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]

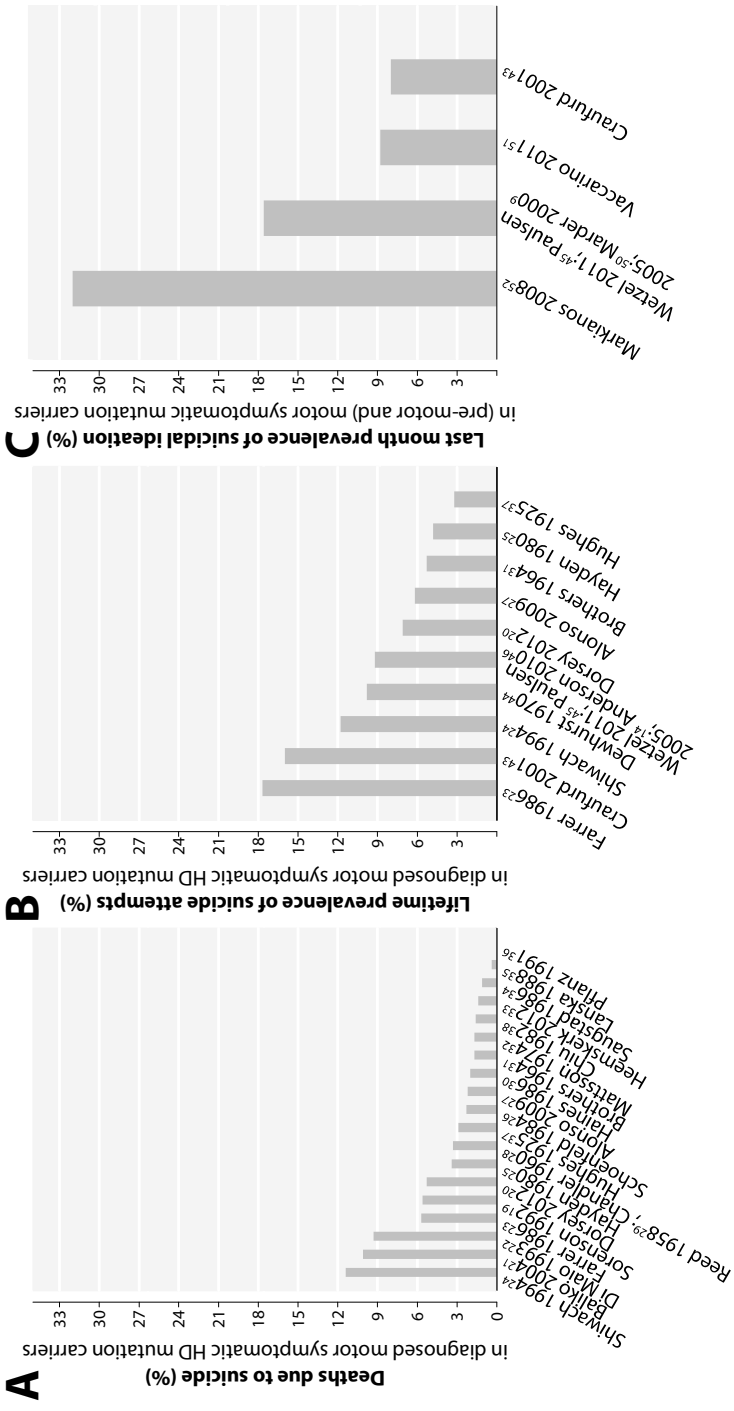

Figure 1. Bar chart showing prevalence of completed suicide (A), suicide attempts (B) and suicidal ideation (C) in HD.
When different studies reported on the same study sample, the mean of the reported prevalence numbers is presented in the bar chart.

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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