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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