor symptomatic mutation carriers. By contrast to our hypothesis, we found no differences in HPA axis activity between both pre-motor and motor symptomatic mutation carriers and controls. Also, no overall statistically significant or clinically relevant associations were found between parameters of HPA axis activity on the one hand, and depressive symptoms or suicidality on the other. Nevertheless, when the population was stratified in pre-motor symptomatic, early and advanced disease stages, the associations varied between the different stages, and the AUC_i was significantly associated with depressive symptoms in mutation carriers from both pre-motor symptomatic and early disease stages.

By contrast to previous studies,[29-33;38] we found no hyperactivity of the HPA axis in HD mutation carriers compared to controls. However, the previous studies differed from our study by including controls who did not grow up in a HD family.[29-31;33;38] There is increasing evidence that, as a result of epigenetic mechanisms, an unfavourable environment during childhood can influence important genes in stress regulation that can affect HPA axis functioning.[22;23;51] The stress of growing up in an HD family, and the fear of being an HD mutation carrier, was most probably also experienced by our control group, which may explain why, compared to non-depressed controls from the general Dutch population,[10] the salivary cortisol concentrations of the controls in the present study were higher at every measured time point (on average 2.65 nmol/l higher).

In addition, these contrasting studies assessed HPA axis functioning by measuring cortisol in serum,[30-33] urine,[29] or cerebrospinal fluid (CSF),[38] whereas the present study, as well as another study that found no differences in HPA axis activity between mutation carriers and controls,[40] assessed HPA axis functioning by measuring salivary cortisol. Most of these measures only indirectly assess central HPA axis functioning and all reflect partially different information regarding its activity, which can lead to different results.[52]

When comparing HPA axis activity within HD mutation carriers, we found a lower CAR in motor symptomatic mutation carriers compared to pre-motor symptomatic mutation carriers, which is in line with previous results from this cohort,[39] and with another study reporting higher morning salivary cortisol concentrations in pre-diagnosed mutation carriers compared to early HD.[40] Long-lasting periods of elevated HPA axis activity in the earlier phases of HD may lead to reduced HPA axis activity[53] in later phases as a result of volume reduction or impaired

functioning of the hippocampus,[26] resulting in a blunted CAR.[21]

The elevated activity preceding down-regulation or exhaustion of the HPA axis in HD might be explained by loss of HPA axis feedback mechanisms as a result of brain pathology, such as hypothalamic alterations, which occur before clinical diagnosis.[34;37] In addition, a loss of GABAergic neurons can result in disinhibition of the HPA axis,[31] and the experience of different kinds of stress because of the presence of HD in their family might have resulted in elevated morning cortisol concentrations. The hypothesis of reduced HPA axis activity after prolonged exposure to stress and elevated parameters of HPA axis activity was also proposed in a depression and anxiety population.[21] Within the HD population, this hypothesis is supported by a postmortem study reporting decreased corticotropin-releasing hormone (CRH) immunoreactivity in the striatum of symptomatic HD patients.[54] Furthermore, the finding that pre-motor symptomatic mutation carriers showed no decrease in parameters of HPA axis activity over time does not support this hypothesis. However, the pre-motor symptomatic group is a heterogeneous population with varying estimated times until motor onset and the individual changes in the CAR from baseline to follow-up differed substantially.

Overall, we found no statistical significant or clinically relevant associations between HPA axis activity and depressive symptoms which is in line with previous HD studies that investigated HPA axis functioning in CSF,[38] blood,[30;31;42] and saliva.[40] However, after stratifying the population of this latter study according to disease stage, salivary morning cortisol concentrations were found to be higher in early HD mutation carriers with mild to severe depressive symptoms compared to non-depressed early HD mutation carriers;[40] this finding is in line with the results of our subgroup analyses. It is possible that, in different stages of HD, disturbed HPA axis functioning may have a different influence on the complex aetiology of depression, for which several mechanisms, both neuropathological and environmental, have been proposed.[2;9]

Although these are only exploratory analyses in small subgroups, the subgroup analyses for the AUC_i do support the hypothesis of hyperactivation of the HPA axis in depressed mutation carriers in earlier disease stages, with exhaustion or down-regulation of the HPA axis after a longer period of stress-induced HPA axis hyperactivity,[21] as indicated by the reverse association in advanced stage motor symptomatic mutation carriers. Two other previous small HD studies that only included early symptomatic mutation carriers ($n = 8$[30] and $n = 56$)[38] did find higher HPA axis activity in depressed mutation carriers, although these associations were not significant. This might be the result of a lack of power, or because one of these studies focused on mean 24-h plasma cortisol concentrations[30] and the other on the afternoon CSF CRH concentration,[38] whereas both in HD and non-HD studies, the CAR was most frequently

associated with depression.[10;11;40]

This is the first study to investigate the relationship between HPA axis activity and suicidality in HD, finding no associations in the entire group of HD mutation carriers. First, the overall null finding might be explained by different associations in different disease stages, especially for the CSR, which was also most commonly associated with suicidality in non-HD populations.[22-24] In addition, previous non-HD studies showed that the relationship between HPA axis and suicidality is most consistent for completed suicide, whereas the results of studies investigating suicide attempts or suicidal ideation are less consistent[22;24;26-28] and might be dependent on the suicidality severity.[26] Because suicidal ideation, attempts, and completed suicides are separate phenotypes with probably only partly shared aetiology,[51] the relatively mild suicidality scores and lack of completed suicides in this cohort might also explain the lack of association in this HD population.

Furthermore, inconsistencies in results from non-HD studies on the association between HPA axis functioning and suicidality have been attributed to the presence of a deleterious childhood environment in study participants,[22;23;51] with early-life stress being a possible confounder in this relationship. It is possible that HD mutation carriers, regardless of whether they do or do not become suicidal, experienced some form of early-life stress. Unfortunately, we did not assess the extent of early-life stress experienced in our study population.

Several limitations of the present study limit causal inference from our results. First, because of the limited number of incident depression and suicidality cases, we focused on cross-sectional analyses. Because timing is crucial in the investigation of HPA axis functioning and the direction of possible relationships cannot be determined in cross-sectional studies, longitudinal studies are needed to investigate changes in the HPA axis preceding the onset of behavioural symptoms. Second, many different mechanisms can result in either hyper- or hypoactivity of the HPA axis, some of which might be associated with depression or suicidality, whereas others might not. This lack of consistency makes it impossible to disentangle the complex causal relationship between HPA axis functioning and behavioural symptoms in an observational study.[55] Third, unknown and unmeasured negative confounding may have prevented us from finding potentially causal associations. Furthermore, the stratified analyses were only explorative in relatively small groups. Another limitation of the present study is the use of peripheral markers that do not necessarily reflect all regulatory processes of central activation of the HPA axis. The sophisticated physical feedback regulation systems might keep peripheral cortisol concentrations at normal levels whereas hormones in the brain regulating peripheral cortisol concentrations might be dysregulated. Also, the relatively mild depressive

symptom and suicidality scores in this population may limit external generalisability of our findings because the associations in more severely affected populations might be different.

Previously, antiglucocorticoid therapy was suggested, for example, for the treatment of behavioural symptoms in HD.[30] However, because of the limitations of this observational study, only a randomised clinical trial with antiglucocorticoid therapy could lead to causal conclusions on the effectiveness of such therapy. However, in line with previous HD studies, the present study, with several strong aspects such as a relatively large HD population, the assessment of multiple parameters of HPA axis activity and adjustment for various confounders, found no evidence for an association between HPA axis activity and behavioural symptoms in HD. The associations between HPA axis activity and depression and suicidality appear to vary in different HD stages, which might be explained by the exhaustion of the HPA axis after prolonged stress-induced HPA axis hyperactivity. Exhaustion of the HPA axis might also explain the diminished concentrations of morning cortisol in motor symptomatic mutation carriers. However, further longitudinal studies are needed to determine the course of HPA axis functioning during disease progression.

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Chapter 6

Suicidality in Huntington's disease: a qualitative study on coping styles and support strategies

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Submitted

Abstract

Background: Huntington's disease (HD) mutation carriers are at increased risk of suicidal ideation, suicide attempts, and completed suicide. However, research is lacking on coping strategies and treatment options that can be offered to suicidal HD mutation carriers. This study explores how HD mutation carriers cope with suicidality, how their partners support them, and their ideas and wishes regarding how relatives and healthcare professionals can help them in coping with suicidality.

Methods: This qualitative study included 11 HD mutation carriers who experienced suicidal ideation or attempted suicide and 3 of their partners. They participated in a focus group discussion or an individual in-depth interview. Two independent researchers fragmented the transcribed interviews, coded these fragments, and grouped them under themes.

Results: HD mutation carriers used four main strategies to cope with suicidality, including talking about suicidality, employing self-management activities, using medication, and discussing end-of-life wishes. Partners, relatives, and healthcare professionals can support suicidal HD mutation carriers in each of those four strategies.

Limitations: Although data saturation was reached within this sample, we included only a limited and selected group of HD mutation carriers and their partners.

Conclusion: Despite the absence of a turnkey solution for suicidality in HD, healthcare professionals can play an important role in supporting suicidal HD mutation carriers by providing an opportunity to talk about suicidality, providing psychoeducation on self-management, prescribing medication, and discussing end-of-life wishes. Future HD-specific intervention studies could investigate the effect of combining these treatment strategies into one holistic approach.

Introduction

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disease.[1] An expanded CAG repeat on the short arm of chromosome 4 causes a mutant polyglutamine chain in the huntingtin protein.[2] The disease is characterised by motor dysfunction, cognitive decline, and neuropsychiatric symptoms. Although some of these symptoms can be treated, the disease cannot be cured.[3]

An important psychiatric sign of HD is the increased risk of suicide, as first described by George Huntington in 1872.[4] More recent studies showed that HD patients were 2-8 times more likely to die by suicide than individuals from the general population,[5-8] which accounts for up to 11.4% of all deaths in motor symptomatic HD patients.[5-24] In addition, lifetime suicide attempts have been reported by 3.2-17.7%[7;9;10;12;13;17;18;25-31] of the mutation carriers, compared with only 2.7% in the general population.[32] Furthermore, 8-34% of the HD mutation carriers experienced some form of suicidal ideation in the month prior to the interview,[25;28;31;33-36] compared with 0% of the first-degree non-carrier relatives.[33] These numbers emphasise the frequent occurrence of suicidal ideation and suicide attempts (together referred to as 'suicidality') in HD. Suicidality is associated with lower quality of life[37;38] and an increased occurrence of completed suicide.[39;40]

Both suicidal ideation and completed suicide occur most frequently in early-to-middle disease stages.[5;7;8;11;31;34] In addition, depression is reported to be the strongest association of suicidality in HD.[26;28;29;31;33;41] Mutation carriers with other psychiatric symptoms like irritability/aggression,[28;31] obsessive and compulsive symptoms,[30] and a previous suicide attempt[31;41] as well as those who used antidepressants[33] or benzodiazepines,[31] were also more likely to experience or develop suicidality.

Despite the high frequency of suicidality in HD, limited information is available about coping with or the treatment of suicidality in HD, comprising only a few case descriptions of suicidal HD patients who were pharmacologically treated.[42-44]

Therefore, we conducted a qualitative study among HD mutation carriers who had experienced suicidal ideation or attempted suicide and among their partners. The primary aim was to examine how HD mutation carriers cope with suicidality and their ideas and wishes regarding how relatives and healthcare professionals can help them cope with suicidality. An additional aim was to explore how the spouses of HD mutation carriers support their partners with regard to suicidality.

Methods

Recruitment procedure and participants
This qualitative study was conducted among HD mutation carriers recruited between February and May 2014 and who had previously participated in a Dutch prospective cohort study on behavioural problems and psychiatric disorders in HD.[45]

Of all mutation carriers who 1) had participated in the last follow-up measurement of the aforementioned cohort study, 2) had given consent to be contacted for future research, and 3) were known not to have died (n = 90), 40 had reported the presence of thoughts of death, suicidal ideation or a previous suicide attempt at one of the measurements of the cohort study. Of these 40 HD mutation carriers, 11 consented to participate in the present qualitative study (Figure 1). If possible, participation in a focus group discussion was the preferred study method.[46;47] Eight mutation carriers participated in a focus group discussion (divided over 2 groups of 4 participants each) and 3 in an individual in-depth interview.

The focus group discussions were analysed first, followed by the individual interviews. Data saturation was reached after these focus group discussions, as no new understandings/ information on support strategies emerged from the individual interviews.[46]

All participants were asked whether they had a partner and, if so, whether he/she knew about their suicidal thoughts. After consent, we contacted their partner for participation in a focus group discussion. Of the 4 partners of participants that we could contact, 3 were willing to participate.

This study was approved by the Medical Ethical Committee of the LUMC and all participants provided written informed consent.

Focus group/individual interview for HD participants
Before the focus group discussion/individual interview, each HD participant had an individual intake appointment to explain: the purpose of the study, the topic list, and the course of the focus group discussion/individual interview. In addition, the presence and severity of depressed mood and suicidality in the last month were assessed by the items 'depressed mood' and 'suicidal ideation' of the Problem Behaviours Assessment (PBA).[25] Also, lifetime suicidality was assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS).[48]

The actual focus group discussions/individual interviews were conducted by a psychiatrist

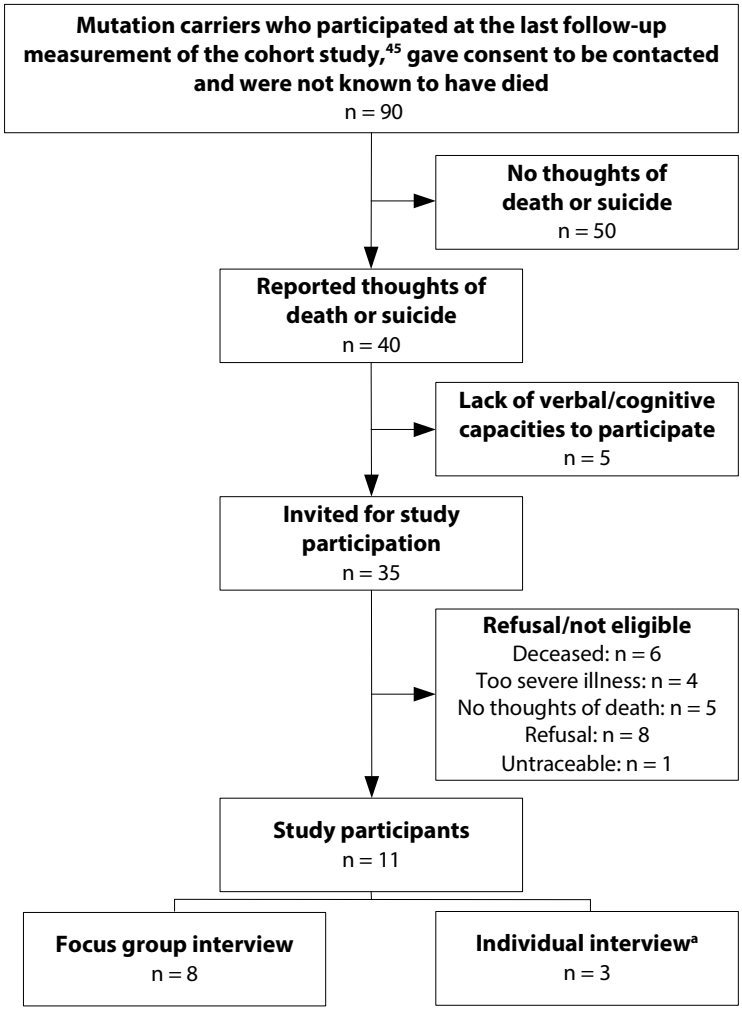

Figure 1. Selection of HD study participants
[a] Two participants were considered too ill to participate in a focus group interview and one participant did not want to talk about her experiences in a group.

(moderator/interviewer) with longstanding experience in the study and treatment of HD mutation carriers (EvD). This researcher was specifically trained in moderating focus groups for the present study. He was also the treating psychiatrist of one of the participants of the focus group discussion. The first author (AAMH), who is experienced in interviewing HD mutation carriers, conducted the intake appointment and was present as note taker during the focus groups and individual interviews. The focus groups lasted 1.5-2 h (including a short break),

and the individual interviews lasted 15-60 min each. During the focus groups and individual interviews, we mainly referred to 'thoughts of death', and explained that this term could cover the whole spectrum of suicidal thoughts: ranging from not wanting to live anymore should the disease become more severe, to actual suicide attempts. The moderator/interviewer ensured that the whole range of thoughts of death was discussed. To introduce this sensitive topic, the focus group discussion/individual interview started with an open question about how participants felt about this study actually being conducted. Subsequent questions were based on what the participants said themselves. A topic list was used as a reminder for the moderator/interviewer and consisted of 3 main items: how the mutation carriers themselves coped with suicidality; how relatives could support suicidal mutation carriers; and how healthcare professionals could help suicidal mutation carriers.

Focus group for partners

The focus group discussion for partners lasted ± 80 min (including a short break). The session started with an open question regarding how participants felt about this study being conducted and subsequent questions depended on the participants' responses. The topic list was based on results of the mutation carrier focus groups and individual interviews, and covered the following items: discussion of suicidal thoughts with partner; support of suicidal partner; and advice for future partners of suicidal HD mutation carriers.

Data analysis

All focus group discussions and individual interviews were recorded on tape and transcribed ad verbatim. The analyses started with fragmenting the transcripts of the HD mutation carriers and open coding of the fragments by two independent researchers (AAMH: medical PhD student and AH: physician). The initial code list included only 3 codes: coping themselves, support from relatives, and help from healthcare professionals, as these were the items on the topic list. Codes were grouped into themes; this involved independent and close examination and comparison of the transcripts by the two researchers. After the coding of each transcript, these researchers discussed their fragments, codes, and themes until consensus was reached, constantly taking into account the previous transcripts. Examples of new codes emerging from the data were 'listening' and 'trust' which were grouped as 'factors influencing talking', which was grouped under the major category 'talking about suicidality'. Having discussed all the transcripts of the HD participants, both researchers independently recognised that all codes and themes which described coping and support strategies could be grouped into four major categories. Subsequently, they independently read and interpreted the fragments that belonged to these four categories. Thereafter, the partner focus group transcripts were coded and interpretive reading was conducted to analyse what the partners had said about these

four major categories. Atlas.ti 7.5 (Scientific Software Development GmbH, Berlin, Germany) was used to code the interviews.

Results

Study population

The disease stage of the participants ranged from self-reported pre-motor symptomatic to participants who had to live in a nursing home. There were three male mutation carriers and one male partner, the age of the participants ranged from 32-71 years, and the number of CAG repeats ranged from 41-47. Table 1 presents the scores on the 'depressed mood' and 'suicidality' items of the PBA.

Table 1. Clinical characteristics of the study participants with Huntington's disease.

Participants	Lifetime thoughts of death[a]	Lifetime thoughts of suicide[a]	Lifetime suicide plan[a]	Lifetime suicide attempt[a]	PBA depressed mood severity[b]	PBA suicidality severity[b]
M1	yes	yes	no	no	0	0
M2	yes	yes	no	no	2	1
M3	yes	yes	yes	no	2	0
M4	yes	yes	no	no	3	1
M5	yes	yes	yes	yes	0	0
M6	yes	yes	yes	yes	3	1
M7	yes	yes	no	no	3	1
M8	yes	yes	no	no	3	0
M9	yes	yes	no	no	0	0
M10	yes	yes	no	no	3	3
M11	yes	no	no	no	0	0

M indicates mutation carrier; PBA, Problem Behaviour Assessment

[a] Lifetime thoughts of death, thoughts of suicide, suicide plan, and attempts as assessed by the Columbia Suicide Severity Rating Scale lifetime.[48]

[b] PBA depressed mood and suicidality severity scores in the last month (range 0-4), with higher scores indicating more severe depressed mood or suicidality.[25]

Support strategies for suicidality in HD

First of all, participants indicated that there is no turnkey solution for suicidality in HD. They mentioned several ways of support that can be grouped in the following categories: 1) talking about suicidality, 2) self-management, 3) medication use, and 4) discussing end-of-life wishes.

1. Talking about suicidality

All participants stressed that they had a great need to talk about their suicidality, even though this was considered difficult and the threshold to do so was high. This is illustrated by one of the participants who said: *"Someone who thinks about death already has difficulty expressing this ... and has feelings of self-disapproval because of this thought [….] But my experience is that it really helps when you eventually do talk about everything - with all your sorrows and misery. This always gives relief."*

Table 2 shows factors that, according to the participants, could facilitate or complicate talking about suicidality. Listening, taking the thoughts seriously and not trivialising these thoughts were the most important factors in helping them to express their feelings to a relative or healthcare professional. The preferred person to talk to varied per participant and included their partner, a family member, friend, care manager, psychologist, or hypnotherapist. Some participants stressed that this person should not be too close, and they preferred someone who is *"a relative outsider"*, because they did not want to hurt their partner or children by telling them about their suicidal thoughts. However, the spouses mentioned that they did want their partner to tell them about suicidal ideation, as was stated by a female spouse: *"I don't want him to think about that all on his own - I think that's far too lonely"*, although the spouses admitted that their partner's expression of suicidal ideation was also a burden on their own lives. When the person to talk to was less close (either a professional or a non-professional), a trustful relationship needed to be established before the mutation carriers felt 'close' enough to talk about suicidal ideation, although the extent of this relationship differed per participant. Furthermore, some participants found it difficult when family members who experienced the same disease process did not want to talk about the disease at all, as illustrated by one participant: *"You'd think you'd have a good relationship with someone […] somebody who lives the same sort of life as you, but who's really very different."*

Participants stated that positive experiences with talking to someone about suicidal thoughts resulted in a decrease of suicidal ideation, and in relief, improved self-esteem, and increased ability to see the positive things in life. A few participants who read up on the disease since the moment they became aware of their genetic status recognised that they had now learned to think more positively when they felt depressed for a longer period, or when someone pointed

out the good things in life. However, most other participants felt that the 'helping person' ignored their suicidal thoughts when they simply responded by pointing out the positive things in life. This difficulty experienced by persons trying to give support is illustrated by one of the partners who said: *"If you even make a small reference to something positive […] this works in a counterproductive way [….] what you're really trying to do is cheer the other person up"* and sometimes it is better *"not go into it"* but *"just be there [for your partner]"*. Also, the mutation carriers themselves mentioned that non-verbal signs of support, like someone putting an arm around you, can be very helpful. Negative experiences with talking about suicidal ideation resulted, for example, in withdrawing from the contact *"which made me feel lonely and yes, that made everything worse."* Others mentioned that they had a negative experience with too much talking about suicidality to too many different healthcare professionals. One mutation carrier attributed this to the fact that she had not yet learned *"to let go"*. The delicate balance between actively facing HD/suicidality on the one hand and taking your mind off suicidality/HD on the other was also important with regard to self-management.

Given the importance of talking about suicidality, the moderator specifically asked participants whether others should actively address the presence of suicidal thoughts. The mutation carriers pointed out that it is best to ask about their mood when others see that they are sad or doing less well; also, when the mutation carrier indicates a depressed mood, questions about suicidality could be asked (Table 2). Partners acknowledged that it is difficult to find the right moment to talk, e.g. due to a busy daily life, and because they did not want to introduce this painful topic when their partner was feeling well. Given the emotional burden for both mutation carriers and partners, one of the partners advised other partners to try and talk about the suicidality during multiple conversations, as a person can only handle a certain amount each time. One participant could talk with her partner about suicidality very well because he *"allowed me to talk about it and he took the time to discuss it."* Talking about suicidality was also difficult for the partners themselves, particularly when they had to decide on the amount of control they wished to exercise in order to prevent suicide. Partners themselves also needed to talk about suicidality with others, which one partner did by joining a peer support group, whereas another partner had negative experiences with such a group because of all the unpleasant stories she heard about what was still to come.

Most participants agreed that healthcare professionals could (or even should) ask about suicidal thoughts, even though they might feel *"taken by surprise"*. This topic should be introduced delicately by asking about sad feelings and, if present, follow-up questions should be asked (Table 2). In case of suicidal thoughts, healthcare professionals should guarantee further possibilities to talk about suicidality, e.g. by referral to a psychologist. Both mutation carriers

Table 2. Factors mentioned by participants that facilitate or complicate talking about suicidality to others (professionals and non-professionals).

Influencing factors	Example quotes
Reaction to expression of suicidal ideation	
Facilitate: Listening, taking thoughts seriously, accepting/allowing thoughts, showing empathy/ understanding, naming and asking questions (like: *"Why now?"*), embracing someone, being there for someone, holding hands, giving someone the time to see positive things themselves	*"For me it's important that other people take me seriously and don't immediately say things like: 'well, life is worth living' or 'look outside, the sun's shining' [….]For me it helps when someone just listens to what I'm saying and … that I can express my … well, my darkest thoughts."*
Complicate: Trivialising, neglecting, denying, panicking, bringing someone further down, distancing, only focusing on practicalities or distraction, giving advice that cannot be put into practice at home	*"I love horses and then they [the psychologist] say: 'Well, you should take up horse riding again.' Then I feel OK for a moment, but at home there's no money for this. So you feel good for a moment, but afterwards ... you can't do anything about it."*
Personality & relationship characteristics	
Facilitate: Feeling a 'click', trusting and feeling safe with someone, being able to be honest with someone, 24/7 availability to be called or reached, knowing about personal history, HD knowledge (HD-specific therapist), no explaining necessary, can be an outsider	*"with thoughts of death … that you actually only need to press a button and then you can talk to someone immediately"* *"just one person that you can be totally honest with"*
Complicate: Very close person whom you will hurt	*"Because at the moment you want to talk about this matter - to my wife - and then I know, oh yeh, that will hurt my wife and that's just what you're not going to do."*

Circumstances	
Facilitate: Taking time, good environment (e.g. in a forest), regular appointments (with healthcare professional), visiting someone to talk to	*"Well, it's like you're a sort of onion - and all the layers need to be peeled off [….] bit by bit actually - and that's what you can't do if you're only once with the doctor."*
Complicate: Costs (for healthcare professionals), limited time (for healthcare professionals)	*"I think that if you ask that question you need to have a lot of interest and concern for the patient … but doctors' appointments are usually only 10 minutes, 20 minutes, or half an hour, but in this sort of a case you should be willing to run over the usual allotted time."*
Follow-up	
Facilitate: Referral to psychologist/psychiatrist/ care manager, regular follow-up meetings, asking how someone is getting on, calling someone up	*"I think that when he [the neurologist] notices this, then he should refer you to a psychologist […] or a care manager, which for me is the ideal solution. That's where it really all comes together."*
Complicate: Not following-up	*"I told my sisters and brothers that I … had suicidal thoughts. But … they didn't do anything about it [....] I thought they might have at least agreed to take it in turns to call me. Once a week, or something like that."*
Moment to address	
Facilitate: When others see you are doing less well, following-up on sad/depressed thoughts	*One participant: "Well he [the professional] could ask something like: Do you have depressing thoughts? And when someone confirms this then he [the professional] should keep on questioning and if someone says 'no' then maybe he/she doesn't have thoughts about death."* *Other participant: "Yes, usually it stops after that question. Indeed, they ask do you have depressing thoughts and when you answer yes or no they usually beat about the bush or something. Maybe they should take it one step further."*
Complicate: Out of the blue, when you come to the doctor for something non-HD and non-mood related.	*"Look, when you walk in happily about something else and they look like they're thinking - 'oh that's a Huntington's patient' - then you shouldn't do it [ask about suicidal ideation]."*

and spouses emphasised that healthcare professionals should have adequate knowledge on HD and *"be familiar with the whole picture"*. A combination of individual therapy for the mutation carrier and therapy sessions that partners could also attend was preferred by the participating spouses.

2. Self-management

Participants mentioned many different activities that they used to cope with suicidality and with HD itself. These activities could result in increased self-esteem and decreased stress and thoughts of death. Most of these activities could be grouped as either 1) actively facing suicidality/HD (e.g. talking about suicidal ideation/HD, gaining information on HD, realising that you are not the only one, contacting an HD support centre, making a crisis plan, setting future goals, healthy living, and hypnotherapy), or 2) taking their mind off it, mainly by exercise and relaxation (e.g. yoga, meditation, going outside, cycling, walking, distraction, focusing on daily life, social contacts, family life, taking rest, and creative therapy). *"The art"* of *"balancing"* these elements was considered important, since activities on both sides of this spectrum could become too extreme (Figure 2) and then worsen their feelings. Reducing suicidal thoughts and getting back in balance after too much confrontation with HD or thoughts of death (e.g. in family, by rumination, listening to sad music or watching films or TV shows about death) could be achieved by taking medication, calling someone, taking rest, letting go, taking distance, focusing on yourself, or having someone who can take you out. At the same time, for some participants, negative experiences were induced by too much avoidance and not wanting to face the disease which resulted in destructive behaviour like taking drugs and alcohol, aggression, or isolating oneself. At that point, participants said they need people who can *"pull you out of the mud, so to speak."* One of the participants gave the following advice: *"Don't stay at home worrying… It is a cliché, but it actually does help: go out for a walk with someone, or go cycling! Or … I don't know … if you stay at home in front of the TV all day, or behind the computer … if you isolate yourself, in my experience, it'll only get worse and worse."*

It was advised to employ such self-management strategies and create an environment of people you can talk to before the disease starts, as it is more difficult to do this when the disease becomes more severe or when someone is depressed. Coping styles witnessed in their own family also influenced how participants dealt with the disease themselves. Several participants criticised the coping styles of their family members, e.g. when they refused to talk about it and/or avoided everything that had to do with HD.

Figure 2. Balance between actively facing Huntington's disease (HD)/suicidality and taking one's mind off it.
Self-management strategies (see Results section) can be grouped into one of these categories; our participants considered it important to aim to keep both sides in balance.

3. Medication use

Almost all participants who used medication (mostly antidepressants) were positive about its effects on their mood and suicidal thoughts. Only one woman reported that she stopped using antidepressants because she always felt unwell after taking these pills. In her opinion the pills suppressed her feelings, and she emphasised that the *"the instruction leaflet already states […] suicidal tendencies."*

The reluctance of some participants to start taking medication was recognised by the participants who were currently using medication from the period before they started. Reasons for this reluctance were: potential side-effects and being unable to separate these from disease symptoms, fear of emotional suppression, and *"wanting to do it on your own strength"*. Some participants needed time and discussion with relatives to decide about starting medication. Participants who used medication for a longer period of time mentioned that they did not want to quit, because of its effectiveness.

Many participants who used medication combined this with talking to someone: the importance of this was stressed by one participant who described an appointment with a neurologist as follows: *"when I mention I feel depressed, [the neurologist says]: 'Well - here's the medication', whereas in fact he could say something like: 'Take this medication, and try and see a psychologist in a couple of days.' People might not always want to do this, but offering this, yes that can help some people [….] I think it often helps to literally say these things out loud to a psychologist or psychiatrist."* Partners recognised the positive effects of medication for various HD symptoms, and one partner stated *"without all of that [HD medication] I couldn't have coped for so long."*

4. Discussing end-of-life wishes

Some participants had a wish and/or advance directive for euthanasia in case the disease became very severe: in the Netherlands, under strictly controlled conditions, this is legal. The prospect of such a way out could help in coping with suicidal thoughts, as explained by one of the participants: *"I kind of made my own crisis plan: what to do if I think I want to jump in front of a train. Because … I don't want to end up that way. So I made arrangements about this [euthanasia directive] and that helps."* Most participants had seen examples of HD in their family and clearly knew what they did not want to experience (such as admission to a nursing home), but some also mentioned that their views might change. Also, some participants in an early stage of the disease did not know whether or not they would want euthanasia, or had not yet thought about this. Some found it difficult to decide at what point you need to think about end-of-life wishes: this was illustrated by one participant who was recently clinically diagnosed and

still fully occupied with accepting the functional decline he experienced: *"When should I start thinking about that [euthanasia directive]? [….] I don't want to face it yet, because I feel reasonably OK […] but there's a point when you'll go further downhill, and then … then you can't properly think about it."* These participants did not want the doctor to actively address euthanasia, or they considered it a topic that should first be discussed with their partner. However, another participant, who had thought about euthanasia since her genetic diagnosis, would like the doctor to address this. Also, one partner thought it was normal that the doctor had asked about euthanasia when his wife was admitted to a nursing home, since they had discussed this together since the beginning of the disease.

Those who expressed a wish for euthanasia emphasised the importance of this being their own choice. One participant described both her positive and negative experiences with healthcare professionals as follows: *"I was always used to the fact that healthcare professionals […] are focused on making sure you won't end your life [….] but at the moment it does help me that I can just be very honest about it and yes … that people understand. That maybe I don't want to continue living at some point in time … and, yes that this is my own choice and not … not someone else's."* The fact that the doctor might not want to carry out their request at the time they have reached this point, which some participants had witnessed in their close surroundings, worried them as *"you have no guarantee"*. Also, one partner expressed such doubts, but acknowledged she had no knowledge about the legal requirements for euthanasia. Once a participant had the confidence that his/her wish would be carried out, this provided some relief. Positive euthanasia experiences in the family strengthened this confidence, and further thoughts about end-of-life wishes were also influenced by family experiences. One participant realised that in an advanced disease stage he might not understand his situation and he wondered *"So who is euthanasia most important for? For me? ... Or for my wife and children?"*

Discussion

This qualitative study shows that HD mutation carriers use various strategies to cope with suicidality including talking about suicidality, employing self-management activities, using medication, and discussing end-of-life wishes. Relatives and healthcare professionals can support suicidal mutation carriers in each of those four strategies.

Coping styles and support strategies

In older non-HD populations with a death wish or suicidal ideation, physicians were less likely to consider treatment and avoided further conversations about it.[49;50] They felt they could not

help[50;51] and considered suicidal ideation in older people more normal and rational.[50] Although healthcare professionals treating HD might have similar feelings, our study participants emphasised the urgent need to talk about their suicidality, either with a healthcare professional or a relative. They also stressed that questions about suicidality should be asked in case of a depressed mood, which is the most important association and predictor of suicidality in HD.[26;28;29;31;33;41] Similar to non-HD populations, the majority of patients do not easily disclose their suicidal thoughts to healthcare professionals[52;53] and general practitioners only asked questions about suicide in 36% of patients with depressive symptoms.[54] Furthermore, both general practitioners and neurologists thought that less than 50% of the patients with suicidal ideation needed psychiatric assessment.[55] It was previously suggested that suicidal persons communicate their thoughts more often to relatives than to healthcare professionals.[56] The participating spouses stressed they wanted their partners to tell them about suicidal thoughts and wanted to be involved in the treatment. A two-hour education program for caregivers of suicidal patients was shown to result in improved caring ability, such as better communicative skills and a more positive attitude.[57] Also, it was shown that the involvement of a significant other in the treatment of suicidal ideation resulted in greater improvement on suicidality, depression, and hopelessness measures.[58]

Applying self-managements strategies while keeping the balance between actively facing HD/suicidality and taking one's mind off, was another strategy that helped mutation carriers to cope with suicidality. Several of the self-management strategies mentioned by the participants (e.g. relaxation and exercise) have been shown effective in reducing suicidal ideation[59-61] and/or depressive symptoms[62-66] in non-HD populations, including patients with a chronic illness.[63] Within HD, positive effects of relaxation[67;68] and exercise[69-72] on several clinical outcomes have been reported, including on depression.[70]

Case reports on treatment for suicidality in HD have only focused on pharmacotherapy;[42-44] positive effects were highlighted by our study participants who used medication. In non-HD populations, antidepressants (most frequently mentioned by our participants) have been shown effective in reducing suicidal ideation in patients with major depressive disorder.[73] Within HD, one case report showed that mirtazapine could reduce suicidal ideation[43] and a HD case series demonstrated the effectiveness of lithium in reducing suicidality.[42] Lithium was not specifically mentioned by our study participants, but in both non-HD unipolar and bipolar patients treatment with lithium resulted in a reduced suicide risk.[74] Pharmacotherapy for depression is recommended in guidelines for non-HD suicidal patients,[52;75] whereas in HD undertreatment of depression is likely[76] and there is insufficient evidence to guide treatment choice.[77]

Finally, discussing end-of-life wishes helped some participants to cope with suicidality; however, this is not one of the treatment strategies recommended in general non-HD guidelines on suicidality and, moreover, is illegal in many countries. It has been estimated that 7% of the affected HD patients in the Netherlands die by euthanasia or physician-assisted suicide.[78] In non-HD populations, euthanasia is often considered to be inconceivable for psychiatric patients with a death wish.[79] It was previously recommended that HD physicians address end-of-life wishes,[80] even though they often do not initiate this conversation.[81] In the present study, not all study participants wanted their physician to actively address euthanasia. As reported previously, [80;82;83] these patients do have thoughts about their future which are mainly based on experiences in their family[82] and are usually discussed first with the family.[80] It was beyond the scope of the present study to disentangle the best moment to address these thoughts. If a patient has a wish for euthanasia, a letter of intent,[81] repeated conversations,[80;84] a trusting relationship[80] and informing patients about legal criteria/requirements[80] were previously suggested strategies that could be offered by physicians. Although not specifically mentioned by participants in our study, this might have resulted in more peace of mind for some of our participants with a wish for euthanasia.

Strengths and limitations

This is the first study to investigate attitudes towards, and coping and support strategies for suicidality in HD, which included HD mutation carriers in various disease stages. Also, the use of focus group discussions facilitated the observation of differences of opinion between participants about the coping and support strategies that were proposed.

Some limitations need to be addressed. First, we included a small and selected group which limits the generalisability of the findings. Although data saturation was reached, some participants mentioned that their family members had more avoiding ways of dealing with the disease, but did not want to participate in research in general. Second, because only three partners participated, their data were used only to determine whether they had similar ideas about treatment strategies as the mutation carriers themselves. Third, the moderator and researchers who analysed the interviews had received medical education, which might have unintentionally focused their attention on strategies that are similar to those used in current clinical practice. Fourth, generalisability of the results to other countries might be limited, especially since (under specific circumstances) euthanasia is permissible in the Netherlands, whereas this is illegal in many other countries.

Clinical recommendations

Despite the absence of a turnkey solution for suicidality in HD, healthcare professionals can

play an important role in all four strategies, which are largely in line with general non-HD suicide guidelines. All healthcare professionals who treat HD mutation carriers should ask about suicidal ideation, especially when symptoms of depression are present, and refer them to a (preferably HD-related) psychologist or psychiatrist for regular sessions to talk about suicidality. Active and non-judgmental listening, and taking their thoughts seriously, will strongly facilitate talking about suicidality. The application of the different self-management strategies might be enhanced with psychoeducation, which should also address the frequent occurrence of suicidality in HD so that patients realise that they are 'not the only one'. If the physician considers prescribing medication, this should always be combined with talking about suicidality. Furthermore, both the effectiveness and side-effects have to be addressed, and time should be allowed for the patient to decide on starting medication. Significant others should also be involved in the treatment and (often) need to receive psychoeducation from healthcare professionals,[52;85] which must at least contain guidance on talking about suicidality and suggestions for support strategies for this person him or herself. If a patient has a wish for euthanasia, and euthanasia is permissible in their country, the healthcare professional should ensure repeated conversations about this topic and show a commitment of best intentions.[80;81]

Recommendations for further study

Future studies on the treatment of suicidality in HD should ideally investigate a combination of the proposed support strategies; this was shown to be effective in elderly populations[86;87] in whom a program of psychoeducation, access to a care manager, behavioural activation, and pharmacotherapy or psychotherapy resulted in lower rates of suicidal ideation and improved quality of life compared with the treatment-as-usual group.[87;88] Also, HD-specific studies should investigate whether involvement of a significant other in the experimental treatment leads to a greater decrease in suicidality for mutation carriers and less stress for caregivers.

Conclusion

This study indicates that the best practice for suicidality in HD is talking about suicidality, self-management strategies, using medication, and discussing end-of-life wishes. Future HD-specific intervention studies should investigate a combined approach of these treatment strategies to establish clinical evidence and improve guidance for the treatment of suicidality in HD.

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Chapter 7

Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: a meta-analysis

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Submitted

Abstract

Background: The association between suicidal ideation and subsequent completed suicide has not been firmly established in different populations and absolute suicide risks after expression are unknown.

Aim: To examine whether the expression of suicidal ideation predicted subsequent completed suicide in various populations.

Method: A meta-analysis of 73 observational studies was conducted.

Results: The risk for completed suicide was clearly higher in people who had expressed suicidal ideation compared with people who had not, with substantial variation between the different populations: risk ratio 3.66 (95% CI = 2.88–4.65) for psychiatric populations and 7.46 (95% CI = 5.16–10.8) for non-psychiatric populations. In contrast, the suicide risk after expression of suicidal ideation in the first year of follow-up was higher in psychiatric patients (risk = 1.21%; 95% CI = 0.64–2.28) than in non-psychiatric participants (risk = 0.26%; 95% CI = 0.10–0.73).

Conclusion: Expression of suicidal ideation in psychiatric patients should prompt secondary prevention strategies to reduce their substantial increased risk of suicide.

Introduction

Almost 90% of those who died by suicide contacted a health care professional in the three months prior to their death.[1] Of those who had contact with a health care professional in the four weeks before their death, 22% expressed suicidal intent.[2] Several authors claim that expression of suicidal ideation is one of the most important predictors of completed suicide.[3-5] However, the association between suicidal ideation and subsequent completed suicide has not been firmly established.[6] Previous studies[7-12] and meta-analyses[13-18] that assessed this association were restricted to specific populations and reported varying results, with odds ratios obtained from the meta-analyses ranging from 1.5 in bipolar disorder[16] to 29.8 in schizophrenia.[15] For the general population and several other psychiatric populations the relationship between suicidal ideation and subsequent completed suicide remains unknown.[6,19,20] As suicidal ideation is quite common, with a lifetime prevalence of almost 10% in the general population,[21] it is important to know not only the relative risk but also the absolute risk of completed suicide for an individual who expresses suicidal ideation. The aforementioned meta-analyses[13-18] did not assess absolute risks of completed suicide. Furthermore, suicidal ideation is strongly correlated with other predictors of completed suicide like the presence of previous suicide attempts[22;23] and has not been firmly established as an independent predictor of completed suicide.[6]

Therefore, we conducted a systematic review and meta-analysis to assess whether expression of suicidal ideation predicted subsequent completed suicide in various populations, including non-psychiatric and psychiatric populations. Secondly, we aimed to estimate the absolute risks of suicide after expression of suicidal ideation in these populations and to investigate whether the expression of suicidal ideation predicted subsequent completed suicide independent of the presence of past suicide attempts.

Method

Search strategy

Ten electronic databases (PubMed, Embase, Web of science, PsycINFO, PsycARTICLES, Psychology and behavioural sciences collection, Cochrane, CINAHL, Academic search premier, and ScienceDirect) were searched until September 16, 2014, without language restrictions. A medical librarian was involved in formulating the search string (supplement S1) designed to identify studies assessing the association between the expression of suicidal ideation and completed suicide in adults.

Eligibility criteria

Relevant articles fulfilling the following inclusion criteria were eligible for inclusion: 1) assessment of presence or absence of suicidal ideation as a distinct determinant (i.e. not combined with suicidal behaviour, so studies with determinants like suicidality or elevated suicide risk were not included). The presence of suicidal ideation was considered present when any form of ideation, ranging from death wish to suicide plans or threats, was expressed; 2) assessment of completed suicide (which could include open verdicts) as a distinct outcome measure; 3) comparison of suicidal ideation vs. no suicidal ideation with respect to risk of subsequent completed suicide 4) cohort or case-control study design; and 5) mean age of the study population ≥ 18 years.

Next, the following exclusion criteria were applied: 1) presence of suicidal ideation was assessed after a suicide attempt; 2) comparison of suicidal ideation versus suicide attempt as determinant in a cohort study; or 3) comparison of those who died by suicide and those who unsuccessfully attempted suicide as outcome in a case-control study.

For the assessment of the absolute risks of completed suicide, we included only cohort studies and nested case-control studies (with the size of the source population specified and random selection of controls from the source population) in which the number of suicides in the suicidal ideation group and the exposed person-time could be extracted or estimated.

To determine whether suicidal ideation predicted subsequent completed suicide independent of the presence of past suicide attempts, articles that assessed the effect of suicidal ideation on subsequent completed suicide adjusted for previous suicide attempts were selected.

Study selection

All retrieved articles in the original search were screened independently by 2 of the 3 reviewers (AAMH, SM, and SHMP), first on title, then abstract and subsequently full-text evaluation to consider final eligibility. Disagreements with regard to final eligibility were discussed to reach consensus or, if necessary, another independent reviewer (EJG) got involved. In addition, the reference lists of eligible articles and relevant review articles identified by the search strategy were examined by one of the reviewers to search for eligible studies. When multiple publications used (partially) overlapping study populations only the largest study or, when similar, the most recent study was included.

Data extraction

For each eligible article, 2 of the 3 reviewers (AAMH and SM or SHMP) independently extracted

data using a standardised form. Disagreements were discussed or another independent reviewer (EJG) got involved if needed. When information necessary to compute the effect size for the primary aim was missing, a request for the missing numbers was emailed to the corresponding author. In case of no response, the study was not included.

Risk of bias assessment

Two independent reviewers (AAMH and SM or SHMP) assessed four risk of bias aspects (selection of study population, assessment of suicidal ideation, assessment of completed suicide, and missing data) as adequate or inadequate or not reported (see supplement S2), judged on the basis of adapted items from the Newcastle-Ottawa scale[24] and the internal validity assessment by Altman.[25]

Statistical analyses

The primary outcome of this meta-analysis was the pooled unadjusted risk ratio for the association between suicidal ideation and completed suicide in a random effects model according to the method of DerSimonian and Laird.[26] Due to expected between study heterogeneity, e.g. due to the varying absolute risks of suicide among different populations,[27] the pooling of risk ratios was stratified for the following populations: affective disorders (including both in & outpatients), (former) psychiatric inpatients (mixed diagnoses), schizophrenic patients (including both in & outpatients), other mixed psychiatric populations (including substance abusers, borderline patients, and mixed diagnosis psychiatric outpatients [sometimes combined with inpatients]), general population, and a residual category that included non-psychiatric study populations that could not be grouped in one of the other categories. Studies in each subgroup were combined using a random effects model with separate estimates of tau-squared.[28] To pool results from different studies, odds ratios, risk ratios and incidence rate ratios were considered to approach the same value, which is reasonable given the low risk of completed suicide. When only chi-square values or p-values were given in combination with a direction of the effect, these were used to estimate risk ratios. If the given p-value was < 0.05, we assumed a p-value of 0.049. There were no eligible studies only reporting a p-value > 0.05. Since several articles reported on multiple suicidal ideation determinants (e.g. thoughts and plans separately) we computed a combined effect across these different determinants based on the mean of the related effect sizes,[29] so each study only contributed one effect estimate to the meta-analysis.

With regard to the risk of suicide after expression of suicidal ideation, we were most interested in the suicide risk during the first year of follow-up. Since studies had varying follow-up times, and we did not expect a constant suicide rate over time, we conducted maximum likelihood meta-regression analyses with mean study follow-up time as determinant and $\log_e$-transformed

rates of completed suicide as outcome. The obtained intercept and regression coefficient were used to calculate the $\log_e$-transformed rate at 1-year follow-up which was back transformed to the suicide risk during the first year of follow-up. Given the limited number of studies per population subgroup, analyses were stratified for psychiatric and non-psychiatric populations only. When one article assessed suicidal ideation at multiple time points (e.g. current and lifetime), we only included the determinant that assessed suicidal ideation closest to baseline.

In order to assess whether suicidal ideation predicted completed suicide independently of previous attempts, the past suicide attempt-adjusted risk ratios were extracted and used for estimation.

To check the robustness of the results, we restricted the analyses to 1) studies with a low risk of bias (see supplement S2), 2) to cohort studies (for the primary research aim only), and 3) studies that assessed suicidal ideation at baseline or in the preceding month (for the secondary research aim only). In addition, we were interested in the results in different subgroups and stratified analyses of the primary outcome for studies with short (≤ 1-year) versus long (> 1-year) timeframe between expression of suicidal ideation and completed suicide and suicidal ideation assessment method. Maximum likelihood meta-regression was applied to examine the effects of mean age and gender in the study populations.

Heterogeneity was assessed using the I^2 statistic, publication bias by inspecting the funnel plot and Egger's test for funnel plot asymmetry. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Comprehensive Meta-analysis software version 2.0.064 (www.meta-analysis.com).

Results

Literature search and study characteristics

The literature search identified 4999 unique articles: 73 articles were finally included (Figure 1). Most studies (n = 20) investigated suicide in psychiatric inpatients (mixed diagnoses), others in schizophrenia (both in- and outpatients) (n =17), general population (n = 11), mixed psychiatric populations (n = 9; including 3 studies on substance abusers, 2 on borderline patients, 2 on mixed diagnosis psychiatric in & outpatients, and 2 on mixed diagnosis psychiatric outpatients), affective disorder (both in- and outpatients) (n = 8), or in the non-psychiatric residual category (n = 8; including 2 studies on military, 1 on veterans, 1 on stalkers, 1 study on HIV infected males, 1 on survivors of childhood cancer, 1 on prisoners, and 1 on emergency department

visitors) (Figure 1). Together these studies included 4,445,979 participants (median 203; range 14–4,045,993), with a total of 7462 completed suicides (median 60; range 3–1429). Reported mean age ranged from 18.3–76.2 years, and studies included median 41.6% (range 0–67.5) females (see supplementary Table 1 in supplement S3).

The majority of included studies were (nested) case-control studies (n = 50, 68.5%). In only 23 studies the absolute risk of completed suicide could be extracted. None of the 73 eligible articles assessed the effect of suicidal ideation on completed suicide with sole adjustment for

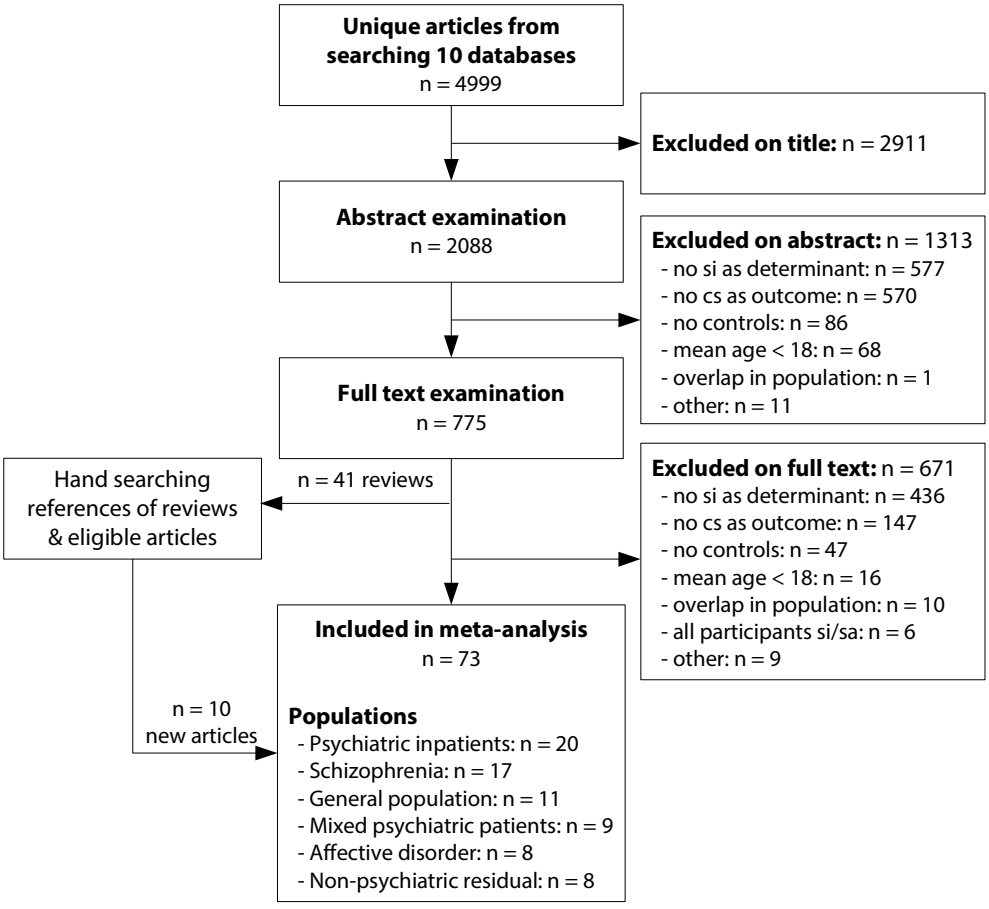
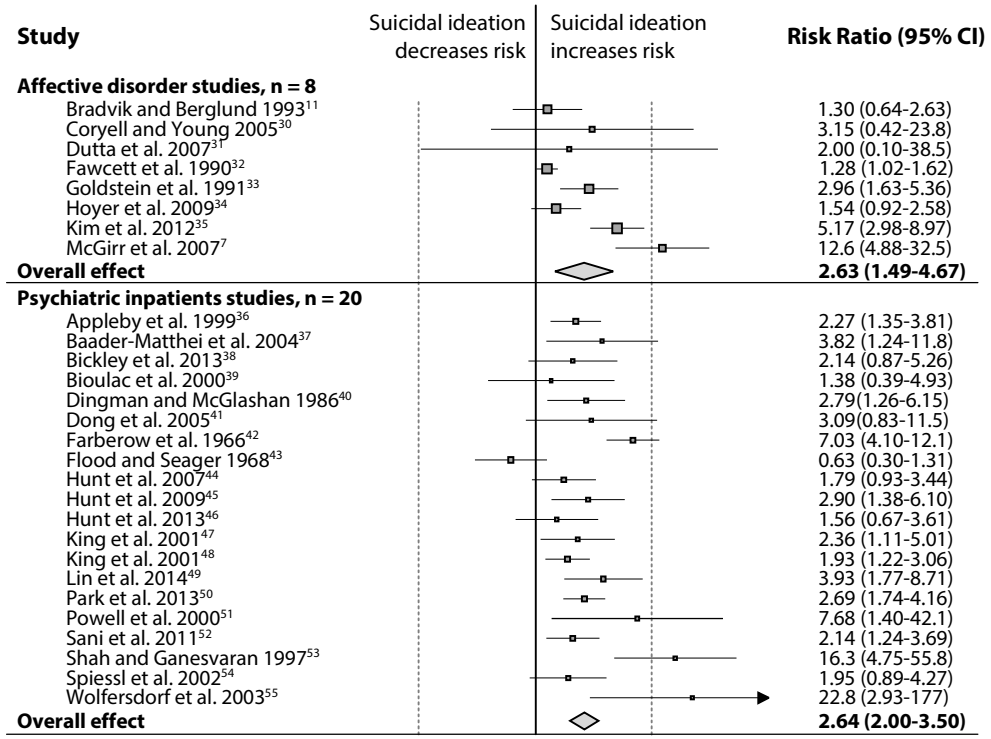


Figure 1. Flowchart of the study selection process.
Si denotes suicidal ideation; cs, completed suicide; sa, suicide attempts.
Databases searched: PubMed, Embase, Web of science, PsycINFO, PsycARTICLES, Psychology and behavioural sciences collection, Cochrane, CINAHL, Academic Search Premier, and Science Direct. Independent screening by 2 reviewers, disagreements with regard to final eligibility were discussed.

previous suicide attempts. However, there were 42 studies that applied a multivariable model, but only 26 adjusted for previous attempts as a separate determinant in this model.

Association between suicidal ideation and subsequent completed suicide

For all population subgroups investigated in this meta-analysis, the pooled risk of suicide was significantly higher in study participants who had expressed suicidal ideation compared with study participants who had not. Whereas the overall risk ratio (RR) was 4.41 (95% CI = 3.44–5.66), the risk ratios per population subgroup varied substantially. The risk ratio was highest in the non-psychiatric residual subgroup (RR = 8.00; 95% CI = 5.46–11.7), followed by the general population (RR = 6.85; 95% CI = 3.56–13.2), schizophrenia (RR = 5.80; 95% CI = 3.18–10.6), mixed psychiatric patients (RR = 5.64; 95% CI = 3.64–8.76), psychiatric inpatients (RR = 2.64; 95% CI = 2.00–3.50), and affective disorder (RR = 2.63; 95% CI = 1.49–4.67) (Figure 2). Overall, the risk ratio was 3.66 (95% CI = 2.88–4.65) in psychiatric populations and 7.46 (95% CI = 5.16–10.8) in non-psychiatric populations (data not shown).



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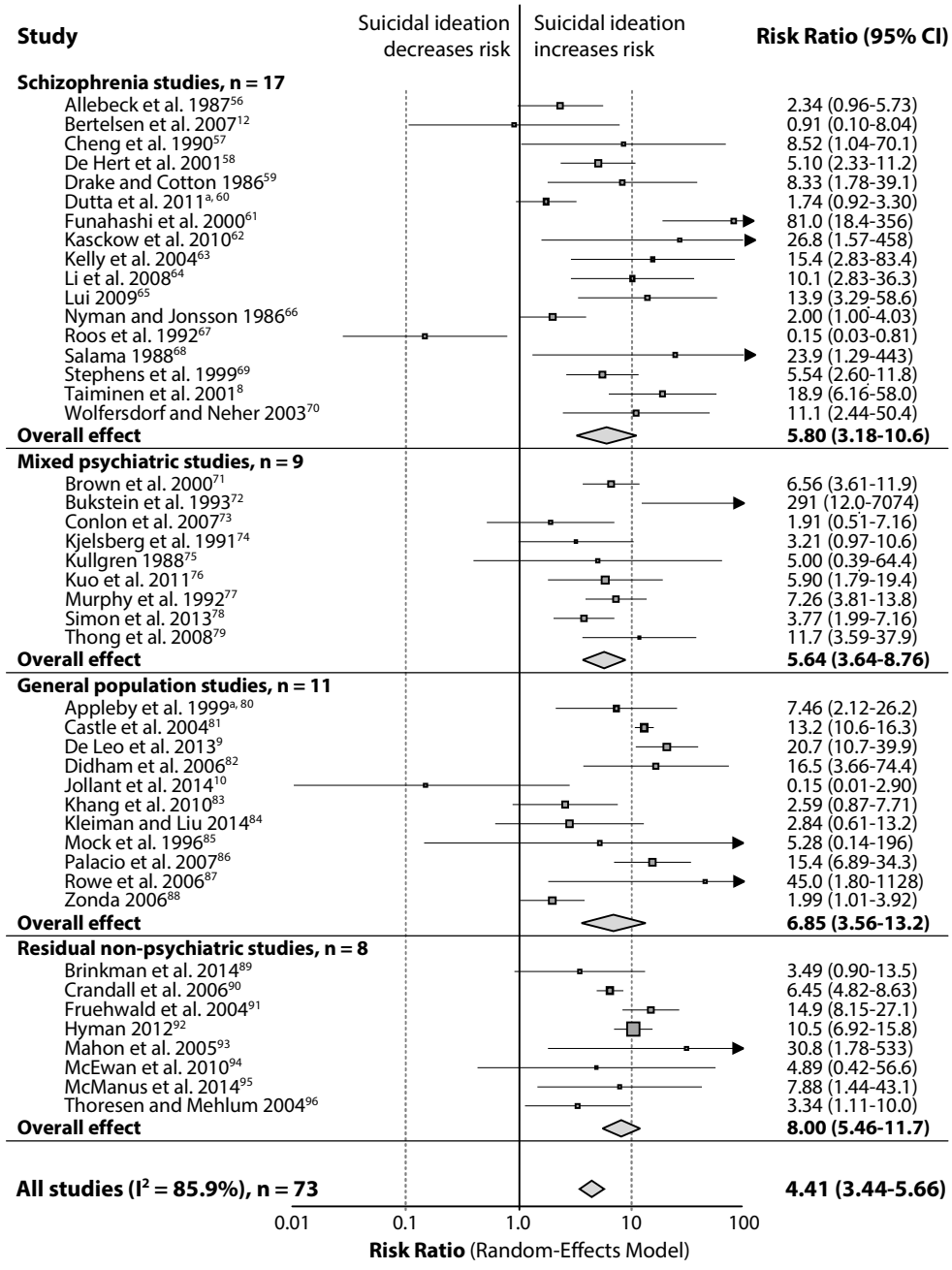


Figure 2. Forest plot showing the association between si and subsequent completed suicide.
CI denotes confidence interval; si, suicidal ideation.
[a] Authors provided additional data to compute effect size.

Risk of completed suicide

Although the psychiatric subgroups had the lowest risk ratios, meta-regression analyses showed the suicide risk was highest in the psychiatric subgroups who had expressed suicidal ideation (risk during first year of follow-up = 1.21%; 95% CI = 0.64–2.28). This was clearly higher than the suicide risk in psychiatric patients who had not expressed suicidal ideation (risk during first year of follow-up = 0.29%; 95% CI = 0.15–0.55). While the difference between study participants who had expressed suicidal ideation and study participants who had not was relatively larger in the non-psychiatric subgroups, the suicide risk in non-psychiatric populations was lower. The suicide risk during the first year of follow-up was 0.26% (95% CI = 0.10–0.73) in non-psychiatric study participants who had expressed suicidal ideation and 0.05% (95% CI = 0.01–0.24) in non-psychiatric study participants who had not (Figure 3 and Figure 4). When grouping all studies, the suicide risk during the first year of follow-up after expression of suicidal ideation was 0.76% (95% CI = 0.33–1.77) (data not shown). The meta-regression line showed that in all populations the suicide rate decreased as time progressed (Figure 4).

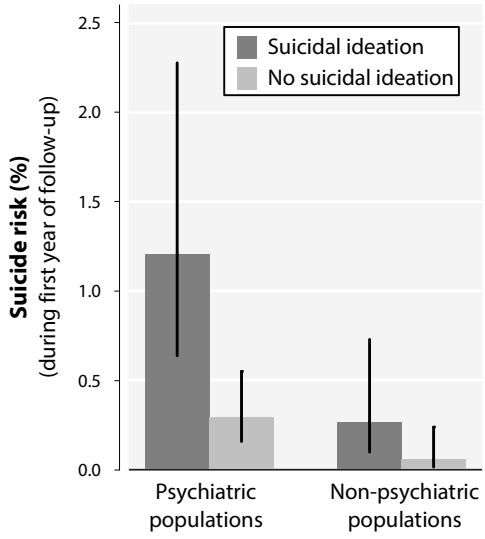


Figure 3. Bar chart showing the suicide risk (%) during first year of follow-up.
Results specified separately for study participants who had expressed suicidal ideation and study participants who had not, stratified for psychiatric and non-psychiatric populations. Lines indicate 95% confidence interval. Percentages calculated using maximum likelihood meta-regression analyses with mean study follow-up time as determinant and $\log_e$-transformed rates of completed suicide as outcome (see Figure 4).

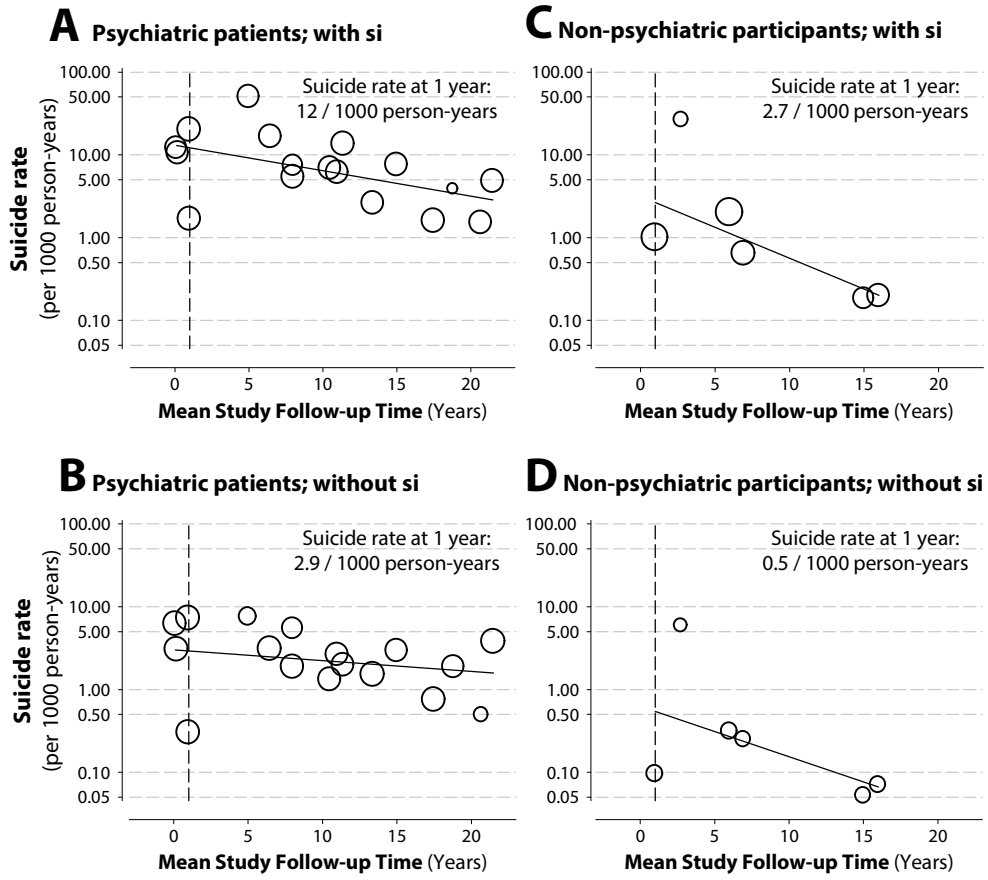


Figure 4. Meta-regression of mean study follow-up time on suicide rate.

SI indicates suicidal ideation. Maximum likelihood meta-regression analyses with mean study follow-up time as determinant and $\log_e$-transformed rates of completed suicide as outcome presented on logarithmic scales. The bubble size is proportional to the study's weight. Vertical line indicates 1-year follow-up.

The suicide risk can be calculated using the following formulas: suicide risk (during first year of follow-up)=1 – $e^{(-\text{rate per person-year at year 1})}$. A and B: Psychiatric subgroup included: Bradvik and Berglund 1993;[11] Coryell and Young 2005;[30] Dutta et al. 2007;[31] Goldstein et al. 1991;[33] Bioulac et al. 2000;[39] Dingman and McGlashan 1986;[40] Lin et al. 2014;[49] Park et al. 2013;[50] Sani et al. 2011;[52] Spiessl et al. 2002;[54] Allebeck et al. 1987;[56] de Hert et al. 2001;[58] Drake and Cotton 1986;[59] Dutta et al. 2011;[60] Stephens et al. 1999;[69] Kuo et al. 2011;[76] Simon et al. 2013;[78]

C and D: Non-psychiatric subgroup included: Khang et al. 2010;[83] Kleiman and Liu 2014;[84] Brinkman et al. 2014;[89] Crandall et al. 2006;[90] Hyman 2012;[92] McEwan et al. 2010.[94]

Risk of bias assessment & sensitivity analyses

Eighty-five percent of the studies adequately selected the study population, 68% adequately assessed the presence of suicidal ideation, 88% adequately assessed completed suicide, and 66% had < 10% missing information (supplement S2 and supplementary Table 1 in supplement S3). When restricting the analyses to studies that scored 'adequate' on all four items (n = 31, 42.5%), the pooled risk ratio (which was 4.41 in the main analysis) decreased slightly to 3.61 (95% CI = 2.81–4.64) and the overall suicide risk during the first year of follow-up (which was 0.76% in the main analysis) remained similar (risk during first year of follow-up = 0.78%; 95% CI = 0.29–2.12). In addition, restricting the primary analysis to cohort studies resulted in a slight decrease in the risk ratio (RR = 3.44; 95% CI = 2.35–5.03). Restricting the secondary analysis to studies that assessed suicidal ideation in the month around baseline resulted in a similar risk (risk during first year of follow-up = 0.75%; 95% CI = 0.31–1.84).

Is suicidal ideation an independent predictor of completed suicide?

Of all studies that used a multivariable model for the prediction of suicide and adjusted for (among other predictors) the presence of a previous suicide attempt (n = 26), only 12 reported the adjusted effect size of suicidal ideation. In 9 of these studies suicidal ideation was a significant independent predictor of completed suicide. The other 14 studies that included previous attempts in their multivariable model either did not include suicidal ideation as a separate predictor (n = 6), or did include suicidal ideation but did not report the adjusted effect size (n = 8), which was non-significant in 7 of these studies. While in at least 9 studies suicidal ideation was a significant independent predictor of completed suicide, which is significantly more than expected by chance, the 12 adjusted effect sizes were not pooled due to large underreporting of mainly non-significant results.

Subgroup analyses

There was considerable heterogeneity (I^2 for overall risk ratio = 86%), even when stratified for specific populations. Results of subgroup analyses regarding the timeframe between the expression of suicidal ideation and completed suicide and suicidal ideation assessment method can be found in supplementary Figure 1 in supplement S4, just like the results of the meta-regression analyses regarding age and gender.

Publication bias

The funnel plot (supplementary Figure 2 in supplement S5) computed for the primary research question showed a rather symmetrical funnel plot. Egger's test indicated no funnel plot asymmetry (2-tailed p-value = 0.82).

Discussion

Meta-analysing 73 eligible studies showed that overall, people expressing suicidal ideation are 4 times more likely to die by suicide than people not expressing suicidal ideation, with a suicide risk during the first year of follow-up of 1.2% in psychiatric populations and 0.26% in non-psychiatric populations. Effect estimates differed substantially among different populations: all in all, psychiatric populations showed the highest absolute suicide risks after expression of suicidal ideation but lowest relative risks, whereas the non-psychiatric populations showed the highest relative risks but lowest absolute risks.

The results of this meta-analysis are in line with previous meta-analyses on suicidal ideation and subsequent completed suicide.[13-15;17;18] The highest relative risk was found in a meta-analysis restricted to schizophrenic patients[15;18] followed by meta-analyses restricted to psychiatric inpatients[13;14] and depressed patients.[17;18] Remarkably one recent meta-analysis[18] reported that the association between suicidal ideation and completed suicide was not significant in patients with a mood disorder, while the current meta-analysis reports a significant association. This is probably explained by the broader definition of suicidal ideation that was applied in the current study, also including expression of death ideation or suicide plans, and the fact that we excluded studies that compared expression of suicidal ideation in suicide completers versus attempters, while this previous meta-analysis included such studies.[18] Unfortunately, none of the previous meta-analyses[13-18] assessed the absolute risks of suicide.

The expression of suicidal ideation is also a significant independent predictor of completed suicide, given the high number of studies that reported this. However, the effect size remains unknown, as past suicide attempt-adjusted risk ratios could not be pooled. Underreporting of non-significant effect sizes would likely have yielded a biased overestimation of the risk ratio. Many studies included in our meta-analysis did develop a prediction model for suicide, although it is widely accepted that it is very difficult to accurately predict suicide for an individual patient,[97] and there is a lot of debate on whether or not clinical risk categorization is helpful in preventing completed suicide.[98;99] It was striking that only less than 60% of these studies included previous suicide attempts as a predictor, whereas this has been reported as one of the most important independent predictors of completed suicide.[98] Future studies on suicide risk assessment should therefore include known predictors from the literature (e.g., previous suicide attempts) rather than only selecting predictors by univariable screening in the developmental dataset.[100]

Strengths and limitations

A major strength of our paper was the attempt to provide risk estimates for different subgroups. Moreover, we strictly excluded studies that might have combined suicidal ideation with behaviour, and included many studies for the primary research aim. There are also limitations that need to be considered. First, the majority of studies only provided long-term follow-up results, while the short-term risk has most clinical value. Although the provided suicide risks should be interpreted with caution due to the declining rates over time and the limited number of studies, especially with short-term follow-up, that could be included in the meta-regression analyses, results clearly show the risk of suicide is higher after expression of suicidal ideation, especially in psychiatric patients. Future studies should focus on short-term suicide risk in the different psychiatric populations. Second, only part of the large amount of heterogeneity could be explained for; several patients characteristics that would be interesting in exploring/explaining this heterogeneity, like duration of suicidal ideation[101] or behavioural traits[102] were not provided in the studied articles. In addition, study level confounding[103] might have influenced the results of our subgroup analyses, e.g. resulted in a significant effect of gender on the association between suicidal ideation and completed suicide, as the percentage of females was lower in certain high risk population subgroups like schizophrenia. Third, the varying or lacking definitions of suicidal ideation in the eligible studies might have been another source of unexplained and unmeasurable heterogeneity. Clear definitions of suicidal ideation are necessary,[104] as different assessment methods may result in different suicide ideation prevalence numbers, even in the same population at the same time point.[105] Also different studies assessed suicidal ideation during different time periods, but sensitivity analyses showed that restricting the meta-regression analysis to studies that assessed suicidal ideation at baseline or the month before resulted in a similar suicide risk. Fourth, some required study parameters could not be directly extracted from the original articles. For example the exposed person-years were conservatively estimated when possible, which could have resulted in an underestimation of the suicide risk.

Implications for clinical practice

For clinical psychiatric care, it is important to inquire about suicidal ideation in psychiatric patients given the substantial risk after expression of suicidal ideation, especially in the first period after expression. Although the relative risk was highest in non-psychiatric populations, the suicide risk after expression of suicidal ideation was lower than in psychiatric populations and decreased faster over time. However, even in psychiatric patients suicidal ideation assessment should be placed in perspective as the suicide risk during the first year of follow-up among psychiatric patients who had not expressed suicidal ideation was 0.29%, which was similar to the suicide risk in non-psychiatric persons who had expressed suicidal ideation.

Clinicians know they should be alert when a psychiatric patient expresses suicidal ideation[106] and the suicide risks provided in this meta-analysis can help clinicians in their stepped care approach to decide whether the considered secondary prevention measure (ranging from further exploring suicidal thoughts to a compulsory admission) is proportionate to the risk of suicide.

In a patient who expresses suicidal ideation, follow-up inquiries are needed about the nature of these thoughts and the assessment of other known risk factors for suicide.[107] As patients will not always express suicidal ideation spontaneously,[97] it is important to ask them about suicidal thoughts. Actually, asking patients about suicidal ideation can reduce future suicidal ideation and follow-up inquiries can benefit long-term mental health.[108] Patients often feel relieved by having an opportunity to talk about their suicidal ideas,[109] especially if clinicians take time, show empathy, and acknowledge the suicidal feelings.[110] Remarkably, in several of the included studies that assessed the presence of suicidal ideation in medical records, this information was missing. This means that it was unavailable to clinicians and appropriate care might have been unnecessarily withheld from these patients.[48]

Fortunately, the majority of patients with suicidal ideation do not die by suicide. Nevertheless, assessment of suicidal ideation is of priority in people with psychiatric illnesses and when a patient expresses suicidal ideation, prompt secondary prevention strategies are necessary to reduce their substantial increased risk of suicide.

Acknowledgments

We would like to thank medical librarian J.W. Schoones, Walaeus Library, Leiden University Medical Center for his help in conducting the literature search. In addition, we would like to thank the authors that provided additional information on their studies.

Supplements

Supplement S1. Search strategy

The following search strategy was used in Pubmed on September 16th, 2014. Combining the results of search strategy part 1 and part 2 with OR resulted in 3416 references in PubMed. In addition, Embase, Web of Science, PsycINFO, PsycARTICLES, Psychology and Behavioural Sciences Collection, COCHRANE, CINAHL, Academic Search Premier, ScienceDirect were searched for eligible articles (total 4999 references).

Search strategy part 1 focusing on prediction of suicide in adults

(((predict*[all fields] OR "predict"[all fields] OR "predictors"[all fields] OR "predictor"[all fields] OR "predictive"[all fields] OR "predicted"[all fields] OR "prediction"[all fields] OR "predictions"[all fields] OR predict*[all fields] OR traject*[all fields] OR "course"[all fields] OR "Time factors"[mesh] OR "Risk Factors"[mesh] OR "Risk"[mesh] OR "Probability"[mesh] OR "Prognosis"[mesh] OR prognos*[all fields] OR "time factors" [all fields] OR "risk factor"[all fields] OR "risk factors"[all fields]) AND ("Suicide"[majr:noexp] OR "Suicide, Attempted"[majr] OR "suicide"[ti] OR "completed suicide"[ti] OR "eventual suicide"[ti] OR "completed suicides"[ti] OR "eventual suicides"[ti] OR "later suicide"[ti] OR "later suicides"[ti] OR "subsequent suicide"[ti] OR "subsequent suicides"[ti] OR "suicide"[ti] OR "suicides"[ti] OR "suicidal behaviour"[ti] OR "suicidal behaviour"[ti] OR "suicidal behaviours"[ti] OR "suicidal behaviours"[ti] OR "suicide behaviour"[ti] OR "suicide behaviour"[ti] OR "suicide behaviours"[ti] OR "suicide behaviours"[ti]) AND ("Adult"[mesh] OR "adult"[all fields] OR "adults"[all fields])) OR ((predict*[all fields] OR "predict"[all fields] OR "predictors"[all fields] OR "predictor"[all fields] OR "predictive"[all fields] OR "predicted"[all fields] OR "prediction"[all fields] OR "predictions"[all fields] OR predict*[all fields] OR traject*[all fields] OR "course"[all fields] OR "Time factors"[mesh] OR "Risk Factors"[mesh] OR "Risk"[mesh] OR "Probability"[mesh] OR "Prognosis"[mesh] OR prognos*[all fields] OR "time factors" [all fields] OR "risk factor"[all fields] OR "risk factors"[all fields]) AND ("Suicide"[majr:noexp] OR "Suicide, Attempted"[majr] OR "suicide"[ti] OR "completed suicide"[ti] OR "eventual suicide"[ti] OR "completed suicides"[ti] OR "eventual suicides"[ti] OR "later suicide"[ti] OR "later suicides"[ti] OR "subsequent suicide"[ti] OR "subsequent suicides"[ti] OR "suicide"[ti] OR "suicides"[ti] OR "suicidal behaviour"[ti] OR "suicidal behaviour"[ti] OR "suicidal behaviours"[ti] OR "suicidal behaviours"[ti] OR "suicide behaviour"[ti] OR "suicide behaviour"[ti] OR "suicide behaviours"[ti] OR "suicide behaviours"[ti]) NOT ("Adolescent"[mesh] OR "Child"[mesh]) NOT "Adult"[mesh])))
AND ("Case-Control Studies"[mesh] OR "Case-Control"[all fields] OR "Case-Controlled"[all fields] OR "Retrospective"[all fields] OR Retrospectiv*[all fields] OR "Retrospective Studies"[all fields] OR "Retrospective Study"[all fields] OR "Cohort Studies"[mesh] OR "Cohort"[all fields] OR "Cohorts"[all fields] OR "Longitudinal Studies"[all fields] OR "Longitudinal Study"[all

fields] OR "Follow-Up Studies"[all fields] OR "Follow-Up Study"[all fields] OR "Follow-Up"[all fields] OR "Prospective Studies"[all fields] OR "Prospective Study"[all fields] OR "Multivariate Analysis"[Mesh] OR "Multivariate"[all fields])

Search strategy part 2 focusing on suicidal ideation and suicide in adults

((("Suicidal Ideation"[mesh] OR "suicide ideation"[all fields] OR "suicidal ideation"[all fields] OR "suicide thoughts"[all fields] OR "suicide thought"[all fields] OR "suicidal thoughts"[all fields] OR "suicidal thought"[all fields] OR "suicide idea"[all fields] OR "suicide ideas"[all fields] OR "suicide ideator"[all fields] OR "suicide ideators"[all fields] OR "suicidal idea"[all fields] OR "suicidal ideas"[all fields] OR "suicidal ideator"[all fields] OR "suicidal ideators"[all fields] OR "suicidality"[all fields] OR "suicidal tendencies"[all fields] OR "death wishes"[all fields] OR "suicidal tendency"[all fields] OR "death wish"[all fields] OR "talk of suicide"[all fields] OR "threat of suicide"[all fields] OR "suicidal communication"[all fields]) AND (predict*[all fields] OR "predict"[all fields] OR "predictors"[all fields] OR "predictor"[all fields] OR "predictive"[all fields] OR "predicted"[all fields] OR "prediction"[all fields] OR "predictions"[all fields] OR predict*[all fields] OR traject*[all fields] OR "course"[all fields] OR "Time factors"[mesh] OR "Risk Factors"[mesh] OR "Risk"[mesh] OR "Probability"[mesh] OR "Prognosis"[mesh] OR prognos*[all fields] OR "time factors" [all fields] OR "risk factor"[all fields] OR "risk factors"[all fields]) AND ("Suicide"[mesh:noexp] OR "Suicide, Attempted"[mesh] OR "suicide"[all fields] OR "completed suicide"[all fields] OR "eventual suicide"[all fields] OR "completed suicides"[all fields] OR "eventual suicides"[all fields] OR "later suicide"[all fields] OR "later suicides"[all fields] OR "subsequent suicide"[all fields] OR "subsequent suicides"[all fields] OR "suicide"[all fields] OR "suicides"[all fields] OR "suicidal behaviour"[all fields] OR "suicidal behaviour"[all fields] OR "suicidal behaviours"[all fields] OR "suicidal behaviours"[all fields] OR "suicide behaviour"[all fields] OR "suicide behaviour"[all fields] OR "suicide behaviours"[all fields] OR "suicide behaviours"[all fields]) AND ("Adult"[mesh] OR "adult"[all fields] OR "adults"[all fields])) OR (("Suicidal Ideation"[mesh] OR "suicide ideation"[all fields] OR "suicidal ideation"[all fields] OR "suicide thoughts"[all fields] OR "suicide thought"[all fields] OR "suicidal thoughts"[all fields] OR "suicidal thought"[all fields] OR "suicide idea"[all fields] OR "suicide ideas"[all fields] OR "suicide ideator"[all fields] OR "suicide ideators"[all fields] OR "suicidal idea"[all fields] OR "suicidal ideas"[all fields] OR "suicidal ideator"[all fields] OR "suicidal ideators"[all fields] OR "suicidality"[all fields] OR "suicidal tendencies"[all fields] OR "death wishes"[all fields] OR "suicidal tendency"[all fields] OR "death wish"[all fields] OR "talk of suicide"[all fields] OR "threat of suicide"[all fields] OR "suicidal communication"[all fields]) AND (predict*[all fields] OR "predict"[all fields] OR "predictors"[all fields] OR "predictor"[all fields] OR "predictive"[all fields] OR "predicted"[all fields] OR "prediction"[all fields] OR "predictions"[all fields] OR predict*[all fields] OR traject*[all fields] OR "course"[all fields] OR "Time factors"[mesh] OR "Risk Factors"[mesh] OR "Risk"[mesh] OR "Probability"[mesh] OR "Prognosis"[mesh] OR

prognos*[all fields] OR "time factors" [all fields] OR "risk factor"[all fields] OR "risk factors"[all fields]) AND ("Suicide"[mesh:noexp] OR "Suicide, Attempted"[mesh] OR "suicide"[all fields] OR "completed suicide"[all fields] OR "eventual suicide"[all fields] OR "completed suicides"[all fields] OR "eventual suicides"[all fields] OR "later suicide"[all fields] OR "later suicides"[all fields] OR "subsequent suicide"[all fields] OR "subsequent suicides"[all fields] OR "suicide"[all fields] OR "suicides"[all fields] OR "suicidal behaviour"[all fields] OR "suicidal behaviour"[all fields] OR "suicidal behaviours"[all fields] OR "suicidal behaviours"[all fields] OR "suicide behaviour"[all fields] OR "suicide behaviour"[all fields] OR "suicide behaviours"[all fields] OR "suicide behaviours"[all fields]) NOT ("Adolescent"[mesh] OR "Child"[mesh]) NOT "Adult"[mesh])))
AND ("Case-Control Studies"[mesh] OR "Case-Control"[all fields] OR "Case-Controlled"[all fields] OR "Retrospective"[all fields] OR Retrospectiv*[all fields] OR "Retrospective Studies"[all fields] OR "Retrospective Study"[all fields] OR "Cohort Studies"[mesh] OR "Cohort"[all fields] OR "Cohorts"[all fields] OR "Longitudinal Studies"[all fields] OR "Longitudinal Study"[all fields] OR "Follow-Up Studies"[all fields] OR "Follow-Up Study"[all fields] OR "Follow-Up"[all fields] OR "Prospective Studies"[all fields] OR "Prospective Study"[all fields] OR "Multivariate Analysis"[Mesh] OR "Multivariate"[all fields])

Supplement S2. Risk of bias assessment
Adapted from Newcastle-Ottawa scales[24] and framework by Altman[25]

Case-control studies

1. Selection of study population
   (1) Adequate: Cases are a consecutive or obviously representative series of cases. Controls are a randomly selected sample from the cases' source population.
   (2) Inadequate or not reported: Selected cases are not representative or controls are not randomly selected from cases' source population.

2. Assessment of determinant (presence of suicidal ideation)
   (1) Adequate: description of suicidal ideation assessment is provided and is the same for cases and controls, and information on presence of suicidal ideation is obtained from a source that was blind for the outcome (e.g. reported in medical record at time before suicide).
   (2) Inadequate or not reported: no description of suicidal ideation assessment provided, or assessment is different for cases and controls, or information on presence of suicidal ideation came from a source that was not blind for the outcome (e.g. asked to next of kin after suicide).

3. Assessment of outcome (completed suicide)
   (1) Adequate: Use of death certificates/coroners verdicts/medical verdicts/registries to avoid misclassification of suicides.
   (2) Inadequate or not reported: No use of death certificates/coroners verdicts/medical verdicts/registries, misclassification of suicides likely.

4. Missing information on determinant (presence of suicidal ideation)
   (1) Adequate: No or small number of participants with missing information on determinant: ≤ 10%.
   (2) Inadequate or not reported: Large number of participants with missing information on determinant: > 10%. Participants who were eligible for participation but had missing medical files or no informant that was willing to provide information on the presence of suicidal ideation were considered as participants with missing information.

Cohort studies

1. Selection of study population
   (1) Adequate: Participants are a random (consecutive) sample of eligible patients, most

important aspect: non-exposed cohort drawn from same community as the exposed cohort and at the same time point in course of disease.
(2) Inadequate or not reported: Participants are not a random sample of eligible patients, especially inadequate when non exposed cohort is drawn from different source or at different time point in course of disease.

2. Assessment of determinant (presence of suicidal ideation)
   (1) Adequate: description of suicidal ideation assessment provided.
   (2) Inadequate: no description of suicidal ideation assessment provided.

3. Assessment of outcome (completed suicide)
   (1) Adequate: Use of death certificates/coroners verdicts/medical verdicts/registries to avoid misclassification of suicides.
   (2) Inadequate or not reported: No use of death certificates/coroners verdicts/medical verdicts/registries, misclassification of suicides likely.

4. Missing information on follow-up
   (1) Adequate: no or small number of participants lost to follow-up: ≤ 10%. If death registries were used with expected coverage > 90%, this item was scored adequate.
   (2) Inadequate or not reported: large number of participants lost to follow-up: >10%.

Scoring system
Total score is computed by adding scores on four items (range 0–4 points).
Low risk of bias: total score 4 points
Medium risk of bias: total score 5-6 points
High risk of bias: total score 7-8 points

Supplement S3. Literature table

Supplementary Table 1. Details of studies included in the meta-analysis for answering the primary research aim.

First author, year	Study design[a]	Sample size	Suicides	Age (years)[b]	% female	SI assessment[c]	Q1[d]	Q2	Q3	Q4
Affective disorder										
Bradvik & Berglund 1993[11]	Matched nested cc	178	89	46.7	57.3	Medical record	1	1	1	1
Coryell & Young 2005[e, 30]	Cohort	785	33	38.8	67.5	Interview part.	1	1	1	1
Dutta et al. 2007[31]	Cohort	239	8	33.2	56.6	Medical record	1	1	1	1
Fawcett et al. 1990[32]	Cohort	954	32	38.1	58.0	Interview part.	1	1	1	?
Goldstein et al. 1991[33]	Cohort	1906	46	41.2	60.7	Medical record	1	1	1	1
Hoyer et al. 2009[34]	Matched cc	270	135	44% ≤ 55	51.1	Medical record	1	1	1	1
Kim et al. 2012[35]	Matched nested cc	636	324	58	12.4	Medical record	1	1	1	1
McGirr et al. 200[77]	Case control	237	156	42.5	22.8	Interview NOK	1	2	1	2
Psychiatric inpatients										
Appleby et al. 1999[36]	Matched cc	298	149	med 38	35.7	Medical record	1	1	1	1
Baader-Matthei et al. 2004[37]	Matched nested cc	64	32	46.1	46.9	Medical record	1	1	1	1
Bickley et al. 2013[38]	Case control	200	100	med 42	44	Quest. clinician	1	2	1	1
Bioulac et al. 2000[39]	Cohort	200	10	41.2	54	Interview part.	1	1	2	1
Dingman & MacGlashan 1986[40]	Cohort	460	38	?	54.2	Medical record	1	1	2	1
Dong et al. 2005[41]	Matched nested cc	184	92	41.1	47.8	Medical record	1	1	1	1
Farberow et al. 1966[42]	Nested cc	438	218	40.1	0	Medical record	1	1	1	1
Flood and Seager 1968[43]	Matched nested cc	216	73	49	65	Medical record	1	1	1	2
Hunt et al. 2007[44]	Matched nested cc	444	222	med 39	42.8	Quest. clinician	1	2	1	1

Table continued on the next page.

First author, year	Study design[a]	Sample size	Suicides	Age (years)[b]	% female	SI assessment[c]	Q1[d]	Q2	Q3	Q4
Hunt et al. 2009[45]	Matched nested cc	476	238	med 39.5	41.6	Quest. clinician	1	2	1	1
Hunt et al. 2013[46]	Matched nested cc	214	107	med 40	40.2	Quest. clinician	1	2	1	1
King et al. 2001[47]	Matched nested cc	165	59	?	45.8	Medical record	1	1	1	2
King et al. 2001[48]	Matched nested cc	665	234	44.0	37.5	Medical record	1	1	1	2
Lin et al. 2014[49]	Matched nested cc	203	41	34	49.3	Medical record	1	1	1	1
Park et al. 2013[50]	Cohort	8403	96	41	57.2	Medical record	1	1	1	1
Powell et al. 2000[51]	Matched nested cc	187	97	43.5	50.8	Medical record	1	1	1	2
Sani et al. 2011[52]	Matched nested cc	288	96	?	44.8	Psychol. autopsy	1	2	?	1
Shah and Ganesvaran 1997[53]	Matched nested cc	120	60	med 32 (s)	45	Medical record	1	1	1	2
Spiessl et al. 2002[54]	Cohort	21062	30	47.1	46.5	Medical record	1	1	1	1
Wolfersdorf et al. 2003[55]	Matched nested cc	128	64	45.2	36	Medical record	1	2	1	?
Schizophrenia										
Allebeck et al. 1987[56]	Nested cc	96	32	36.8	52.1	Medical record	1	1	1	?
Bertelsen et al. 2007[12]	Cohort	547	7	26	41	Interview part.	1	1	1	1
Cheng et al. 1990[57]	Matched nested cc	148	74	31.1	41.9	Medical record	1	1	?	1
de Hert et al. 2001[58]	Matched nested cc	126	63	28.6	22.2	Psychol. autopsy	1	2	?	1
Drake and Cotton 1986[59]	Cohort	104	15	31.4	45.1	Medical record	1	1	1	1
Dutta et al. 2011[60]	Cohort	2132	51	36.1	47.9	Medical record	1	1	1	1
Funahashi et al. 2000[61]	Matched cc	160	80	35.6	23.8	Medical record	2	1	1	?
Kasckow et al. 2010[62]	Case control	98	74	45.0	31.6	Interview NOK	2	2	1	2
Kelly et al. 2004[63]	Case control	97	15	48.1	35.1	Psychol. autopsy	2	2	?	2
Li et al. 2008[64]	Matched nested cc	128	64	34.6	51.9	Medical record	1	1	1	1

Lui 2009[65]	Cohort	234	8	21.9	44.4	Medical record	1	1	1	1
Nyman and Jonsson 1986[66]	Cohort	110	10	30.4 (s)	34.5	Medical record	1	1	1	1
Roos et al. 1992[67]	Matched cc	66	33	34.5	30.3	Psychol. autopsy	2	2	?	1
Salama 1988[68]	Cohort	139	5	?	39	Medical record	1	2	1	1
Stephens et al. 1999[69]	Cohort	1212	28	28	52.6	Medical record	1	1	1	2
Taiminen et al. 2001[8]	Matched cc	138	69	39.7	39.1	Psychol. autopsy	1	2	1	1
Wolfersdorf & Neher 2003[70]	Matched cc	160	80	?	?	Medical record	1	1	1	1
Mixed psychiatric										
Brown et al. 2000[71]	Cohort	6891	49	36.3	55.8	Interview part.	1	1	1	1
Bukstein et al. 1993[72]	Matched cc	35	23	18.3	5.4	Interview NOK	1	2	1	2
Conlon et al. 2007[73]	Matched nested cc	78	39	41.8	28.2	Medical record	1	1	1	?
Kjelsberg et al. 1991[74]	Matched nested cc	42	21	33.5	42.9	Medical record	1	1	1	?
Kullgren 1988[f, 75]	Case control	14	8	34.1	0	Medical record	1	1	1	1
Kuo et al. 2011[76]	Matched nested cc	114	38	28.9	18.4	Medical record	1	1	1	2
Murphy et al. 1992[77]	Case control	315	67	45.1	0	Historical data	2	2	1	1
Simon et al. 2013[78]	Cohort	84418	46	?	?	Interview part.	1	1	1	1
Thong et al. 2008[79]	Matched cc	246	123	43 (s)	45.4	Medical record	1	1	1	2
General population										
Appleby et al. 1999[80]	Matched cc	148	84	26.7	19	Psychol. autopsy	1	2	1	2
Castle et al. 2004[81]	Case control	5624	1429	47.2	37	Interview NOK	2	2	1	2
De Leo et al. 2013[9]	Case control	443	261	57.5	24.2	Interview NOK	2	2	1	2
Didham et al. 2006[82]	Matched nested cc	884	221	med 37.2 (s)	25.8 (s)	Medical record	1	1	1	1
Jollant et al. 2014[10]	Matched nested cc	45	15	30 (s)	47.7	Interview NOK	1	2	2	1

Table continued on the next page.

First author, year	Study design[a]	Sample size	Suicides	Age (years)[b]	% female	SI assessment[c]	Q1[d]	Q2	Q3	Q4
Khang et al. 2010[83]	Cohort	5414	13	>30	53.4	Interview part.	1	1	1	1
Kleiman and Liu 2014[84]	Cohort	20014	25	47.6	53.1	Interview part.	1	1	1	1
Mock et al. 1996[85]	Matched nested cc	84	21	21	20	Medical record	1	1	1	1
Palacio et al. 2007[86]	Matched cc	216	108	med 29	19.4	Psychol. autopsy	2	2	1	1
Rowe et al. 2006[87]	Case control	18	14	76.2	27.8	Psychol. autopsy	1	2	1	2
Zonda 2006[88]	Matched cc	200	100	52.2	33	Interview NOK	2	2	1	1
Various										
Brinkman et al. 2014[89]	Cohort	10072	10	25.0	49.7	Interview part.	1	1	1	1
Crandall et al. 2006[90]	Cohort	218263	408	34.5	49.0	Medical record	1	1	1	1
Fruehwald et al. 2004[91]	Matched nested cc	660	220	34.2	2.7	Medical record	1	1	1	2
Hyman 2012[92]	Cohort	4045993	406	29.3	15.0	Military record	1	1	?	1
Mahon et al. 2005[93]	Matched nested cc	126	63	29	0	Military record	2	1	1	1
McEwan et al. 2010[94]	Cohort	138	3	36.4	10.9	Interview part.	1	1	1	1
McManus et al. 2014[95]	Matched nested cc	81	17	41.3	0	Medical record	1	1	1	1
Thoresen & Mehlum 2004[96]	Nested cc	88	43	30.5	0	Interview NOK	2	2	1	2

(s) denotes the value is only given for the suicide group; cc, case control; SI, suicidal ideation; Q, quality criterion; med, median; NOK, next of kin; part.., participant; psychol., psychological; quest., questionnaire.

[a] If case control studies only did time matching (e.g. same admission date) we did not consider this a matched case control study.

[b] Mean age of study population is shown unless otherwise specified.

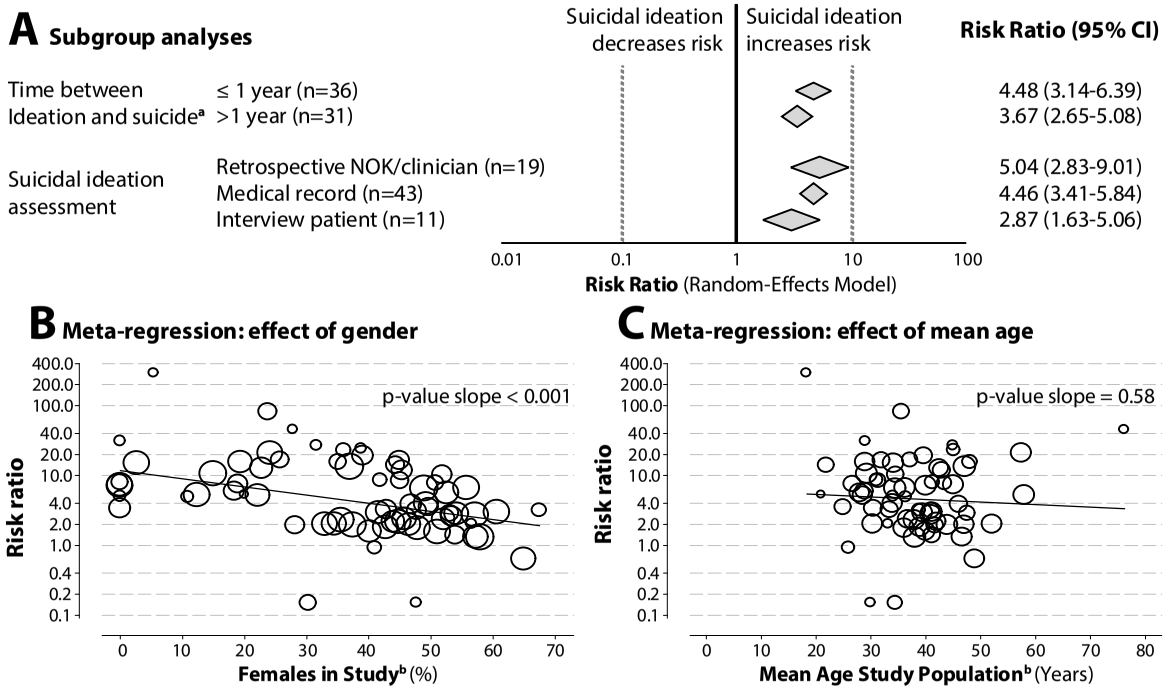
[c] Questionnaire clinician and interview next of kin were retrospective suicidal ideation assessment methods after the participant had reached study end point.

[d] Quality criteria, for specification see supplement S2.

[e] Study participants who attempted suicide were excluded before calculation of the effect size because it was unclear whether they had expressed suicidal ideation.

[f] Only data for male participants was used as the suicidal ideation effect size could only be calculated for males in this study.

Supplement S4. Subgroup analyses.



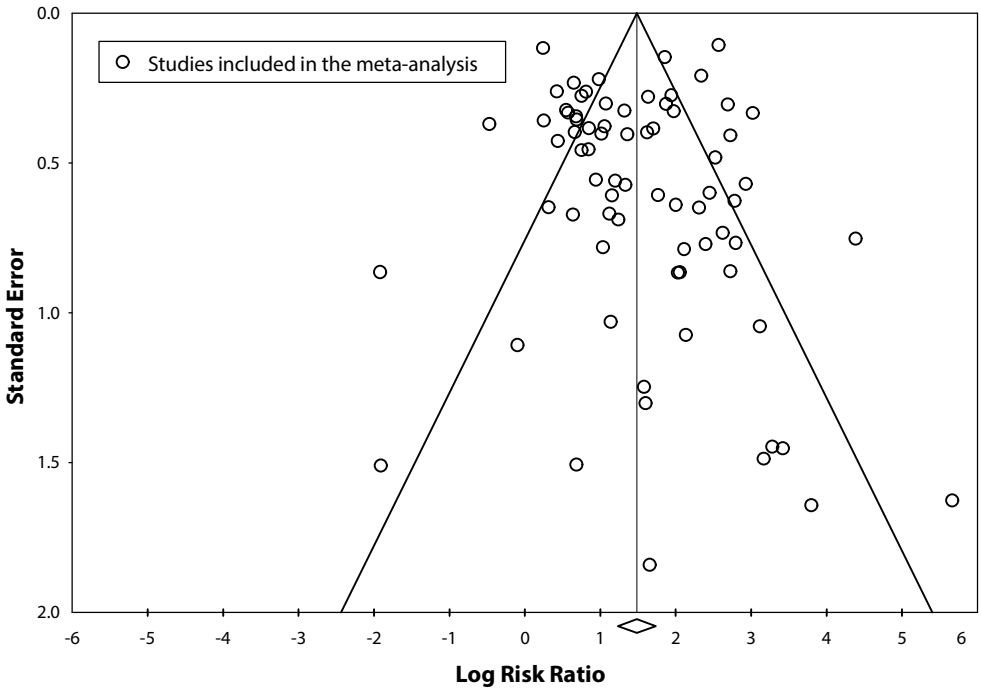
Supplementary Figure 1. Subgroup analyses.

Subgroup analyses showing the association between the expression of suicidal ideation and subsequent completed suicide in different subgroups.
RR indicates risk ratio; CI, confidence interval; NOK, next of kin. B & C: Maximum likelihood meta-regression analysis with % of females in study (for B) and mean age of the study population (for C) as determinant and $\log_e$-transformed risk ratio as outcome presented on logarithmic scales. The bubble size is proportional to the study's weight.

[a] Total does not add up to 73, as in 8 studies the time interval could not be extracted and in 2 studies separate outcomes for ≤ and > 1 year were reported. When suicidal ideation was assessed at admission and suicide during admission, we assumed a time ≤ 1 year unless otherwise specified in the article.

[b] In 2 studies the % of females and in 8 studies the mean age of the study population was not provided.

Supplement S5. Publication bias



Supplementary Figure 2. Funnel plot displaying effect estimates from included studies.
Egger's test for funnel plot asymmetry: p = 0.82.

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Chapter 8

Summary and general discussion

Summary

In this thesis the epidemiology of suicidal ideation and suicide attempts (together referred to as 'suicidality') in Huntington's disease (HD) is investigated, and coping styles and support strategies that may serve to help suicidal HD mutation carriers are explored. Prevalence and incidence, as well as sociodemographic, clinical and biological cross-sectional and longitudinal associations with suicidality were studied in a Dutch and in a European cohort of HD mutation carriers. In a qualitative study we explored how HD mutation carriers coped with suicidality and what their ideas and wishes were regarding how relatives and healthcare professionals could help them in coping with suicidality. Additionally, we examined how spouses of HD mutation carriers supported their partners with regard to suicidality. Finally, we examined whether the expression of suicidal ideation predicted subsequent completed suicide in various populations.

Previous studies showed an increased prevalence of suicidal ideation, suicide attempts and completed suicide in both pre-motor and motor symptomatic mutation carriers, compared with the general population (Chapter 1). Although various characteristics associated with suicidality and suicide have been reported, there appeared to be a lack of prospective studies to identify HD mutation carriers at highest risk of developing suicidality.

The results of the studies described in chapters 2 and 3 of this thesis confirm that suicidality frequently occurs in HD, with up to 20% of both pre-motor and motor symptomatic mutation carriers reporting suicidality in the month prior to the interview, compared with 0% of the controls. Mutation carriers who were most likely to currently experience suicidal ideation or suicidality had a shorter disease duration, were anxious, aggressive, previously attempted suicide, used antidepressants, and had a depressed mood. The presence of a depressed mood and the use of benzodiazepines were the only significant independent predictors of incident suicidal ideation or suicidality.

Apart from the sociodemographic and clinical associations, we also investigated cross-sectional biological associations of suicidality in HD, in particular the functioning of the immune system (Chapter 4) and the hypothalamus-pituitary-adrenal (HPA) axis (Chapter 5). In a Dutch cohort of HD mutation carriers, no cross-sectional associations were found between markers of the acute phase response (i.e. C-reactive protein and albumin) and suicidality. However, we did find associations between markers of the acute phase response proteins and several other clinical characteristics (e.g. disease stage), but these associations disappeared after adjusting for the use of antipsychotics (Chapter 4). Also, in the same cohort, it was shown that parameters of HPA axis activity were not associated with the severity of depressive symptoms or suicidality.

However, subgroup analyses revealed varying associations in pre-motor, early and late disease stages, with significantly higher morning cortisol levels in depressed pre-motor and early stage motor symptomatic HD mutation carriers, compared with non-depressed HD mutation carriers from these disease stages (Chapter 5).

Given the increased frequency of suicidality in HD compared with controls (Chapter 2) and the lack of treatment guidelines, we conducted a qualitative study in which HD mutation carriers who had experienced suicidal ideation or attempted suicide and their partners were interviewed (Chapter 6). HD mutation carriers generally used four strategies to cope with suicidality: talking about suicidality, employing self-management activities, using medication and discussing end-of-life wishes. Partners, relatives, and healthcare professionals can support suicidal HD mutation carriers in carrying out each of these strategies.

Suicidal ideation, sometimes combined with suicide attempts, was the outcome in all our studies. Therefore, the systematic review and meta-analysis described in chapter 7 examined whether the expression of suicidal ideation predicted subsequent completed suicide in different clinical and non-clinical populations. The risk of completed suicide was 3-8 times higher (depending on the population investigated) in individuals who had expressed suicidal ideation compared with individuals who had not. All in all, psychiatric populations showed the highest absolute suicide risks after expression of suicidal ideation but the lowest relative risks, whereas (vice versa) the non-psychiatric populations showed the highest relative risks but the lowest absolute risks. However, none of the included studies investigated the association between suicidal ideation and subsequent completed suicide in HD.

General discussion

Overall, we can conclude that suicidality frequently occurs in both pre-motor and motor symptomatic HD mutation carriers. Therefore, it is important to regularly assess HD mutation carriers for suicidality, especially when they have a depressed mood. Healthcare professionals can play a crucial role in supporting suicidal HD mutation carriers by providing an opportunity to talk about suicidality, providing psychoeducation on self-management, prescribing medication, and discussing end-of-life wishes.

Do HD mutation carriers at risk of suicidality differ from those at risk in non-HD populations?
The presence of psychiatric disorders and symptoms, in particular depression and a previous suicide attempt, are the most important associations and predictors of suicidality and suicide in

both the general population and other clinical populations.[1-16] In the thesis, mainly psychiatric conditions, in particular the presence of a depressed mood, were shown to be associated with or predictive of suicidality in HD (Chapter 2 and 3), as well as in other HD studies.[17-20] However, suicidality assessment in non-HD clinical populations mainly focuses on the presence of actual full-blown mood disorders, rather than on the presence of a depressed mood.[21;22] We found that in HD a DSM-IV diagnosis of depression was no longer associated with suicidality after other psychiatric symptoms had been included in the regression model (Chapter 2). A possible explanation for this is the limited statistical power of the study. Also, an actual DSM diagnosis of depression might be less applicable in HD and less suited as a predictor of suicidality in HD, since several of the symptoms of a DSM diagnosis of depression (e.g. weight loss and sleep disturbance) also occur as physical symptoms of HD.[23] Another discrepancy with results from non-HD studies is that a previous suicide attempt did not predict incident suicidal ideation, as described in chapter 3. This might be because suicidal ideation is clinically different from suicide attempts and completed suicide.[22;24] Nevertheless, these three different aspects of the suicidality spectrum are associated but, for example, only 1.2% of the psychiatric patients who had expressed suicidal ideation actually died by suicide in the following year (Chapter 7). The clinical differences between individuals who think of, attempt, or die by suicide might explain why we found no sociodemographic associations of suicidality (Chapter 2 and 3). This is in contrast to studies on suicide in both HD and Western non-HD populations, which showed that being male was associated with a 2-4 times increased risk of completed suicide.[12;25;26] In contrast, females were more likely to think of or attempt suicide, as shown in both one HD study[19] and in various non-HD studies[9;16;27-29] However, these latter associations were smaller and less consistent than those reported for male gender and suicide.

Moreover, some clinical characteristics known to be associated with suicidality in non-HD populations were not investigated in this thesis. For example, alcohol misuse is one of the most common psychiatric disorders in persons who die by suicide[12] and increases the risk of suicidality.[30] Also, HD mutation carriers with the most severe suicidal ideation were more likely to report alcohol abuse.[18] Hopelessness and other psychological stressors are also prominent predictors of suicidal ideation and important in the risk of attempted and completed suicide in adults.[31] Hopelessness in HD was shown to be increased in the first week after predictive testing and rose again 7-10 years after predictive testing, which could be the period when mutation carriers start to notice the first symptoms of the disease given their mean age of 45 years.[32] Feelings of hopelessness may also have resulted from the onset of HD in family members, loss of relatives, and a subsequent decrease in social support.[32] The period around symptom onset was also identified as a high-risk period for suicidal ideation in HD.[33] An association between hopelessness and both suicidality and suicide has not been found in HD;

however, this was investigated in only one study with 13 suicidal events.[19] Other personality traits (like impulsivity) might also be associated with suicidality in HD, as was found in non-HD populations,[12;31;34] given the disrupted frontal-subcortical circuits.[18;35] While impulsivity was not investigated in this thesis or in other HD studies,[18;19] suicidal ideation was associated with aggression (Chapter 3).[18] Aggression is related to impulsivity and is even considered by some as a single phenotype.[34]

The only non-psychiatric characteristic we found to be associated with suicidality in HD was a shorter duration of HD (Chapter 3). This is in line with results from other HD studies showing that suicidal ideation and completed suicide occur more frequently in pre-motor, early symptomatic and middle symptomatic stages, than in later disease stages.[25;33;36-38] Therefore, HD disease stage is an additional factor that should be taken into account when aiming to identify HD mutation carriers at highest risk of suicidality. Currently, a clinical diagnosis of HD is mainly based on motor symptoms.[39] However, suicidality already occurs in 20% of the pre-motor symptomatic HD mutation carriers (Chapter 2) and up to 30% of the pre-motor symptomatic mutation carriers reported other neuropsychiatric symptoms.[23;40] Many patients and their caregivers consider these symptoms to be the most distressing aspect of the disease.[41] In case of such early neuropsychiatric symptoms, regular assessments and adequate symptomatic treatment are essential before motor symptoms become manifest. This questions whether the current criteria for a clinical HD diagnosis (that mainly rely on motor symptoms[39]) are adequate, or whether alternative criteria should be formulated which also take into account neuropsychiatric and cognitive symptoms.[40;42]

The associations between the immune system and HPA axis functioning on the one hand and suicidality on the other, as found in several studies on non-HD clinical populations,[43-50] were not replicated in our Dutch HD cohort (Chapter 4 and 5). First of all, this could be explained by the fact that studies that previously reported on these associations in other populations often assessed other biological parameters or used different suicidality outcomes and assessment methods. For example, in non-HD populations, lower levels of interleukin 2 and 4 were more consistently associated with suicidality than elevated CRP levels.[43] Furthermore, the association between HPA axis functioning and completed suicide was more consistently reported in non-HD populations than its association with suicidality,[46;48;51] whereas we assessed the association with suicidality using a single item of the Problem Behaviours Assessment.[52] Apart from these methodological considerations and other explanations discussed in the related chapters, it is possible that in HD, compared with non-HD populations, different mechanisms result in altered biological parameters or that these dysregulated systems have a different effect on clinical outcomes. Also within HD, there might be different mechanisms

for and influences of disturbed biological parameters in different disease stages. In chapter 5 and in another HD study[53] an association was shown between higher salivary morning cortisol concentrations and depressive symptoms in early disease stage mutation carriers, but not in the overall cohort. Causal relations between biological parameters and suicidality cannot be disentangled in observational studies due to the lack of consistency.[54] Also from non-HD studies it is questionable whether the associations found between these biological characteristics and suicidality are causal. The use of biological markers for treatment, or for risk assessment purposes, is not recommended in clinical guidelines.[21;22]

Medication use and suicidality

In this thesis, several associations were found between medication use: specifically, antidepressants and benzodiazepines, and suicidality (Chapter 2 and 3). However, because we investigated associations, no conclusions can be drawn regarding causality. In non-HD studies, the debate continues about the efficacy and risk of antidepressant use and, to a lesser extent, about the risk of benzodiazepine use for attempted and completed suicide.[55;56] Some studies and meta-analyses reported that attempted and completed suicide in adults can occur as a side-effect of benzodiazepine or antidepressant use;[56-59] however, such conclusions are hampered by methodological limitations of these studies[60-62] and results from other studies.[62-64] However, in several meta-analyses the efficacy of antidepressants in reducing repeated self-harm or completed suicide could not be demonstrated.[63-65]

Whether antidepressants or benzodiazepines cause suicidality cannot be inferred from the few ecological and observational studies to date, e.g. due to simultaneous changes in other risk factors and confounding by indication.[61;66;67] Also, causal inference is hindered by methodological limitations of the experimental clinical studies which assessed the efficacy and risks of antidepressants on suicide attempts and completed suicide.[60;62;64;66] Lack of power due to the infrequent occurrence of these events is one of the limitations, which could not even be solved by conducting a meta-analysis, because 1.9 million participants would be needed in a trial to detect a 20% decrease in completed suicide risk.[63] Given the low number of events in these studies, the overall outcome could be completely changed by an error in reporting or not reporting a few cases.[60] Additionally, randomised controlled trials on the efficacy of antidepressants have a short follow-up (< 10 weeks) while in clinical practice the treatment may take 3-4 months to exert maximal benefit;[66] also, there is a larger drop-out in the placebo group which might result in underreporting of suicidal events in this group,[61] and information on adverse events is likely to be selectively reported[62] and/or is missing in a large number of participants.[58]

Thus, there is insufficient evidence to allow any causal conclusions to be drawn about associations between certain medication use and suicidality, mainly due to the methodological limitations of the studies. Nevertheless, the results of this thesis show that it is important for HD healthcare professionals to regularly assess suicidality in HD mutation carriers who use antidepressants and benzodiazepines, as they are a vulnerable group most likely to currently experience suicidality or develop suicidality in the future.

Prediction versus aetiology

In chapters 2-5 of this thesis sociodemographic, clinical and biological characteristics associated with suicidality in HD were investigated. Two of these studies (Chapter 2 and 3) aimed to discover and evaluate characteristics that might be useful in identifying HD mutation carriers at highest risk of suicidality, while two other studies (Chapter 4 and 5) aimed to explain the occurrence of suicidality in HD.

The first steps in prediction research involve investigating the prognostic factors[68] for suicidality in HD and determining which sociodemographic and clinical characteristics independently contribute to the estimation of the probability of suicidality, and to quantify to what extent.[69;70] Ideally, future studies can use such characteristics identified in previous research as building blocks for a prediction model. Chapter 7 shows that this is rarely done in studies that aim to predict suicide in non-HD populations. Most prediction studies in both HD and non-HD populations only determine which characteristics independently contribute to the suicidality or suicide risk, without taking it a step further by developing a prediction model and validating this in a different sample.[71] If a prediction model is developed, it is essential that absolute risks of suicidality or suicide can be calculated. This is not always possible due to a missing intercept value, from which the probability of the outcome in an individual patient can be derived when the other variables in the model are set to zero.[72] The development and validation of a prediction model was not pursued in this thesis. The limited number of suicidality cases in our studies together with the lack of previously identified predictors would likely have resulted in overly optimistic models. This optimism would probably be too large to be corrected for by shrinkage techniques, which reduce the regression coefficients to less extreme values. In such a case, the obtained prediction model cannot be generalised to other samples as the predicted probabilities will be too extreme in new samples, i.e. too high for the participants with the outcome and too low for those without the outcome.[69;70;73]

The value of a prediction model in estimating the absolute risk of future suicidal events for an individual patient is debatable.[74-76] It is currently not possible to accurately predict the risk of suicide in an individual, even though there are characteristics associated with suicidality and

suicide at group level.[22;77;78] The low base rate of suicide results in low positive predictive values and in the majority of the suicides occurring in the group that is classified as low-risk according to the prediction model.[6;75;77;79;80] It is important to note that these studies are carried out in a clinical environment where interventions will be applied if a patient is considered to be at high risk of suicide, which might have resulted in an underestimation of the positive predictive value.[6;22]

Although checklists based on associations of suicidality and suicide cannot predict the long-term suicide risk in an individual, suicide risk assessment in clinical practice remains important.[74;80;81] There are several important differences between prediction models for suicidality or suicide and clinical suicide assessment in clinical practice. First of all, the issue of imminent suicide risk in the patient's current context is addressed in clinical practice,[82] while chapter 7 shows that studies which assessed the suicide risk had a follow-up of up to 22 years, with only 22% of these studies assessing this risk within the first year of follow-up. Most importantly, suicide risk assessment in clinical practice should not merely be based on a 'tick box' approach[74] that classifies patients as either high or low risk on the basis of a list of risk factors.[22] Suicidality assessment in clinical practice should include a detailed analysis of current and previous suicidality using a systematic approach and investigation of relevant vulnerability and stress factors.[22] In order to decide on the appropriate intervention, the healthcare professional has to clinically weigh all information obtained from the patient and relatives, which is most valid and reliable when the healthcare professional establishes a therapeutic alliance by actively listening and showing empathy and trust.[22;83] This not only improves risk assessment, but talking about suicidality in a safe environment can help patients in coping with suicidality, as shown in chapter 6.

In contrast to prediction research, etiological research focuses on modifiable targets for treatment interventions. In chapters 4 and 5 of this thesis, biological associations of suicidality in HD were studied with the aim to explain the occurrence of suicidality in HD. If causes of suicidality are identified they can become targets for interventions. However, causality cannot be inferred from these cross-sectional studies, even though we corrected for confounders, e.g. due to lack of consistency[54] and exchangeability.[84] In chapter 4 an association was found between the use of antipsychotics and an elevated acute-phase response in HD, which remained significant after correction for confounders. However, confounding by indication is difficult to control for given the complexity of the indication. Mutation carriers using antipsychotics, which are prescribed for motor symptoms,[85] were in a more severe disease stage, implying that they also have most immune activation[86] and the most neuropsychiatric[87] and cognitive symptoms. An additional problem for causal inference was the fact that there were hardly any

mutation carriers in the pre-motor or early disease stages who used antipsychotics.[84]

The causes of suicidality in HD remain elusive. With the use of observational aetiological research we will probably never be able to fully identify all causes of suicidality in HD. However, it is important that future studies focus on treatment strategies, so that effective strategies can be identified and provided to suicidal HD mutation carriers and HD mutation carriers at high risk of developing suicidality.

Recommendations for future research

Evidence-based treatment guidelines for suicidality in HD might be established faster if qualitative studies (like the study described in chapter 6) are considered as a starting point for future quantitative research, rather than first establishing possible causal determinants in observational research which are later examined and treated in experimental studies. The combination of the proposed strategies (talking about suicidality, self-management strategies, medication use, and discussing end-of-life wishes) are likely targets for (some of) the multifactorial causes of suicidality in HD and should be investigated in future HD specific pragmatic trials. Additional support strategies for suicidal HD mutation carriers may also result from qualitative studies in other countries, where euthanasia is not possible.

In addition, future observational studies should focus on associations of completed suicide in HD, which might differ from associations of suicidality. Large observational cohort studies with regular assessments of clinical, motor, psychiatric, and cognitive signs and symptoms, like REGISTRY,[88] COHORT,[89] and especially ENROLL[90] make such studies possible if causes of death are adequately registered. Such registries also allow to investigate which suicidal mutation carriers are most likely to act on their thoughts in the future.

Future studies that investigate suicidality in HD should also focus on characteristics that have not yet been investigated, such as impulsivity. We recommend to include different suicidality outcome measures, as non-HD studies have shown that different suicidality assessments can result in varying prevalence numbers even if administered to the same participants at the same time.[91] So far, studies in HD assessed suicidality using one single item of the Unified Huntington's Disease Rating Scale (Chapter 3)[92] or Problem Behaviour Assessment (Chapter 2 and 4-6).[52] However, for more elaborate documentation and in clinic trials the use of the Columbia-Suicide Severity Rating Scale (C-SSRS)[93] is recommended by the National Institute of Neurological Disorders and Stroke (NINDS).[94] However, the C-SSRS has not yet been validated

in HD and to date has not been used to assess the frequency or associations of suicidality in HD.

Clinical recommendations

Although there is no turnkey solution for suicidality in HD, healthcare professionals can play an important role in the diagnostic process and treatment of suicidal HD mutation carriers. First of all, clinicians working with HD mutation carriers should be aware of the increased risk of suicidal ideation, suicide attempts, and completed suicide. Assessment of suicidality is already important in pre-motor symptomatic mutation carriers and should be introduced by asking about a depressed mood, which is the most important association and predictor of suicidality in HD. If a mutation carrier experiences suicidality they must be referred to a (preferably) HD-related psychologist or psychiatrist for regular sessions to talk about suicidality. Listening to and taking the thoughts seriously are the most important factors to facilitate talking about suicidality. Apart from talking about suicidality, advice can be given on self-management activities, with the aim to maintain the balance between actively facing HD/suicidality and taking one's mind off them. Medication, especially antidepressant use, may be effective in reducing suicidal thoughts, but should be combined with talking about suicidality; this was deeply appreciated by the participating suicidal HD patients. If a mutation carrier has a wish for euthanasia and this is legal in their country, the healthcare professional should provide adequate information about the legal requirements, regularly discuss the end-of-life wishes, and show a commitment of best intentions.[95;96] Spouses should be involved in the supportive treatment, given the high burden of suicidality on spouses of HD mutation carriers and the support spouses can provide. Many spouses need guidance on talking about suicidality with their partner. Furthermore, suggestions for support strategies for the caregiver may help to alleviate the caregiver's burden.

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Addendum

Nederlandse samenvatting
Curriculum vitae
List of publications
Acknowledgements/dankwoord

Nederlandse samenvatting

In dit proefschrift worden de resultaten beschreven van een onderzoek naar de epidemiologie van suïcidaliteit (suïcidale gedachten en suïcidepogingen) bij de ziekte van Huntington (ZvH) en naar copingstijlen en ondersteuningsstrategieën die suïcidale ZvH patiënten kunnen helpen. In een Nederlands en in een Europees cohort van ZvH gendragers werden, naast de prevalentie en incidentie van suïcidaliteit, de sociodemografische, klinische en biologische kenmerken die cross-sectioneel en longitudinaal geassocieerd zijn met suïcidaliteit onderzocht. In een kwalitatief onderzoek werd daarna geëxploreerd hoe ZvH gendragers zelf omgaan met suïcidaliteit en wat hun ideeën en wensen zijn ten aanzien van hoe naasten en gezondheidszorgprofessionals hen kunnen helpen bij het omgaan met suïcidaliteit. Ook werden de partners van deze ZvH gendragers geïnterviewd om te onderzoeken hoe zij hun partners ondersteunen bij het omgaan met suïcidaliteit. Tot slot werd in verschillende populaties onderzocht of het uiten van suïcidale gedachten voorspellend is voor een latere suïcide.

In de introductie (Hoofdstuk 1) wordt belicht dat de prevalentie van suïcidale gedachten, suïcidepogingen en suïcides bij zowel pre-motor als motor symptomatische ZvH gendragers hoger is dan in de algemene bevolking. Hoewel in een aantal eerdere onderzoeken de kenmerken die samenhangen met de aanwezigheid van suïcidaliteit en met suïcides bij ZvH gendragers werden nagegaan, bleek er een gebrek aan longitudinale studies waarin onderzocht wordt welke ZvH mutatiedragers de grootste kans hebben om suïcidaal te worden.

De in hoofdstuk 2 en 3 beschreven resultaten bevestigen dat suïcidaliteit frequent bij de ziekte van Huntington voorkomt. Tot 20% van zowel de pre-motor als motor symptomatische ZvH gendragers rapporteerde suïcidale gedachten in de maand voorafgaande aan het interview, vergeleken met 0% van de controle onderzoeksdeelnemers. ZvH gendragers die ten tijde van het interview suïcidale gedachten of suïcidaliteit ervoeren, hadden een kortere ziekteduur, waren vaker angstig en agressief, hadden vaker een eerdere suïcidepoging gedaan, gebruikten vaker antidepressiva en hadden vaker een depressieve stemming. De aanwezigheid van een depressieve stemming en het gebruik van benzodiazepines waren de enige onafhankelijke voorspellers van incidente suïcidale gedachten of suïcidaliteit.

Naast sociodemografische en klinische associaties hebben we ook associaties tussen biologische parameters en suïcidaliteit bij de ZvH onderzocht, in het bijzonder het functioneren van het immuunsysteem (Hoofdstuk 4) en de hypothalamus-hypofyse-bijnier (HHB) as (Hoofdstuk 5). Er werden geen cross-sectionele associaties gevonden tussen parameters van

de acute-fase-reactie (i.e. C-reactief proteïne en albumine) en suïcidaliteit in een Nederlands cohort van ZvH gendragers. We vonden wel associaties tussen parameters van de acute-fase-reactie en verschillende andere klinische karakteristieken, zoals ziektestadium, maar deze associaties verdwenen na correctie voor het gebruik van antipsychotica (Hoofdstuk 4). Daarnaast bleek in ditzelfde cohort dat parameters van HHB as activiteit niet geassocieerd waren met de ernst van depressieve symptomen of suïcidaliteit. Subgroep analyses lieten echter zien dat de onderzochte associaties varieerden tussen pre-motor, en vroeg- en laat-ziektestadium gendragers, waarbij depressieve gendragers uit het pre-motor en vroeg-motor symptomatische ziektestadium hogere ochtend cortisol niveaus hadden vergeleken met niet-depressieve gendragers uit deze ziektestadia (Hoofdstuk 5).

Aangezien de prevalentie van suïcidaliteit bij de ZvH verhoogd is vergeleken met controle onderzoeksdeelnemers (Hoofdstuk 2) en er momenteel geen behandelrichtlijnen zijn voor suïcidaliteit bij de ZvH, hebben wij een kwalitatief onderzoek uitgevoerd (Hoofdstuk 6). In dit onderzoek werden ZvH gendragers die eerder suïcidale gedachten hadden gehad of een suïcidepoging hadden gedaan en hun partners geïnterviewd. ZvH gendragers gebruikten doorgaans vier strategieën om met suïcidaliteit om te gaan, namelijk: praten over suïcidaliteit, zelfmanagement activiteiten, gebruik van medicatie en het bespreken van levenseindewensen. Partners, naasten en gezondheidszorgprofessionals kunnen suïcidale ZvH gendragers ondersteunen bij elk van deze vier strategieën.

De aanwezigheid van suïcidale gedachten, soms gecombineerd met suïcidepogingen, was de uitkomst variabele van al onze studies. Daarom hebben we een systematische review en meta-analyse uitgevoerd (Hoofdstuk 7), waarin werd onderzocht of het uiten van suïcidale gedachten voorspellend is voor een latere suïcide in verschillende klinische en niet-klinische populaties. Het risico op een suïcide was 3 tot 8 keer hoger (afhankelijk van de populatie die werd onderzocht) bij individuen die suïcidale gedachten hadden geuit, vergeleken met individuen die dat niet hadden gedaan. In psychiatrische populaties was het absolute suïciderisico na het uiten van suïcidale gedachten het hoogst maar het relatieve risico was hier het laagst, terwijl (vice versa) in niet-psychiatrische populaties het relatieve risico het hoogst was maar het absolute risico het laagst. Geen van de in de meta-analyse geïncludeerde studies onderzocht echter de relatie tussen suïcidale gedachten en een latere suïcide bij de ZvH.

Curriculum Vitae

Marloes Hubers was born on March 13th, 1990 in Zoetermeer, the Netherlands. After completing her pre-university education and international baccalaureate at the 'Alfrink College' in Zoetermeer in 2008, she started her medical studies at the University of Leiden, the Netherlands.

In her second year of medical school, she became involved in the research project 'Psychopathology and behavioural problems in Huntington's disease' at the department of Psychiatry of the LUMC as part of the LUMC's Excellent Student Program. In 2011, she obtained her Bachelor's degree in medicine (cum laude). In the meantime, she continued her research at the department of Psychiatry, specifically focusing on suicidality in Huntington's disease. This resulted in a grant for a PhD position from the board of directors of the LUMC in 2012. She interrupted her medical studies to work fulltime on her PhD project, under supervision of Prof. Dr. R.C. van der Mast (department of Psychiatry), Prof. Dr. R.A.C. Roos (department of Neurology), Dr. E.J. Giltay (department of Psychiatry) and Dr. E. van Duijn (department of Psychiatry).

Marloes combined her PhD with a training in epidemiology and will be registered as a clinical epidemiologist in the near future. During her PhD she was also an active member of the behavioural phenotype working group of the European Huntington's Disease Network. She presented her work at several national and international conferences and was an invited speaker at the 2013 World Congress on Huntington's Disease in Rio de Janeiro. Furthermore, in 2014, she was co-project leader of an awarded grant by ZonMW for a research proposal on reducing aggression among chronic psychiatric inpatients through nutritional supplements. At the end of her PhD, she visited the University of Oxford Centre for Suicide Research for 3.5 months to work on various suicide related systematic reviews under supervision of Prof. Dr. K. Hawton.

In August 2015, Marloes started her clinical rotations at the Leiden University Medical Center to obtain her MD degree.

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