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Prevalence and burden of pain in Huntington's disease

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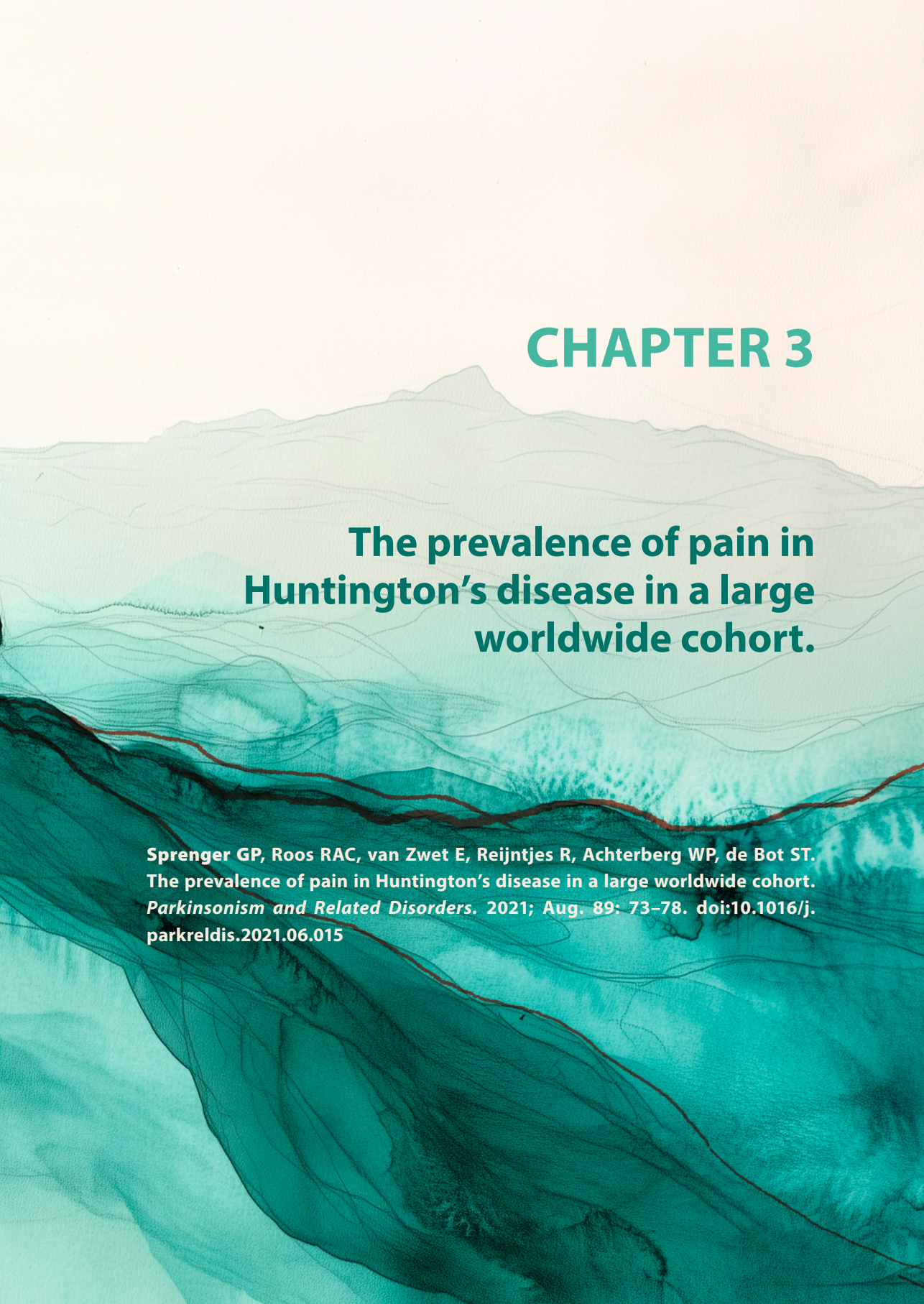
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CHAPTER 3

The prevalence of pain in Huntington's disease in a large worldwide cohort.

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The prevalence of pain in Huntington's disease in a large worldwide cohort.
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Abstract

Introduction: Pain could be an unknown non-motor symptom in Huntington's disease (HD). The aim is therefore, to study the prevalence of pain interference, painful conditions and analgesic use across the different stages of HD and compare these levels to non-HD gene mutation carriers.

Methods: A cross-sectional analysis of the Enroll-HD study was conducted in premanifest, manifest HD gene mutation carriers ($n = 3989$ and $n = 7485$, respectively) and in non-HD gene mutation carriers ($n = 3719$). To investigate group differences, multivariable logistic regression analysis was performed with pairwise comparisons.

Results: In the HD mutation carriers, the overall prevalence of pain interference was 34% (95% CI 31% - 35%), of painful conditions 17% (95% CI 15% - 19%) and analgesic use 13% (95% CI 11% - 15%). Compared to non-mutation carriers, the prevalence of pain interference was significantly higher in the middle stage of HD (33% [95% CI 31% - 35%] vs 42% [95% CI 39% - 45%], $P = 0,02$), whereas the prevalence of painful conditions was significant lower in the late and middle stage of HD (17% [95% CI 16% - 18%] vs 12% [95% CI 10% - 14%], 15% [95% CI 13% - 17%], $P < 0,01$). No significant group difference was present in analgesic use.

Conclusions: The prevalence of pain interference increases as HD progresses, however, the prevalence of painful conditions and analgesics do not increase accordingly. Further studies are necessary to investigate the aetiology of pain in HD and the risk for undertreatment of pain.

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, caused by an increased CAG repeat in the gene which encodes the protein, Huntingtin.¹ The resulting abnormally long polyglutamine repeat in the Huntingtin protein causes neuronal loss in the brain, particularly in the basal ganglia², which subsequently leads to a variety of motor and non-motor symptoms, such as neurocognitive and neurobehavioral disturbances.³

The basal ganglia are also involved in acute as well as chronic pain.⁴ In Parkinson's disease (PD), also a disease of the basal ganglia, pain is one of the four most prevalent complaints.⁵ Moreover, pain in PD is significantly associated with a diminished Health-Related Quality of Life ((HR)-QoL).⁶ The prevalence of pain in PD can be as high as 80%, which is significantly higher than in the general population.⁷ The compromised function of the basal ganglia in HD makes an alteration in pain processing and perception more than likely. In HD, the available experimental studies demonstrated a significant prolongation of processing painful stimuli at spinal cord level in the manifest stage, compared to healthy controls and individuals in the premanifest stage.⁸⁻¹⁰ In addition, an abnormal subcortical and cortical activation of sensory information has been demonstrated in HD.¹¹

One study showed an increase in the prevalence of pain in HD from 32% in the premanifest stage to 50% in the late stage.¹² A recent meta-analysis estimated the overall mean prevalence of pain in HD to be around 41% (95% confidence interval: 36% - 46%).¹³ It also revealed that the pain burden, measured in terms of pain intensity and interference with daily activities using the pain items of the SF-36, is lower in HD compared with that in the general population.¹³ However, due to lack of studies, it is unclear whether the diminished pain burden applies to all stages of HD. Furthermore, the proportion of patients with HD reporting pain interference with daily activities is not yet known.

Another way to investigate the pain burden is to study the prevalence of painful conditions and the use of analgesics. No studies are available which investigated the prevalence of painful conditions in HD. One pilot study is available on the use of analgesics, demonstrating a 49% use in the premanifest stage.¹⁴ Unfortunately, it is not clear whether the proportion of analgesic use changes as HD progresses, nor whether the usage is different from that in the general population.

CHAPTER 3

Considering the findings of pain in PD and the limited studies about pain in HD, which might highly interfere with key symptoms like depression, irritability, and anxiety, systematic studies focusing on pain in HD are warranted. The aim of this study is to study the prevalence of pain interferences with daily activities, painful conditions and analgesic use in different stages of HD and compare these to the levels in non-HD gene mutation carriers.

2. Methods

We applied the fourth periodic database of the Enroll-HD study (released March 2019) (Supplementary material: e-Methods). Enroll-HD is a global clinical research platform designed to facilitate clinical research in HD. Core datasets are collected annually from all research participants as part of this multi-center longitudinal observational study. Data are monitored for quality and accuracy using a risk-based approach. In the fourth release of Enroll-HD, standardized data of 15 301 participants are collected.

This study included all baseline assessments of individuals with genetically confirmed HD gene mutation and non-HD mutation carriers (family controls (spouses, partners, caregivers) and genotype-negatives). The baseline assessment gathered data on: age, gender, region, race, international standard classification of education [ICSED], marital status, CAG-repeat length, motor symptoms, stage of disease, comorbidities, medication use and indication, Short Form Health Survey-12-version 2 (SF-12v2)¹⁵, Mini-Mental State Examination (MMSE)¹⁶ and the Hospital Anxiety and Depression Scale (HADS).¹⁷

2.1 Outcomes

The degree of pain interference with daily activities was based on the bodily pain interference item of the SF-12v2.¹⁵ The version used in the Enroll-HD study was: 'During the *past week*, how much did pain *interfere* with your normal work, including both outside the home and housework?'. The possible answers were based on an ordinal five-point scale: 'Not at all', 'A little bit', 'Moderately', 'Quite a bit' and 'Extremely'. The presence of pain interference was defined as an individual score of "A little bit" or higher.

The comorbidities and medication use in the Enroll-HD database were classified according to the tenth edition of the International Classification of Diseases (ICD-10, version 2014) and the Anatomical Therapeutic Chemical (ATC) Classification System, respectively.^{18,19} Inclusion criteria were postulated to identify painful conditions and analgesic use (Supplementary material: eMethods).

The prevalence of pain interference, painful conditions and analgesic use were investigated for each stage of the disease. HD mutation carrier status was defined as subjects with 36 or more CAG repeats in the Huntingtin gene. A Total Motor Score (TMS) of five or lower and a Diagnostic Confidence Level (DCL) of three or lower on the Unified Huntington's Disease Rating Scale (UHDRS), was defined as the premanifest stage of HD.²⁰ According to the TRACK-HD studies, the premanifest stage was divided at baseline group median (10.8 years) for predicted years to onset into PreHDA (≥ 10.8 years from predicted onset) and PreHDB (< 10.8 years), by using the Langebehn formula.^{20,21} The manifest stage was divided into an early, middle and late stage, according to international standards, by using the Total Functional Capacity (TFC) score of the UHDRS.^{22,23} A TFC score between 7 and 13 indicated the early stage, between 4 and 6 the middle stage, and a score between 0 and 3 the late stage.²³ Depression or anxiety symptoms were present if a participant scored an eight or higher on the HADS.¹⁷ A score of 23 points or lower on the MMSE indicated the presence of cognitive disturbances.¹⁶

2.2 Statistical analysis

The analyses were conducted using IBM SPSS statistics versions 26 and for more details regarding the analyses see supplementary material (e-Methods).²⁴ All outcomes (pain interference, painful conditions and analgesic use) were dichotomized in order to calculate the prevalence. Multivariable logistic regression analyses were performed, with a pairwise comparison (Bonferroni correction), to investigate differences in the prevalence of the pain outcomes between premanifest, manifest HD gene mutation carriers and in non-HD gene mutation carriers. These analyses were adjusted for age. Multiple imputations were carried out in order to assess the impact of the missing data on socio-demographic, clinical factors and the outcomes (Supplementary material: eMethods and eImputed data sets).

3. Results

3.1 Overall

The total sample size at baseline included 15 301 participants, 108 (0.7%) of whom were not categorized into subgroups due to missing data, like for example: diagnostic confidence score. The sample ($n = 15\ 193$) consisted of non-HD mutation carriers ($n = 3719$; 24%), PreHDA ($n = 2556$; 17%), PreHDB ($n = 1433$; 9%), early ($n = 4867$; 32%), middle ($n = 1360$; 9%) and late stage patients with HD ($n = 1258$; 8%) (Table 1).

CHAPTER 3

3.2 Socio-demographic characteristics

At baseline, the proportion of females in the non-mutation carriers, premanifest and manifest mutation carriers was 61% ($n = 2260$), 58% ($n = 2331$) and 54% ($n = 3852$), respectively. The mean age was 47.2 (SD 14.7), 42.2 (SD 12.0) and 54.4 (SD 12.5). The mean age was lowest in the PreHDA (37.2 (SD 11.0)) and highest in the late stage (56.8 (SD 12.3)). Of the total sample, 61% of participants were from Europe, 35.0% from Northern America, 3.5% from Australasia and around 0.7% from Latin America (Table 1).

Table 1. Characteristics of groups of participants from Enroll HD included in the present study.

Socio-demographic factors				Clinical Variables						
Groups	N	Age Mean (SD)	Gender N° (%)	Region N° (%)	CAG-repeat Mean (SD)	UHDRS-TMS Mean (SD)	UHDRS-TFC Mean (SD)	MMSE Mean (SD)	HADS-depression Mean (SD)	HADS-anxiety Mean (SD)
NMC	3719	47.2 (14.7) Miss.: 4 (0.1%)	F: 2260 (60.8) M: 1459 (39.2)	E: 1718 (46.2) LA: 32 (0.9) NA: 1863 (50.1) AU: 106 (2.9)	20.2 (3.6)	1.7 (3.5) Miss.: 14 (0.4%)	12.9 (0.7) Miss.: 3 (0.1%)	28.9 (1.5)	3.5 (3.3) Miss.: 894 (24.0%)	5.2 (3.8) Miss.: 895 (24.1%)
PreHDA	2556	37.2 (11.0)	F: 1533 (60.0) M: 1023 (40.0)	E: 1505 (59.0) LA: 7 (0.3) NA: 910 (35.5) AU: 134 (5.2)	41.8 (2.4)	2.4 (3.9) Miss.: 11 (0.4%)	12.7 (1.1) Miss.: 4 (0.2%)	28.8 (1.7)	3.6 (3.6) Miss.: 750 (29.3%)	5.8 (4.2) Miss.: 748 (29.3%)
PreHDB	1433	47.1 (12.3)	F: 798 (55.7) M: 635 (44.3)	E: 779 (54.4) NA: 564 (39.4) AU: 90(6.3)	43.8 (3.1)	7.4 (8.5) Miss.: 6 (0.4%)	12.1 (1.8) Miss.: 5 (0.4%)	28.0 (2.4)	4.3 (3.7) Miss.: 482 (33.9%)	5.6 (4.0) Miss.: 481 (33.6%)
Early	4867	52.0 (12.2) Miss.: 3 (0.1%)	F: 2393 (49.2) M: 2474 (50.8)	E: 3206 (65.9) LA: 41 (0.8) NA: 1484 (30.5) AU: 136 (2.8)	43.8 (3.6)	30.4 (14.0)	10.2 (2.0)	26.1 (3.0)	5.7 (4.0)	6.0 (4.2)
Middle	1360	54.4 (12.9) Miss.: 1 (0.1%)	F: 728 (53.6) M: 632 (46.4)	E: 928 (68.2) LA: 15 (1.1) NA: 376 (27.6) AU: 41 (3.0)	44.5 (4.4)	48.2 (16.2)	5.1 (0.8)	22.9 (4.3)	7.3 (4.4)	6.2 (4.3)

Table 1. Characteristics of groups of participants from Enroll HD included in the present study. (continued)

Socio-demographic factors				Clinical Variables						
Groups	N	Age Mean (SD)	Gender N° (%)	Region N° (%)	CAG-repeat Mean (SD)	UHDS-TMS Mean (SD)	UHDS-TFC Mean (SD)	MMSE Mean (SD)	HADS-depression Mean (SD)	HADS-anxiety Mean (SD)
Late	1258	56.8 (12.3)	F: 731 (58.1)	E: 1057 (84.0)	44.8 (4.2)	70.5 (18.9)	1.7 (1.1)	18.1 (6.4)	8.0 (4.8)	5.8 (4.4)
			M: 527 (41.9)	LA: 11 (0.9)						
				NA: 168 (13.4)				Miss.: 687 (54.6%)	Miss.: 850 (67.6%)	Miss.: 853 (67.8%)
				AU: 22 (1.7)						

After multiple imputation of missing data, no significant differences were found compared with the original data set. Abbreviations: AU, Australasia; CAG- repeat, Cytosine-Adenine-Guanine repeat; E, European; F, female; HADS, Hospital Anxiety and Depression Scale; LA, Latin-American; M, male; Miss, missing data; MMSE, Mini-Mental State Examination – total score; UHDS- TMS or TFC, Unified Huntington’s Disease Rating Scale – Total Motor Score or Total Functional Capacity.

3.3 Pain interference with daily activities

From the 15 301 participants, 10 912 participants completed the pain interference item of the SF-12v2. The non-mutation carriers included 2998 (27%) participants, the PreHDA 2037 (19%), PreHDB 1099 (10%), early 3464 (32%), middle 810 (7%) and late stage HD 504 (5%). Data of the SF12v2 pain interference scale were absent in 4281 (28%) participants.

The overall mean prevalence of pain interference in HD mutation carriers (n = 7914) was 34% (95% confidence interval (CI) 31% - 35%), with significant differences between the groups (χ^2 (5) = 130.34, $p < 0.01$) (PreHDA 26%; PreHDB 29%; early 38%; middle 42%; late 38%; non-mutation carriers 33%) (Figure 1). When adjusting for age, only a significant higher prevalence of pain interference was demonstrated in the middle stage of HD, compared to non-mutation carriers (42% (95% CI 39% - 45%) vs 33% (95% CI 31% - 35%), $P = 0.02$). For additional significant between group differences see supplementary material (Supplementary material: eFigure 1). The prevalence of pain interference varied between the different demographic regions, with the greatest differences within the early and middle stage HD, with the highest pain interference reported in Latin America in both stages (Supplementary material: eTable 1).

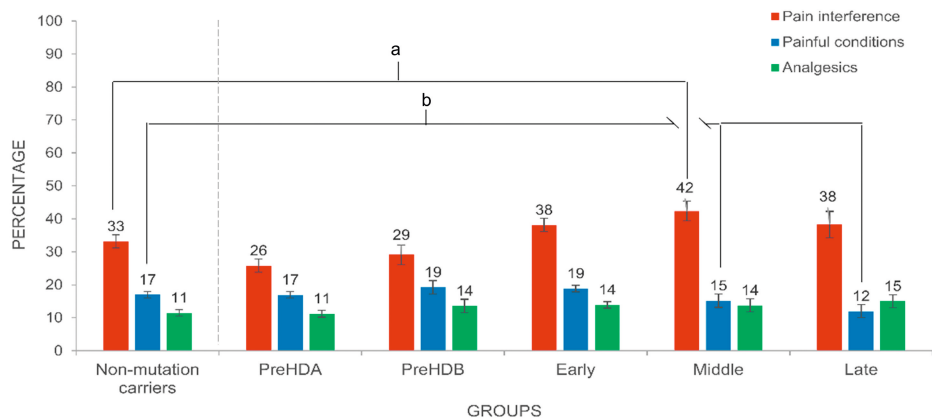


Figure 1. The prevalence of pain interference¹, painful conditions and analgesic use across the different groups.

¹The cut-off for pain interference was set at a score of 'A little bit' or higher on the pain interference item of the SF12v2. Rounded to whole numbers. Error Bar (I), Total Sample Size (N); Pain interference: Non-mutation carriers (N = 2998), PreHDA (N = 2037), PreHDB (N = 1099), Early (N = 3464), Middle (N = 810), Late (N = 504); Painful conditions and analgesics: Non-mutation carriers (N = 3719), PreHDA (N = 2556), PreHDB (N = 1433), Early (N = 4867), Middle (N = 1,360), Late (1258).

a. Middle vs Non-mutation carriers ($P = 0.02$); b Middle vs Non-mutation carriers ($P < 0.01$) AND Late vs Non-mutation carriers ($P < 0.01$).

3.4 Painful conditions

Overall, 17% (95% CI 15% - 19%) of the HD gene mutation carriers (n = 11 474) reported a painful condition. A significant group difference was present (χ^2 (5) = 35.46, $p < 0.01$) (PreHDA 17%; PreHDB 19%; early 19 %; middle 15%; late 12%; non-mutation carriers 17%) (Figure 1). When adjusting for age, only a significantly lower prevalence of painful conditions was found in the middle or late stage of HD, compared to non-mutation carriers (15% (95% CI 13% - 17%), 12% (95% CI 10%-14%) vs 17% (95% CI 16-18%), $P < 0.01$). For additional significant group differences, see supplementary material (eFigure 2). The prevalence of painful conditions varies slightly between the different demographic regions (Supplementary material: eTable 2).

In the group reporting a painful condition, the proportion of the thirteen clusters of painful conditions, varies across the different stages (Supplementary material: eTable 3). Those reported most often were headache, limb, back, abdominal pain and pain due to fractures (Figure 2). As HD progressed, reporting of abdominal pain and pain caused by fractures increased, while the number of reports of headache decreased. The majority of the patients with pain reported only one pain condition (around 78%). The proportion with two, three or more painful conditions varies between the groups (Supplementary material: eTable 4). The proportion of painful conditions commonly associated with chronic pain decreased as HD progressed, while the proportion of acute painful conditions increased (Supplementary material: eTable 5).

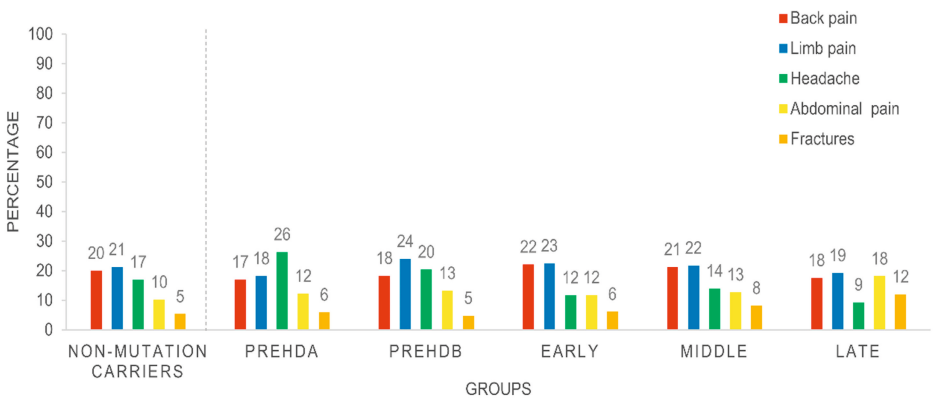


Figure 2. The proportion of the five most-reported conditions causing pain across the different groups. No correction was carried out if patients reported two or more painful conditions. Rounded to whole numbers. For group size, see supplementary material: eTable 3.

3.5 Analgesic use

The overall prevalence of analgesic use in the HD gene mutation carriers ($n = 11\,474$) was 13% (95% CI 11% - 15%). A significant prevalence difference was found between the groups ($\chi^2(5) = 23,95, p < 0,01$) (PreHDA 11%; PreHDB 14%; early 14%; middle 14%; late 15%; non-mutation carriers 11%) (Figure 1). After controlling for age, no significant group differences were present. The prevalence of analgesic use was the highest in Europe in the middle and late stage of HD (Supplementary material: eTable 6).

In the group reporting the use of analgesics, the top three most often used across the different stages of HD were Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), paracetamol, anti-epileptics. As HD progressed, the use of paracetamol (PreHDA 17%; Late stage 41%) and strong opioids (PreHDA 8%; Late stage 14%) increased, while the use of NSAIDs decreased (PreHDA 40%; Late stage 25%) (Supplementary material: eTable 7). The majority of the patients reported the use of only one type of analgesic (around 71%) (Supplementary material: eTable 8).

3.6 Other possible (co)factors affecting pain interference

In general, participants with a painful condition reported more pain interference, compared to those without a pain condition (Figure 3). Also, the use of analgesics was greater in participants reporting a pain condition, compared to the group without a pain condition.

As HD progressed, the proportion of pain interference increased in both groups: with and without painful conditions. This is in contrast to the use of analgesics, which increased slightly in the group without a painful condition but remained the same in the group with a painful condition. The proportion of cognitive disturbances and depression increased equally in both groups as HD progressed. Finally, the proportion of participants reporting anxiety disturbances did not differ between the two groups, nor between the different HD stages.

CHAPTER 3

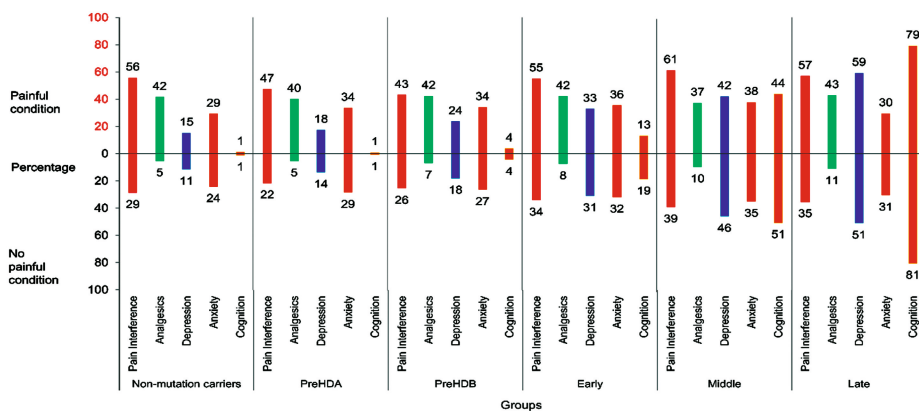


Figure 3. The proportion of pain interference¹, analgesic use and the presence of mood² and cognitive³ disturbances demonstrated in two different groups (with/ without a painful condition). ¹Pain interference was stated as a score of 'A little bit' or higher on the pain interference item of the SF12v2. ²HADS score of eight or higher indicated depressive or anxiety symptoms. ³Cognition: MMSE score of 23 points or lower was defined as presence of cognitive disturbance. Rounded to whole numbers. The frequencies are reported in the Supplementary material: eTable 9.

4. Discussion

Based on the large worldwide Enroll-HD database, we found that in HD gene mutation carriers, the overall prevalence of pain interference was 34% (and even 39% in the manifest stage of HD), of painful conditions 17% and of analgesic use 13%. Compared to non-HD mutation carriers, the prevalence of pain interference was significant higher in the middle stage of HD (33% (95% CI 31% - 35%) vs 42% (95% CI 39% - 45%), respectively), whereas the prevalence of painful conditions was significant lower in the late and middle stage of HD (17% (95% CI 16% - 18%) vs 12% (95% CI 10% - 14%), 15% (95% CI 13% - 17%), respectively) (Figure 1). There were no significant group differences in the prevalence of analgesic use.

The lack of coherence between the prevalence of pain interference, painful conditions and the use of analgesics is interesting. This could be due to several factors. First of all, HD on its own may induce pain, which could be an aspect of which physicians might be insufficiently aware, resulting in a low analgesic use and prescription. The present study demonstrates that, as HD progressed, the increase in pain interference could not be explained fully by the included painful conditions (Figures 1 and 3). This was also supported by a slight increase in analgesic use in the group without a painful condition as HD progressed (Figure 3). Even when a stricter cut-off score for pain interference

was used or the analysis was conducted only within the group with available pain interference data, the incoherence between the outcomes remained in the manifest stage of HD (Supplementary material: eFigure 3 and eFigure 4, respectively). Systematic studies are, however, necessary to explore this speculation. Secondly, the lack of coherence might be explained by dysfunction of the basal ganglia, causing on the one hand an increase in the severity of pain (interference) as HD progresses, but on the other, resulting in an inadequate pain behavior, possibly due to the disturbances in the sensory, affective and/ or cognitive dimensions of pain.⁴ Thirdly, the neurocognitive disturbances in HD might also contribute to the lack of coherence. In particular the diminished awareness of deficits (loss of insight) in HD makes it challenging and less reliable to collect data using self-reported pain scales. In the majority of the literature, a minimum score of 18 on the MMSE is recommended for using a self-assessment pain scale.²⁵ Fourthly, depression and anxiety are important factors associated with pain interference in the general population.²⁶ As demonstrated in this study, depression and anxiety are most prevalent in the manifest stages of HD. The association between mood, cognitive disturbances, HD and pain is, however, complex, as illustrated by a network (Supplementary material: eFigure 5). Finally, the incoherence in the prevalence could also be caused by the in- and exclusion criteria applied for painful condition and analgesics. In practice, there are more painful conditions, as well as pharmacological and non-pharmacological treatments, than those adopted in this study. For instance, specific -sometimes painful- dystonia was not included as a painful condition, while this symptom may be present in the manifest stage of HD and well-known in inducing pain.²⁷ This might have resulted in a lower prevalence of painful conditions as well analgesic use.

The present study revealed some interesting findings with regard to the prevalence of specific painful conditions and analgesic use. In the final stage of HD, abdominal pain and pain caused by fractures were more frequently reported, while the proportion of headache decreased as HD progressed. The increase in abdominal pain could be explained by the high prevalence of a variety of upper and lower gastrointestinal dysfunctions in patients with HD.²⁸ Furthermore, the increase in the report of pain caused by fractures, might be related to falls and lower bone density in patients with late stage HD.²⁹ The decrease in the proportion of headache (migraine) as HD progressed, corresponds with that in PD, where, after disease onset, it seems to be reported less frequently.³⁰ With regard to analgesics, the use of paracetamol and strong opioids seems to increase as HD progresses, while this study found a tendency for the use of NSAIDs to decrease. This is compliant with the recommendations about the use of NSAIDs in vulnerable and older patient groups and demonstrates the robustness of our data.

CHAPTER 3

A limitation of the present study, is that only patients who were motivated and capable of participating in the Enroll-HD study were included. In addition, 28% of the data of the SF12v2 pain interference scale was missing. Multiple imputation did not lead, however, to different conclusions compared to the complete case analysis. Nevertheless, there is a risk of selection bias. The use of only one ordinal scale for assessing the degree of pain interference is too limited to understand the effect of pain on performing different daily activities and also enhances the risk of scale attenuation effects (including ceiling and floor effects). The significant group differences found in this study, does not always imply clinical relevance, in particular for the group differences concerning the prevalence of painful conditions. Finally, the scope of this study did not allow inclusion of potential mediators and moderators, such as social demographic variables, neurocognitive and mood disturbances in the analysis.

The strengths of the present study are the use of a large, high quality, world-wide database of genetically confirmed (non-) HD gene mutation carriers, increasing the generalizability of the findings. The approach to investigating prevalence of painful conditions and analgesic use was objective and conservative.

The effect of HD on pain and its aetiology should be further investigated. A proposed framework for investigating the different causes of pain in PD may be helpful for future HD studies.³¹ Despite the similarities between the compromised function of the basal ganglia in HD and PD, the motor and non-motor symptoms differ significantly. The manifestation of pain in HD might be different and unique compared to PD. Future studies should also take into account the clinical observations of patients with HD with (severe) painful conditions, however, not complaining about it or vice versa. In addition, future studies could also use a more recent formula (PIN score) to differentiate between PreHDA and PreHDB. In our study, however, the use of the PIN score did not result in different findings.³² Finally, especially for the final stages of HD, validation of pain assessments, including observational pain instruments, is required.

Contributorship: 1) Research project: A. Conception and Design: Gregory P. Sprenger; Wilco P. Achterberg; Susanne T. de Bot; Raymund A.C. Roos; B. Organization: Gregory P. Sprenger; C. Execution: Gregory P. Sprenger 2) Acquisition and analysis of the data: A. Acquisition data from Dataset: Gregory P. Sprenger; Robert H. Reijntjes; B. Statistical Design: Erik van Zwet; B. Execution: Gregory P. Sprenger; C. Review analysis and Critique: Erik van Zwet; 3) Manuscript: A. Writing the first draft: Gregory P. Sprenger; B. Review and Critique: Raymund A.C. Roos; Erik van Zwet; Robert H. Reijntjes; Wilco P. Achterberg; Susanne T. de Bot.

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Chapter 3: Supplementary material

eMethods

eImputed data sets of clinical and socio-demographic factors

eFigure 1. The significant group differences in the prevalence of pain interference

eTable 1. Prevalence of pain interference demonstrated in each demographic region and groups.

eFigure 2. The significant group difference in the prevalence of painful conditions

eTable 2. Prevalence of painful conditions demonstrated in each demographic region and groups.

eTable 3. The proportions of the thirteen clusters of painful conditions across the different groups

eTable 4. The proportion of the total amount of reported painful condition across the different groups

eTable 5. The proportion of acute and chronic painful conditions across the different groups

eTable 6. The proportions of the use of analgesics across the groups and participating demographic regions

eTable 7. The proportion of analgesic use across the different groups.

eTable 8. The proportion of the total amount of analgesic use across the different groups.

eTable 9. The frequency of pain interference, analgesics, depression, anxiety of cognitive disturbances in two different groups (with/ without a painful condition)

eFigure 3. Prevalence of pain interference, conditions causing pain and analgesic use across the different stages.

eFigure 4. Prevalence of pain interference, conditions causing pain and analgesic use across the different stages within the population that has the SF12v2 (pain item) available.

eFigure 5. A modified network demonstrating the association between Huntington's Disease and pain (interference)

eReferences

eMethods

Enroll study:

Data used in this work were generously provided by the participants in the Enroll-HD study and made available by CHDI Foundation, Inc. Enroll-HD is a global clinical research platform designed to facilitate clinical research in Huntington's disease. Core datasets are collected annually from all research participants as part of this multi-center longitudinal observational study. Data are monitored for quality and accuracy using a risk-based monitoring approach. All sites are required to obtain and maintain local ethical approval.

Painful conditions:

To identify the painful conditions, a validated list of more than 9000 common pain conditions and their corresponding ICD-10 Clinical Modification (CM) codes was used and transformed to the original ICD-10 codes.^{1,2} As proposed by the United States National Pain Strategy (US-NPS), the painful conditions were clustered in conditions commonly associated with chronic pain like back pain; neck pain; limb/extremity pain (e.g. joint pain and non-systematic, non-inflammatory arthritic disorders); fibromyalgia; headache (e.g. migraine); orofacial, ear and temporomandibular disorder pain; abdominal and bowel pain; urogenital, pelvic and menstrual pain; chest pain; neuropathy; systematic disorders or diseases causing pain; other painful conditions (e.g. cancer-related pain); and conditions commonly associated with acute pain like fractures, sprains and strains.³

Analgesics and co-analgesics:

Analgesics and co-analgesics were represented by the ATC codes N01, N02, M01, M02, N05 (psycholeptics), N06A (antidepressants) and N03 (anti-epileptics).⁴ Both were only included if the indication for the drug corresponded to an ICD-10 pain condition or if words such as pain, -algia or analgesic therapy were used. Drugs used for pain, -algia or for analgesic therapy were also included as analgesic. (Co-) analgesics prescribed without an indication or indications such as fever, cardiovascular diseases, depression, anxiety or prophylaxis were excluded. Based on the generic name and the classification of the ATC, the (co-) analgesics were divided into groups (such as paracetamol, NSAIDs, opioids etcetera).

Statistical analysis:

Data of interest were extracted from the Enroll-HD study database using R software.⁵ All pain outcomes (pain interference, painful conditions and analgesic use) were dichotomized in order to calculate proportions. Unfortunately, there was considerable

CHAPTER 3

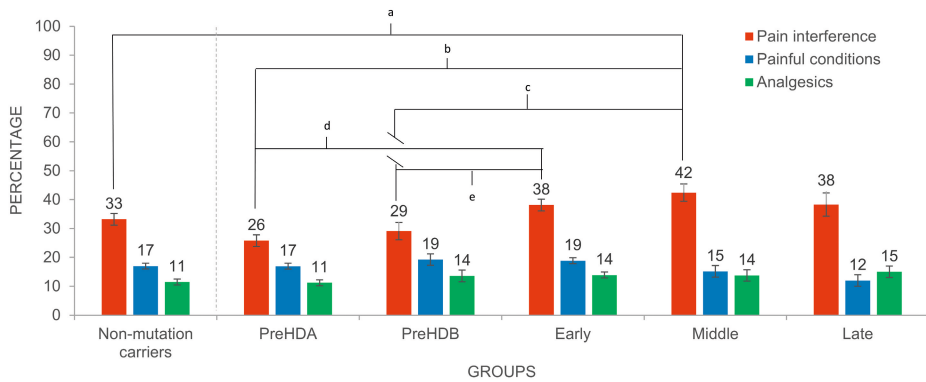
missing data among the included variables. According to criteria definition, the missing data complies to Missing at Random (MAR).^{6,7} To account for missing outcomes, as a sensitivity analysis, we performed a 5-fold multiple imputation. The variables included in the imputation model were age, gender, region, CAG-repeat, UHDRS- Total Motor Score and Total Function Category, group (non-HD mutation carriers, PreHDA, PreHDB, early, middle and late), depression, anxiety, cognition, SF12v2 (pain interference scale), painful conditions and analgesic use. The custom method for scale variables was set on Predictive Mean Matching. The results from this analysis were very similar to those obtained by the complete case analysis, and therefore we reported only the latter in this study (Supplementary material: elmputed datasets). More data, supporting the findings of this study, are available from the corresponding author on request.

elmputed data sets of clinical and socio-demographic factors

Please scan the following QR code or contact the author of this thesis.



Prevalence of pain in Huntington's disease



eFigure 1. The significant group differences in the prevalence of pain interference¹.

¹Pain interference was defined as a score of 'A Little Bit' or higher on the pain interference item of the SF12v2. Rounded to whole numbers. Total Sample Size (N). 95% confidence interval (I).

Pain interference: Non-mutation carriers (N = 2998); PreHDA (N = 2037); PreHDB (N = 1099); Early (N = 3464); Middle (N = 810); Late (N = 504)

a. Non-mutation carriers vs Middle ($P = 0.018$); b. PreHDA vs Middle ($P < 0.01$); c. PreHDB vs Middle ($P < 0.01$);

d. PreHDA vs Early ($P < 0.01$); e. PreHDB vs Early ($P < 0.01$)

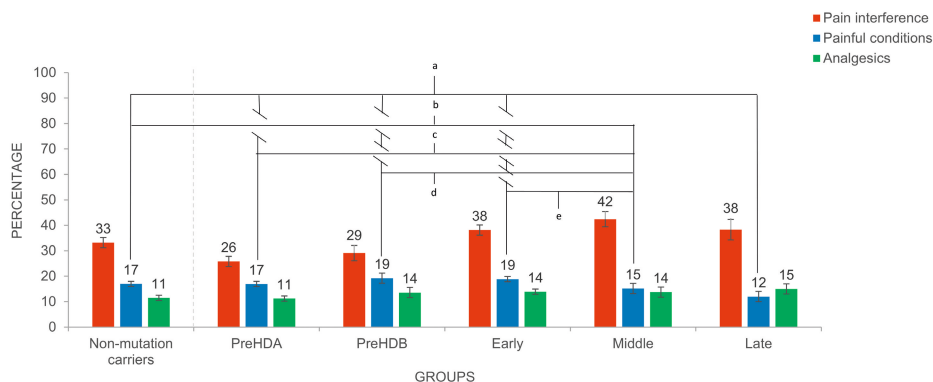
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eTable 1. Prevalence of pain interference¹ demonstrated in each demographic region and groups.

Groups						
	Non-mutation carriers (N = 2,998)	PreHDA (N = 2,037)	PreHDB (N = 1,099)	Early (N = 3,464)	Middle (N = 810)	Late (N = 504)
Region						
Yes N ^o (%)						
Australasia	32 (32)	24 (19)	15 (19)	21 (21)	11 (38)	6 (46)
Europe	447 (33)	308 (26)	185 (32)	894 (39)	239 (44)	148 (38)
Latin America	4 (40)	1 (25)	N.A.	17 (57)	10 (71)	3 (33)
Northern America	512 (34)	191 (27)	119 (27)	389 (37)	84 (38)	36 (41)
Total	995 (33)	524 (26)	319 (29)	1,321 (38)	344 (42)	193 (38)

¹Pain interference was defined as a score of 'A Little Bit' or higher on the pain interference item of the SF12v2. Not available (N.A.). Number of reports (N^o).

CHAPTER 3



eFigure 2. The significant group difference in the prevalence of painful conditions Rounded to whole numbers. Total Sample Size (N). 95% confidence interval (I) Painful conditions and analgesics: Non-mutation carriers (N = 3719); PreHDA (N= 2556); PreHDB (N= 1433); Early (N= 4867); Middle (N= 1360); Late (1258)
a. Non-mutation carriers vs Late ($P < 0.01$) AND PreHDA vs Late ($P < 0.01$) AND PreHDB vs Late ($P < 0.01$) AND Early vs Late ($P < 0.01$); b. Non-mutation carriers vs Middle ($P < 0.01$); c. PreHDA vs Middle ($P < 0.01$); d. PreHDB vs Middle ($P < 0.01$); e. Early vs Middle ($P < 0.01$)

eTable 2. Prevalence of painful conditions demonstrated in each demographic region and groups.

	Groups					
	Non- mutation carriers (N = 3719)	PreHDA (N = 2556)	PreHDB (N = 1433)	Early (N = 4867)	Middle (N = 1360)	Late (N = 1258)
Region						
Yes N° (%)						
Australasia	25 (24)	23 (17)	17 (19)	30 (22)	8 (20)	6 (27)
Europe	276 (16)	214 (14)	131 (17)	522 (16)	124 (13)	113 (11)
Latin America	3 (9)	0 (0)	N.A. ^a	2 (5)	1 (7)	1 (9)
Northern America	336 (18)	188 (21)	123 (22)	349 (24)	68 (18)	36 (21)
Total	640 (17)	425 (17)	271 (19)	903 (19)	201 (15)	156 (12)

Not available (N.A.).^a No data available as well for 'Yes' or 'No' painful conditions. Rounded to whole numbers. Number of reports (N0)

eTable 3. The proportions of the thirteen clusters of painful conditions across the different groups.

	Groups					
	Non-mutation carriers (N° = 744)	PreHDA (N° = 489)	PreHDB (N° = 333)	Early (N° = 1071)	Middle (N° = 244)	Late (N° = 182)
Painful conditions						
N° (%)						
Back pain	149 (20)	83 (17)	61 (18)	237 (22)	52 (21)	32 (18)
Limb pain*	158 (21)	89 (18)	80 (24)	241 (23)	53 (22)	35 (19)
Headache	126 (17)	129 (26)	68 (20)	125 (12)	34 (14)	17 (9)
Abdominal pain	76 (10)	60 (12)	44 (13)	126 (12)	31 (13)	33 (18)
Fractures	40 (5)	29 (6)	16 (5)	66 (6)	20 (8)	22 (12)
Other painful conditions**	30 (4)	23 (5)	16 (5)	62 (6)	13 (5)	10 (5)
Neck pain	45 (6)	17 (3)	10 (3)	68 (6)	15 (6)	9 (5)
Fibromyalgia	35 (5)	20 (4)	16 (5)	36 (3)	10 (4)	2 (1)
Neuropathic pain	22 (3)	6 (1)	7 (2)	31 (3)	0 (0)	2 (1)
Urogenital pain	10 (1)	16 (3)	4 (1)	22 (2)	4 (2)	3 (2)
Systematic disorders	41 (6)	14 (3)	5 (2)	33 (3)	7 (3)	10 (5)
Orofacial pain	5 (1)	1 (0)	0 (0)	6 (1)	1 (0)	3 (2)
Chest pain	7 (1)	2 (0)	6 (2)	18 (2)	4 (2)	4 (2)

Number of reports (N°). No correction was carried out if patients reported two or more painful conditions. Rounded to whole numbers.

* limb/extremity pain (e.g. joint pain and non-systematic, non-inflammatory arthritic disorders)

**other painful conditions (e.g. cancer-related pain)

eTable 4. The proportions of the total amount of reported painful condition across the different groups.

	Groups					
	Non-mutation carriers (N = 640)	PreHDA (N = 425)	PreHDB (N = 271)	Early (N = 903)	Middle (N = 201)	Late (N = 156)
Amount of painful conditions						
N° (%)						
1	507 (80)	340 (80)	206 (76)	701 (78)	152 (76)	126 (81)
2	99 (15)	69 (16)	40 (15)	134 (15)	40 (20)	21 (13)
≥ 3	34 (5)	16 (4)	25 (9)	67 (7)	9 (4)	9 (6)
	100%	100%	100%	100%	100%	100%

Number of reports (N°). Rounded to whole numbers.

CHAPTER 3

eTable 5. The proportions of acute and chronic painful conditions across the different groups

	Groups					
	Non-mutation carriers (N° = 744)	PreHDA (N° = 489)	PreHDB (N° = 333)	Early (N° = 1071)	Middle (N° = 244)	Late (N° = 172)
Type pain						
N° (%)						
Chronic pain ^a	704 (95)	460 (94)	317 (95)	1005 (94)	224 (92)	160 (88)
Acute pain ^b	40 (5)	29 (6)	16 (5)	66 (6)	20 (8)	22 (12)
	100%	100%	100%	100%	100%	100%

No correction was carried out if patients reported two or more painful conditions. Number of reports (N°). Rounded to whole numbers.

^aConditions commonly associated with chronic pain are all the included painful condition, except fractures, sprains and strains.

^bConditions commonly associated with acute pain (e.g. fractures, sprains and strains).

eTable 6. The proportions of the use of analgesics across the groups and participating demographic regions.

	Groups					
	Non-mutation carriers (N = 3719)	PreHDA (N = 2556)	PreHDB (N = 1433)	Early (N = 4867)	Middle (N = 1360)	Late (N = 1258)
Region						
Yes N° (%)						
Australasia	10 (0)	12 (0)	8 (1)	22 (0)	6 (0)	4 (0)
Europe	151 (4)	127 (5)	86 (6)	332 (7)	123 (9)	146 (12)
Latin America	3 (0)	0 (0)	0 (0)	3 (0)	1 (0)	1 (0)
Northern America	263 (7)	148 (6)	100 (7)	321 (7)	57 (4)	38 (3)
Total	427 (11)	287 (11)	194 (14)	678 (14)	187 (14)	189 (15)

Rounded to whole numbers.

eTable 7. The proportions of analgesic use across the different groups.

	Groups					
	Non-mutation carriers N° (557)	PreHDA N° (395)	PreHDB N° (248)	Early N° (871)	Middle N° (248)	Late N° (237)
(Co-) Analgetica						
N° (%)						
NSAID	247 (44)	157 (40)	103 (42)	366 (42)	84 (34)	59 (25)
Paracetamol	70 (13)	69 (17)	44 (18)	151 (17)	59 (24)	96 (41)
Weak opioids	39 (7)	21 (5)	10 (4)	48 (6)	13 (5)	6 (3)
Anti-migraine	33 (6)	36 (9)	25 (10)	40 (5)	14 (6)	4 (2)
Anti-epileptics	56 (10)	30 (8)	21 (8)	85 (10)	18 (7)	18 (8)
Strong opioids	42 (8)	32 (8)	11 (4)	67 (8)	19 (8)	32 (14)
COX-2 inhibitors	15 (3)	5 (1)	4 (2)	20 (2)	3 (1)	3 (1)
Anti-inflammatory agent ^a	5 (1)	4 (1)	3 (1)	4 (0)	1 (0)	1 (0)
Codeine	16 (3)	17 (4)	12 (5)	44 (5)	18 (7)	9 (4)
Anti-depressants	22 (4)	18 (5)	10 (4)	23 (3)	16 (6)	5 (2)
Anesthetic	3 (1)	2 (1)	0 (0)	5 (1)	2 (1)	2 (1)
Benzodiazepines	3 (1)	2 (1)	2 (1)	6 (1)	1 (0)	2 (1)
Salicyclic Magnesium trisalicylate	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Analgetica Remaining ^b	6 (1)	2 (1)	3 (1)	11 (1)	0 (0)	0 (0)

No correction was carried out if patients reported two or more painful conditions. Rounded to whole numbers. Number of reports (N°)

^aAnti-inflammatory agent: Chondroitin

^bAnalgetica Remaining: Glucosamine and Flupirtine maleate

eTable 8. The proportions of the total amount of analgesic use across the different groups.

	Groups					
	Non-mutation carriers (N = 427)	PreHDA (N = 287)	PreHDB (N = 194)	Early (N = 678)	Middle (N = 187)	Late (N = 189)
Amount of anal- gesic use						
1	309 (72)	185 (64)	136 (70)	494 (73)	134 (72)	144 (76)
2	84 (20)	80 (28)	49 (25)	143 (21)	36 (19)	34 (18)
≥ 3	34 (8)	22 (8)	9 (5)	41 (6)	17 (9)	11 (6)
	100%	100%	100%	100%	100%	100%

Rounded to whole numbers.

CHAPTER 3

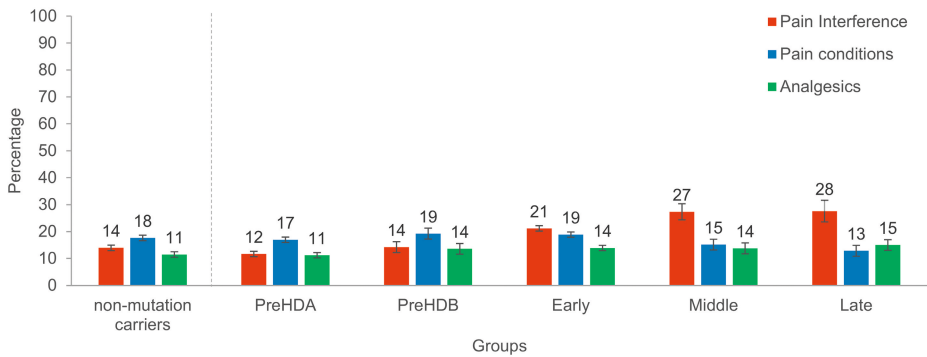
eTable 9. The frequency of pain interference, analgesics, depression, anxiety of cognitive disturbances in two different groups (with/ without a painful condition)

			Outcomes									
			Pain Interference		Analgesics		Depression		Anxiety		Cognition	
Groups			No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Non-mutation carriers	Pain present (N ⁰)	No	1.778	711	2.918	161	2.079	268	1.781	565	2.222	24
		Yes	225	284	374	266	405	73	338	140	469	6
PreHDA	Pain present (N ⁰)	No	1.338	366	2015	116	1.312	208	1.088	434	1.159	11
		Yes	175	158	254	171	236	50	190	96	293	3
PreHDB	Pain present (N ⁰)	No	656	225	1.083	79	627	138	564	203	732	33
		Yes	124	94	156	115	142	44	122	63	176	7
Early	Pain present (N ⁰)	No	1.852	962	3.667	297	1.691	756	1.666	782	2.136	488
		Yes	291	359	522	381	376	184	361	199	512	78
Middle	Pain present (N ⁰)	No	418	268	1.047	112	307	261	370	199	342	352
		Yes	48	76	126	75	55	40	59	36	59	46
Late	Pain present (N ⁰)	No	281	153	980	122	173	181	244	107	100	413
		Yes	30	40	89	67	22	32	38	16	12	46

¹Pain interference was stated as a score of 'A little bit' or higher on the pain interference item of the SF12v2.

² HADS score of eight or higher indicated depressive or anxiety symptoms. ³Cognition: MMSE score of 23 points or lower was defined as presence of cognitive disturbance.

Prevalence of pain in Huntington's disease

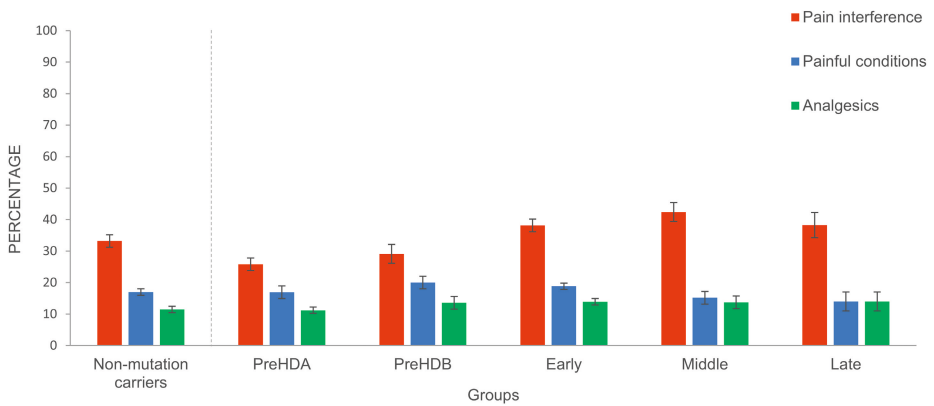


eFigure 3. Prevalence of pain interference¹, conditions causing pain and analgesic use across the different stages.

¹Pain interference was defined as a score of 'Moderately' or higher on the pain interference item of the SF12v2. Rounded to whole numbers. 95% confidence interval (I). Total Sample Size (N)

Pain interference: Non-mutation carriers (N = 2998); PreHDA (N = 2037); PreHDB (N = 1099); Early (N = 3464); Middle (N = 810); Late (N = 504)

Painful conditions and analgesics: Non-mutation carriers (N = 3719); PreHDA (N = 2556); PreHDB (N = 1433); Early (N = 4867); Middle (N = 1360); Late (N = 1258)



eFigure 4. Prevalence of pain interference¹, conditions causing pain and analgesic use across the different stages within the group with available pain interference data.

¹Pain interference was defined as a score of 'A Little Bit' or higher on the pain interference item of the SF12v2. Rounded to whole numbers. 95% confidence interval (I). Total Sample Size (N)

Non-mutation carriers (N = 2998); PreHDA (N = 2037); PreHDB (N = 1099); Early (N = 3464); Middle (N = 810); Late (N = 504)

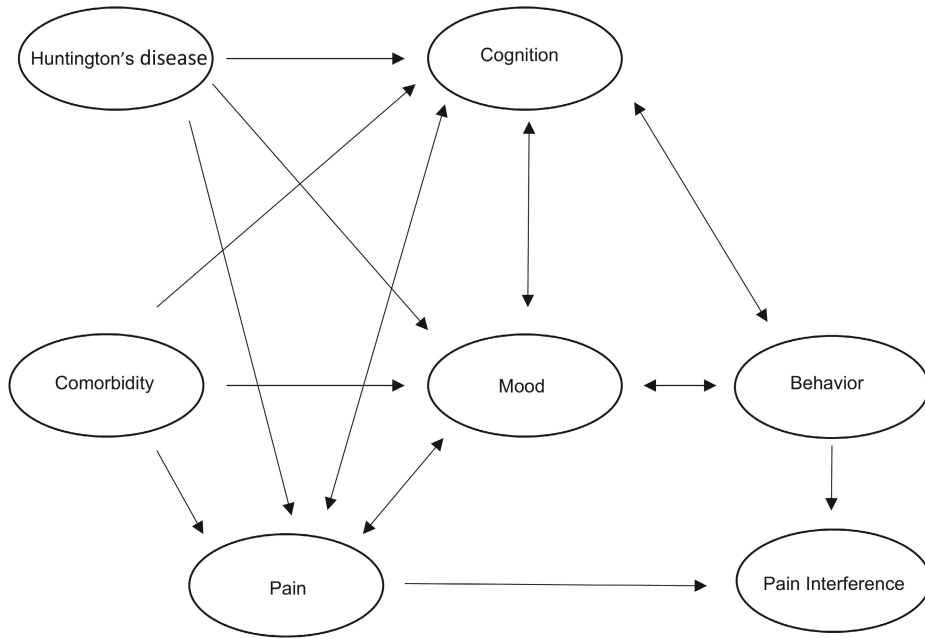


Figure 5. A modified network illustrating the association between Huntington's disease and pain (interference).⁸

The arrows demonstrate the direction of the association between the variables. Cognition can be seen as maladaptive beliefs or disturbances in the neurocognitive functions. Mood is stated as depressive or anxiety symptoms. Behavior are symptoms such as apathy or irritability, but also represents the coping style.

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