Prevalence and burden of pain across the entire spectrum of Huntington's disease

Sprenger, G.P.; Zwet, E.W. van; Bakels, H.S.; Achterberg, W.P.; Roos, R.A.; Bot, S.T. de

Original research

Prevalence and burden of pain across the entire spectrum of Huntington's disease

Gregory P Sprenger ,[1,2] Erik W van Zwet,[3] Hannah S Bakels,[1] Wilco P Achterberg,[4,5] Raymund A Roos,[1] Susanne T de Bot[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-332992).

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[2]Huntington Center, Amstelring, Amsterdam, The Netherlands
[3]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
[5]Huntington Center overduin, Topaz, Leiden, The Netherlands

Correspondence to
Gregory P Sprenger, Neurology, Leiden Universitair Medisch Centrum, Leiden 2333, The Netherlands; gsprenger@amstelring.nl; g.p.sprenger@lumc.nl

Received 12 November 2023
Accepted 9 January 2024
Published Online First 30 January 2024

To cite: Sprenger GP, van Zwet EW, Bakels HS, *et al*. *J Neurol Neurosurg Psychiatry* 2024;**95**:647–655.

ABSTRACT

Background Pain is an important symptom in Huntington's disease (HD), however, not systematically studied and understood. The objective of the current study is to assess the prevalence of pain, pain interference in daily activities, painful conditions, analgesic use and the severity of the pain burden across different disease stages and 'Age at symptom Onset' groups. Additionally, the association between pain and disease burden was investigated.

Methods A cross-sectional analysis was conducted within two large data sets, which included different types of pain scales. Multivariable logistic regression analyses and analyses of variance were performed to compare the pain levels with those in the general population. The analyses were adjusted for sex and age. Locally Estimated Scatterplot Smoothing was used to test the association between pain and the HD pathology score: a measure of disease burden.

Results The mean prevalence of pain in the HD population was 40% and for pain interference around 35% in both data sets. Patients in the early, middle and late stage of HD experience more pain burden compared with what is reported in patients with chronic pain ($p<0.01$). A positive and significant association was demonstrated between pain and disease burden. Patients in late stage HD with pain use significantly less analgesics compared with the general population (5% vs 13%, respectively ($p<0.01$)).

Conclusions Pain is a prevalent and important symptom in HD. Severe pain burden in the HD population is present and positively associated with disease burden. Risk for undertreatment with analgesics is nevertheless present. Awareness of pain in HD needs to be increased, both clinically and scientifically.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pain seems to be an important symptom in Huntington's disease (HD), however, studies concerning this topic are very scarce and fundamental knowledge is lacking for adequate pain management regimens.

WHAT THIS STUDY ADDS

⇒ To our knowledge this is the first study including different large world-wide data sets, providing an unique opportunity to assess pain from different perspectives in the entire spectrum of HD. Current study demonstrated that pain is a serious symptom, with an even more severe pain burden compared with patients with chronic pain. Additionally, this study demonstrated a potential risk for undertreatment of pain in HD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Current study emphasise the necessity, both clinically and scientifically, to increase the awareness of pain in HD and to improve the pain management regimens in this vulnerable patient population.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, caused by an increased number of cytosine-adenine-guanine (CAG) repeats in the DNA sequence in *HTT*, the gene that encodes huntingtin.[1] The resulting abnormally long polyglutamine repeat in the huntingtin protein causes neuronal loss in the brain, particularly in the striatum.[2] HD is characterised by involuntary movements, neurocognitive impairments and neurobehavioral changes. Besides the well-known triad of symptoms and signs in HD, other non-motor symptoms in HD are described such as weight loss, sleep disturbances and autonomic changes.[3] Another rather unrecognised non-motor symptom is pain. The mean prevalence of pain in HD has been estimated to be around 41%.[4] Until now, conflicting data have been reported on the prevalence of pain across different disease stages: one study showed a lower prevalence of pain in the advanced stage (26%) as compared with non-HD mutation carriers, while another study demonstrated an actual increase of the prevalence of pain up to 50%.[5 6]

The neurocognitive decline and speech impairments in HD certainly challenge pain assessments and subsequently adequate pain management. A recent study demonstrated a discrepancy in the prevalence of pain interference on daily activities and analgesic use (34% vs 13%, respectively).[7] Additional studies concerning this topic in HD are lacking.

Therefore, our aim was to broaden the knowledge on pain and pain burden in HD, not only the prevalence in different stages, but also in different 'Age at symptom Onset' groups, including Juvenile HD. In order to validate previous findings from one pain scale outcome within the Enroll-HD study, another cohort will be studied (Registry-HD study),

Table 1 Characteristics of the subjects in the Enroll-HD study (PDS-5) across the *different stages* of HD

		Socio-demographic factors			Clinical variables							
Groups	N	Age Mean (SD)	Gender N^0 (%)	Region N^0 (%)	CAG-repeat Mean (SD)	UHDRS-TMS Mean (SD)	UHDRS-TFC Mean (SD)	Disease duration- Years Mean (SD)	HD Pathology score Mean (SD)	Cognition Mean (SD)	HADS-depression Mean (SD)	HADS-anxiety Mean (SD)
NMC	4996	46.7 (14.8)	F: 3056 (61.2) M: 1940 (38.8)	E: 2477 (49.6) LA: 72 (1.4) NA: 2288 (45.8) AU: 159 (3.2)	20.2 (3.6)	1.6 (3.3)	12.9 (0.7)	n/a		MMSE: 28.9 (1.5) SDMT: 49.9 (12.1) C_FL: 21.9 (5.6) L_FL: 40.7 (12.5) Stroop_C: 74.4 (14.2) Stroop_W: 95.5 (17.4) Stroop_I: 42.6 (11.2)	3.4 (3.3)	5.2 (3.8)
PreHDA	3199	36.3 (10.6)	F: 1988 (62.1) M: 1211 (37.9)	E: 1930 (60.3) LA: 23 (0.7) NA: 1077 (33.7) AU: 169 (5.3)	41.7 (2.4)	1.4 (2.2)	12.9 (0.7)	n/a	210.4 (62.6)	MMSE: 29.0 (1.3) SDMT: 55.0 (9.6) C_FL: 22.5 (5.5) L_FL: 41.9 (12.3) Stroop_C: 77.1 (13.6) Stroop_W: 98.1 (16.6) Stroop_I: 46.6 (10.5)	3.2 (3.3)	5.6 (4.0)
PreHDB	2516	46.0 (12.3)	F: 1385 (55.0) M: 1131 (45.0)	E: 1419 (56.4) LA: 14 (0.6) NA: 928 (36.9) AU: 155 (6.2)	43.4 (3.1)	7.1 (7.7)	12.1 (1.7)	n/a	330.8 (68.5)	MMSE: 27.9 (2.3) SDMT: 38.9 (10.7) C_FL: 18.4 (5.7) L_FL: 34.3 (12.8) Stroop_C: 63.2 (15.3) Stroop_W: 81.8 (19.4) Stroop_I: 36.2 (10.7)	4.6 (3.9)	6.0 (4.3)
Early	6849	52.1 (12.3)	F: 3377 (49.3) M: 3472 (50.7)	E: 4590 (67.0) LA: 88 (1.3) NA: 1982 (28.9) AU: 189 (2.8)	43.8 (3.7)	30.1 (13.9)	10.3 (2.0)	6.1 (4.7)	396.6 (87.9)	MMSE: 26.1 (3.0) SDMT: 26.2 (11.1) C_FL: 13.6 (5.2) L_FL: 23.5 (12.3) Stroop_C: 46.8 (14.7) Stroop_W: 62.4 (19.3) Stroop_I: 25.8 (10.3)	5.7 (4.0)	6.0 (4.2)
Middle	1800	54.8 (13.0)	F: 971 (53.9) M: 829 (46.1)	E: 1246 (69.2) LA: 27 (1.5) NA: 466 (25.9) AU: 61 (3.4)	44.5 (4.6)	48.0 (16.3)	5.2 (0.8)	9.6 (5.7)	442.4 (99,0)	MMSE: 22.9 (4.3) SDMT: 15.4 (8.8) C_FL: 9.2 (4.3) L_FL: 15.0 (9.8) Stroop_C: 32.5 (13.0) Stroop_W: 43.4 (17.5) Stroop_I: 16.8 (9.0)	7.3 (4.3)	6.2 (4.3)
Late	1573	56.6 (12.9)	F: 906 (57.6) M: 667 (42.4)	E: 1306 (83.0) LA: 19 (1.2) NA: 220 (14.0) AU: 28 (1.8)	45.1 (5.1)	69.8 (19.0)	1.7 (1.1)	12.7 (6.0)	487.6 (117.1)	MMSE: 18.3 (6.2) SDMT: 6.2 (7.2) C_FL: 5.4 (3.9) L_FL: 8.2 (7.0) Stroop_C: 19.1 (13.9) Stroop_W: 24.77 (18.6) Stroop_I: 9.9 (8.3)	8.0 (4.9)	6.0 (4.4)

After multiple imputation of missing data, no significant differences were found compared with the original data set.
AU, Australasia; CAG-repeat, Cytosine-Adenine-Guanine repeat; C_FL, Category Fluency Test – total correct in 60 s; E, European; F, female; HADS, Hospital Anxiety and Depression Scale; HD, Huntington's disease; LA, Latin-American; L_FL, Letter Fluency Test – total correct in 3 min; M, male; Miss, missing data; MMSE, Mini-Mental State Examination – total score; NA, Northern America; n/a, not applicable; NMC, non-mutation carriers; PDS-5, fifth periodic database; SDMT, Symbol Digit Modality Test – total correct in 90 s; SF-12, Short-Form Survey; Stroop_C, Stroop Color - total correct in 45 s; Stroop_I, Stroop Interference – total correct in 45 s; Stroop_W, Stroop Word- total correct in 45 s; UHDRS - TMS or TFC, Unified Huntington Disease Rating Scale – Total Motor Score or Total Function Category.

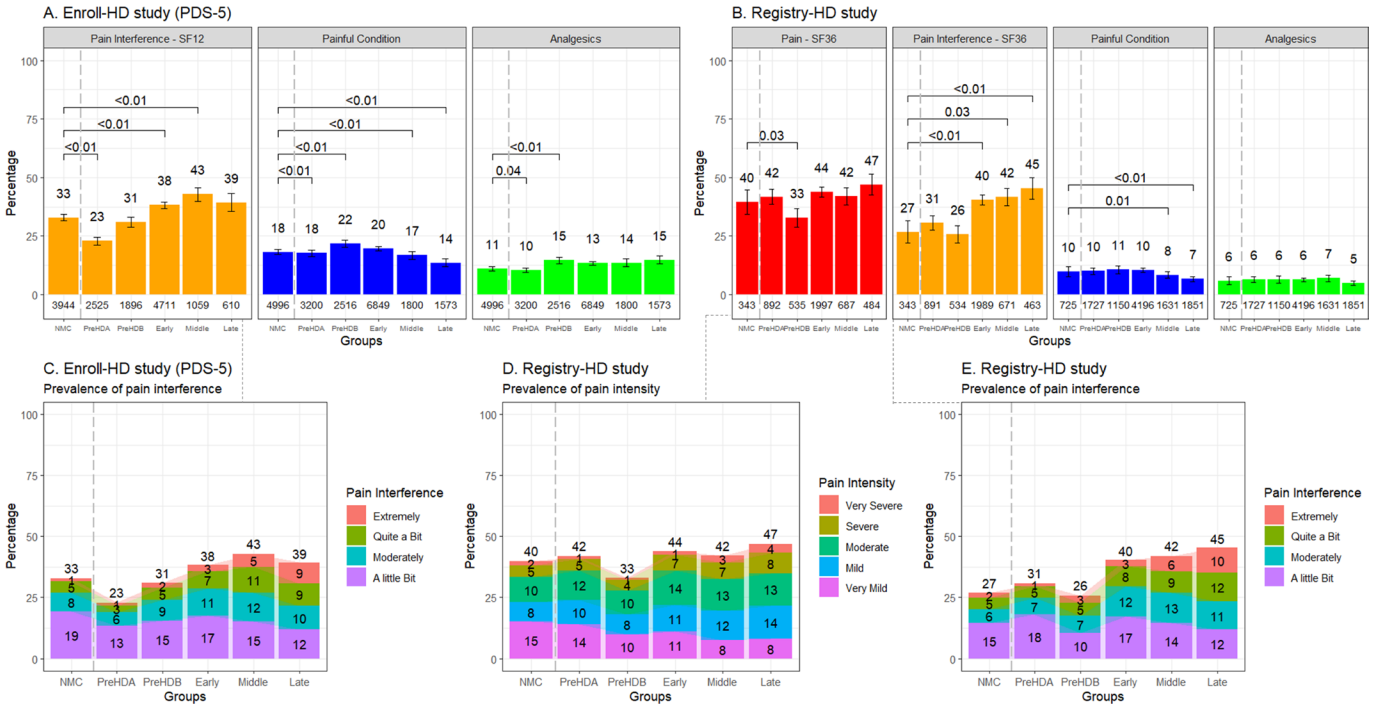

Figure 1 The prevalence of different pain outcomes across the stages of Huntington's Disease compared with non-mutation carriers. The total sample sizes of each group are demonstrated beneath the bars. Due to missing data of the SF-36 and SF-12, the sample sizes are smaller compared with the total sample. 95% CI (I). NMC, non-mutation carriers; SF-12, Short-Form Health Survey-12; SF-36, Short-Form Health Survey-36.

which also includes more extensive pain measures. The use of these large data sets provided an unique opportunity to study pain in HD profoundly and from different perspectives. In addition, in order to assess the impact of HD pathophysiology on the pain burden, an exploratory analysis will be conducted by using the HD pathology score (disease burden). This score is an indirect measure of the striatal pathology, an important localisation for HD pathology. The striatum is also involved in central pain modulation and in particular in pain inhibition.[8 9] We hypothesised that the striatal pathology also affects the pain inhibition.

METHODS

We applied the data sets of the Registry-HD study (RDS) and the fifth periodic database (PDS-5) of the Enroll-HD study. The Registry-HD study was a European study, started in 2004 and was completed in 2017. Established in July 2012, the Enroll-HD study is operating worldwide. The Enroll-HD study included 6247 participants from the Registry-HD study who reconsented to continue participation and data transfer. Registry-HD and Enroll-HD are both clinical research platform studies designed to facilitate clinical research in HD. Core data sets are collected annually from all participants as part of this multicentre longitudinal observational study. Data are monitored for quality and accuracy using a risk-based monitoring approach. All the sites were required to obtain and maintain local ethical approval.

The RDS and PDS-5 included 12 881 and 21 116 participants, respectively. For our study the baseline assessments of both data sets (RDS and PDS-5) were used of individuals with a genetically-confirmed HD gene mutation and non-HD mutation carriers (family controls (spouses, partners, caregivers) and genotype-negatives). Deduplication was performed within the RDS. Data deduplication between the different databases (RDS and PDS-5) was not performed because the databases were not merged due to their different nature.

The baseline assessment gathered data on: age, sex, region, race, International Standard Classification of Education, marital status, CAG-repeat length, motor symptoms, stage of disease, comorbidities, medication use and indication. The cognitive functions were assessed according to the Unified Huntington Disease Rating Scale (UHDRS), using the Symbol Digit Modality Test (SDMT), Category and Letter Fluency Test and the Stroop Test.[10] Additionally, the Mini-Mental State Examination was used to assess general cognitive function.[11] In the PDS-5, the Hospital Anxiety and Depression Scale was used as a questionnaire to assess symptoms of anxiety and depression.[12] In the RDS, the Beck Depression Inventory was additionally used as a mood questionnaire.[13]

Pain scales

In the RDS, the pain intensity and interference items of the Short-Form Health Survey-36 version 1 and 2 (SF-36v1 or SF36-v2) were available to assess pain.[14–16] In the PDS-5, the pain interference item of the Short-Form Health Survey-12-version 2 (SF-12v2) was available.[14–16] The pain burden was defined by a composite score of the pain and pain interference items of the SF-36.[16] According to standard procedure of the SF-36, the composite raw score was converted to a transformed score. The range of the transformed scale is from 0 to 100. A higher score indicates less and a lower score indicates more pain burden.[16] The transformed score can be compared with normative data of the general population and patients with chronic (back) pain.[16]

Painful conditions and analgesic use

The comorbidities and medication use in RDS and the PDS-5 database were classified according to the 10th edition of the International Classification of Diseases and the Anatomical Therapeutic Chemical Classification System, respectively.[17 18] Inclusion

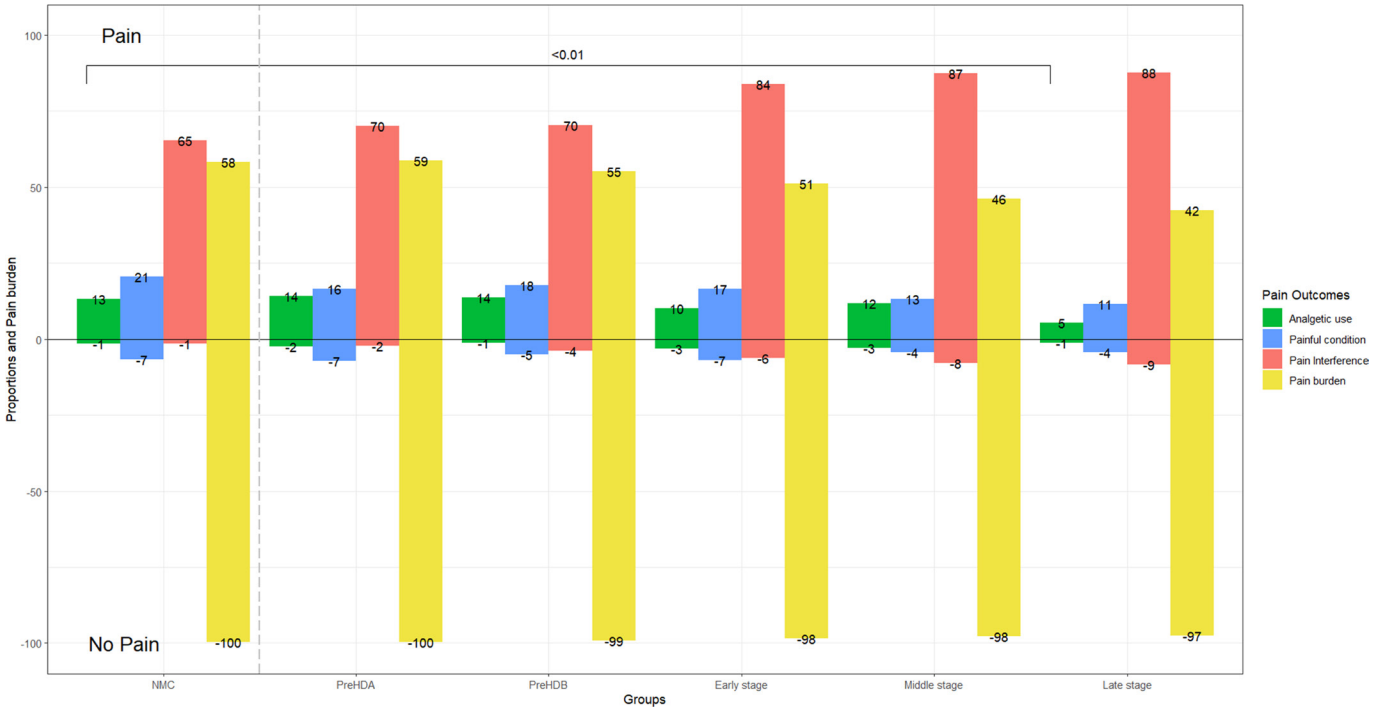

Figure 2 Mirrored barchart: Proportions of pain interference, painful condition and analgesic use demonstrated for the pain and no-pain group and across HD stages (RDS). Negative percentages should be interpreted as positive values. HD, Huntington's disease; NMC, non-mutation carriers; RDS, Registry-HD study.

criteria were postulated to identify painful conditions and analgesic use in both data sets (online supplemental eMethods).

Groups

The disease stages were defined as follows: Non-HD mutation carrier status (NMC) was defined as participants with ≤35 and HD mutation carrier status with 36 or more CAG repeats in the huntingtin gene. Premanifest HD was defined by a Total Motor Score (TMS) of five or lower and a Diagnostic Confidence Level of three or lower on the UHDRS.[19] By using the normed version of the prognostic index (PIN-HD) formula and 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).[19–21] The PIN-HD is a validated and 'normalized' scale to predict progression, with higher scores indicating greater risk of motor diagnosis. The following variables were included for calculating the PIN-scores: TMS, SDMT, age and length of CAG-repeat.[21] The manifest stage of HD was divided into an early, middle and late stage, by using the Total Functional Capacity (TFC) score of the UHDRS.[10 22] 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.[22]

Four 'Age at symptom Onset' HD groups (AO-HD) were determined: (1) patients with childhood-onset juvenile HD (onset ≤10 years; cJHD), (2) patients with adolescent-onset juvenile HD (onset: 11–20 years; aJHD), (3) patients with adult-onset HD with onset of first symptom between 21 years and 59 years (AHD) and (4) patients with late-onset HD with onset of first symptom ≥60 years (LoHD).[23 24] To improve homogeneity within the Juvenile-onset HD (JoHD) groups, participants with a CAG repeat of<40 were excluded and time between first symptom and first motor symptom was limited to 15 years. For the AHD and LoHD the cut-off of the CAG repeat was set at ≥36. The identification of age at first symptom was retrieved from the HD Clinical Characteristics questionnaire, as defined by the rater, which is a retrospective assessment of the broad spectrum of all HD symptoms and signs.[25]

An exploratory analysis was conducted to assess the association between the pain burden and the HD pathology score (disease burden). The HD pathology score is an indirect measure for striatal pathology, based on a high linear association between age, CAG repeat length and post-mortem striatal pathology (age × (CAG – 35.5)).[26] Larger numbers represent a higher burden of disease. This quotation has been used in a variety of HD biomarker studies to assess the relationship between the disease burden and the variables of interest.[27]

Statistical analysis

The analyses were conducted using the statistical software R (V.4.3.1).[28] To assess the prevalence of pain, pain interference, painful conditions and analgesic use, the scores were dichotomised. Moreover, the presence of pain or pain interference was defined as an individual score of 'little bit' or higher. Multivariable logistic regression analyses were performed for these binary outcomes. The predictors were age, sex, disease stages (NMC, PreHDA, PreHDB, early, middle and late) and 'Age at symptom Onset' groups (cJHD, aJHD, AHD, LoHD), to investigate differences in the prevalence of the pain outcomes across the entire spectrum of HD. We used Bonferroni correction, setting the threshold for statistical significance to 0.05 divided by the number of comparisons; 5 for disease stage (NMC vs the disease stages) and 10 for AO-HD. One-way analyses of variance (ANOVA) were performed to assess whether the pain burden (numeric outcome) differs across the disease stages and AO-HD group. All the analyses were adjusted for age and sex. One sample t-tests were conducted, to assess whether the mean score of the pain burden differs from the normative data of the

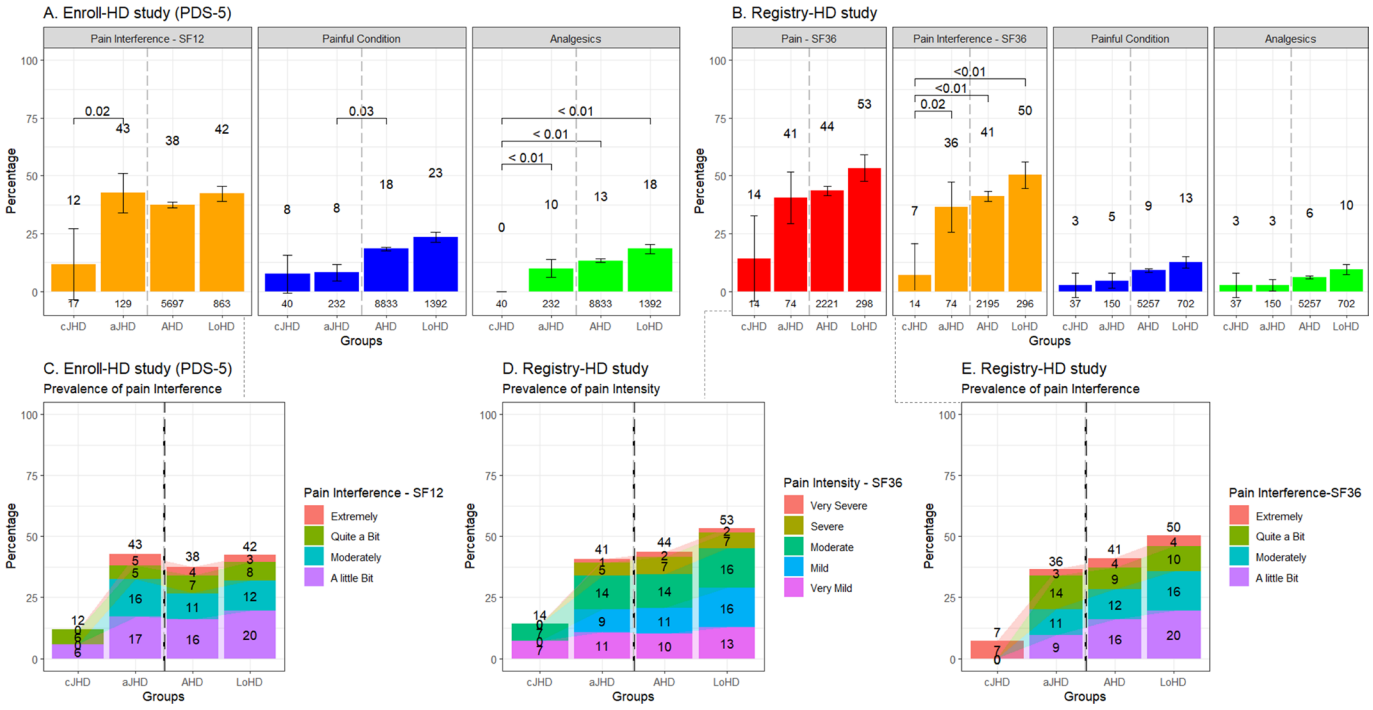

Figure 3 The prevalence of the different pain outcomes across the 'Age of symptom Onset' groups in Huntington's Disease. The total sample sizes of each group are demonstrated beneath the bars. Due to missing data of the SF-36 and SF-12, the sample sizes are smaller compared with the total sample. 95% CI (I). AHD, adult-onset HD; aJHD, adolescent-onset juvenile HD; cJHD, childhood-onset juvenile HD; HD, Huntington's disease; LoHD, late-onset HD; PDS-5, fifth periodic database; SF-12, Short-Form Health Survey-12; SF-36, Short-Form Health Survey-36.

general population and chronic (back) pain patients. An exploratory analysis was conducted to assess the association between the HD pathology score (disease burden) and the pain burden, by fitting a Locally Estimated Scatterplot Smoother (LOESS). This is a non-parametric regression method in which no assumptions are made about the underlying structure of the data. At every value of the pathology score, a local (weighted) average was computed of the pain burden. That is, an average of the pain burden for participants with similar pathology scores.[29 30] Pooling of the pain scales of the RDS and PDS-5 was not suitable due to clinimetric differences. For example, the time frame for assessing the presence of pain in the RDS was the last 4 weeks, whereas in the PDS-5 it was the last week.

Five multiple imputations were carried out in order to account for the missing data on socio-demographic, clinical factors, the pain outcomes and the defined groups (online supplemental eMethods).

RESULTS

Participants

At baseline, the total sample sizes (NMC and HD-mutation carriers) in the RDS includes 12 881 and in the PDS-5 includes 21 116 participants. Due to missing data in the data sets, 1601 (12%) and 183 (0.9%) participants were not categorised in the different disease stages of HD. In addition, in the RDS and PDS-5, respectively 6735 (52.3%) and 10 619 (50.3%) participants were not categorised in an AO-HD group due to missing data (online supplemental etables 1 and 2). The characteristics of the participants at the baseline assessment varied between the different predefined groups (table 1 and online supplemental etables 3–5). In the PDS-5, 4459 participants also had a baseline assessment in the RDS.

Prevalence of the different pain outcomes

Across the stages of HD

In the *RDS*, the overall mean prevalence of pain, pain interference, painful conditions and analgesic in HD mutation carriers was 42%, 37%, 9% and 6%, respectively. In the *PDS-5*, the overall mean prevalence of pain interference, painful conditions and analgesic use in HD mutation carriers was 34%, 19% and 13%, respectively. In both data sets (RDS and PDS-5), significantly higher prevalence of pain interference was demonstrated in the early and middle stage of HD, compared with NMC ($p \leq 0.03$) (figure 1A,B). The prevalence of pain interference was significantly higher in the late stage of HD compared with NMC ($p < 0.01$) in the RDS (figure 1B).

The prevalence of extreme pain interference was higher in the advanced stages of HD (figure 1C and E) in both data sets, RDS and PDS-5. More specifically, the prevalence of extreme pain interference was higher in the late stage of HD (10% and 9% (RDS and PDS-5, respectively)) compared with PreHDA group (1% for both data sets). Concerning the intensity of pain, the distribution of the prevalence was similar across the groups (figure 1D).

Concerning the proportions of analgesic use across disease stages, a significantly lower proportion of analgesic use was demonstrated in patients in the late stage of HD compared with NMC (5% vs 13%, respectively ($p < 0.01$)) (figure 2).

Across the 'Age at symptom Onset'

In the *RDS* and *PDS-5*, the prevalence of the pain outcomes varied across AO-HD groups (figure 3A,B). In both data sets (RDS and PDS-5), a significantly lower prevalence of pain interference was demonstrated in cJHD compared with aJHD ($p = 0.02$). Only in the PDS-5, a significantly lower prevalence of painful conditions was present between aJHD compared with AHD ($p = 0.03$)

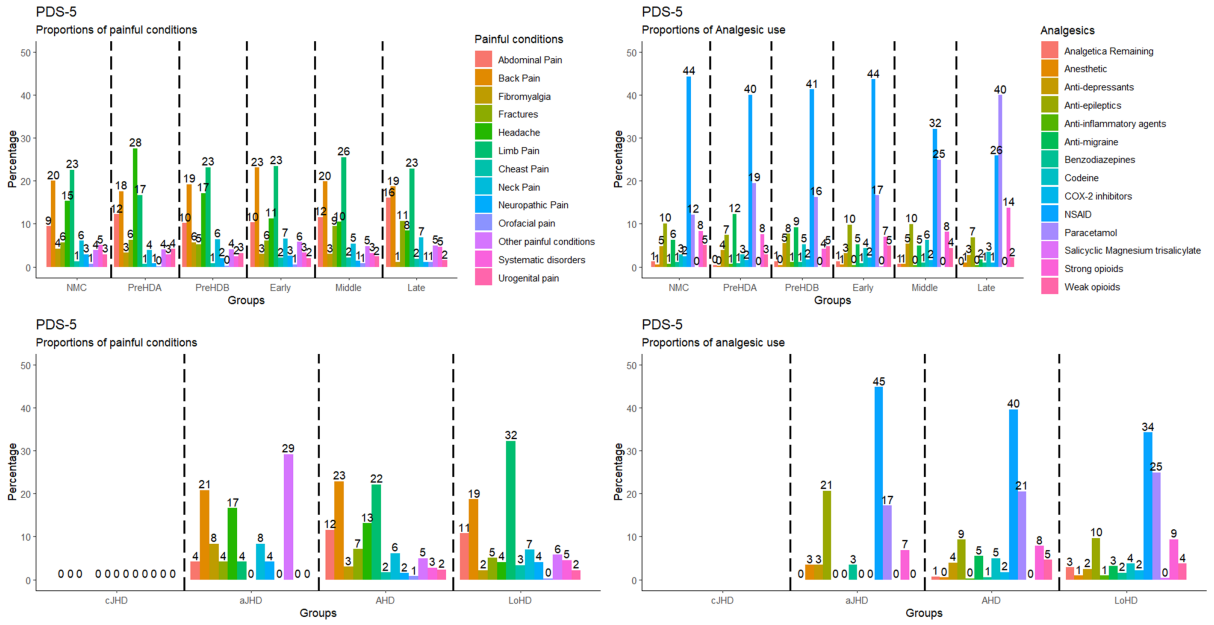

Figure 4 Proportions of specific types of painful conditions and analgesics across disease stages and OA-HD groups, between the RDS and PDS-5. No correction was conducted if patients reported two or more painful conditions. Proportions rounded to whole numbers. *Limb/extremity pain (eg, joint pain and non-systematic, non-inflammatory arthritic disorders). **Other painful conditions (acquired deformities, general pain, restless legs syndrome, postoperative pain, post-trauma pain, etc.). ***Analgetica Remaing: Combination of analgesics. AHD, adult-onset HD; aJHD, adolescent-onset juvenile HD; AO-HD, 'Age at symptom Onset' HD group; cJHD, childhood-onset juvenile HD; HD, Huntington's disease; LoHD, late-onset HD; NMC, non-mutation carriers; NSAID, non-steroidal anti-inflammatory drug; PDS-5, fifth periodic database.

(figure 3A). Furthermore, in the PDS-5, a lower prevalence of analgesic use was demonstrated in cJHD compared with aJHD, AHD or LoHD ($p<0.01$) (figure 3A).

The proportions of painful conditions, as well as the type of analgesics, differ between the AO-HD groups (figure 4). The most reported painful conditions in aJHD belonged to a cluster of different causes such as acquired deformities, restless leg syndrome and post-traumatic pain. Back pain was most frequently reported in AHD and headache in LoHD.

Concerning the analgesics, in all the AO-HD groups, paracetamol and NSAIDs were the most frequently used. Thereafter, anti-epileptics were the most frequently used, in particular in aJHD, and opioids in LoHD (figure 4).

Pain burden

The pain burden was defined as a transformed composite score (range 0–100) of the pain and pain interference items of the SF-36. A higher score indicates less and a lower score indicates more pain burden.[16]

First, the pain burden in the HD population was assessed which included patients with and without pain (yellow error bars) (figure 5A). A one-way ANOVA revealed a significant effect of the stage of HD on the pain burden ($F(5, 4015) = 5.78$, $p<0.01$) (figure 5A). Post hoc comparisons, indicated the pain burden was significant higher in patients in the late stage of HD (M=70.59, SD=32.37) compared with NMC (M=83.23, SD=25.02) ($p<0.01$).

Second, the pain burden was only assessed in patients with pain (red error bars). A significant effect of the stage of HD on the pain burden was demonstrated ($F(5, 1718) = 13.37$, $p<0.01$). Moreover, post hoc tests indicated a significant higher pain burden in early, middle and late stage of HD (M=51.22, SD=20.90; M=46.06, SD=22.42; M=42.43, SD=22.37, respectively) compared with NMC (M=58.15, SD=22.96) ($p\leq0.01$) (figure 5A). No significant group differences were present in the pain burden across the AO-HD groups ($F(3, 2568) = 0.84$, $p=0.47$) (figure 5B).

Significant group differences were present depending on the disease stages and AO-HD groups, compared with normative data of the general population (M=75.15, SD=23.69) and patients with chronic (back) pain (M=59.34, SD=24.63).[14–16] For instance, patients with pain in the PreHDB, early, middle and late stage of HD report significant more pain burden compared with the normative data of patients with chronic (back) pain ($p<0.01$) (figure 5A,B).

HD pathology and pain burden

From the LOESS fitted curve we observed a positive association between the HD pathology (disease burden) score between 200 and 360 and the pain burden in the overall HD population (figure 6A). In the HD population reporting pain, a positive association was also observed between the pain and disease burden between 200 and 375 (figure 6B). As the HD pathology score increased, independent of the presence of pain, the CIs widened accordingly, caused by the reduced amount of data.

DISCUSSION

Our findings regarding the prevalence of pain (40%) and pain interference (35%) in the overall HD population are in line with previously conducted studies.[4–7] Only at subgroup level, there are differences between studies regarding the prevalence and the severity of pain in HD. This is potentially due to sample size differences between studies, whereby a small sample affects the robustness of the data. In general, it can be concluded that the prevalence and the severity of pain and pain interference in the advanced stages of HD increases. The discrepancy in the current study regarding the prevalence of pain (interference) versus

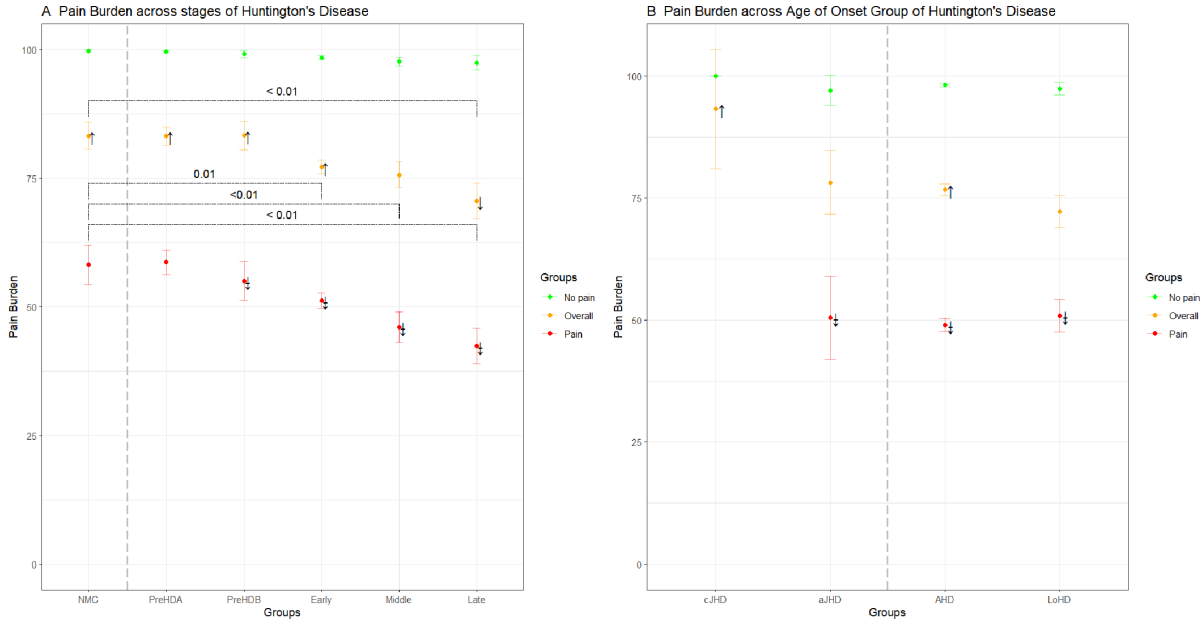

Figure 5 Pain burden in patients with Huntington's disease across the different stages and Age of symptom Onset groups in the RDS. The x-axis includes the transformed score of the pain burden and ranges from 0 to 100. A higher score indicates less and a lower score indicates more pain burden. ↑ significantly higher compared with the overall normative data; ↓ significant lower compared with overall normative; ↓ significant lower compared with normative data of patients with chronic pain. The 'No pain' and pain group represent the participants without and with pain, respectively. The overall group includes both types of participants, with and without pain. All the significant differences had a p value of p<0.01, only the p value for the comparison between the aJHD group and the normative data of patients with chronic pain (p=0.04). AHD, adult-onset HD; aJHD, adolescent-onset juvenile HD; cJHD, childhood-onset juvenile HD; HD, Huntington's disease; LoHD, late-onset HD; NMC, non-mutation carriers; RDS, Registry-HD study.

painful conditions and analgesic use are in line with our previous findings in an older release of the Enroll-HD study (PDS-4), validating the earlier conducted procedures.[7] This discrepancy could be due to several factors. First, HD in itself can cause pain, which may be an aspect that physicians are not sufficiently aware of as a cause of a painful condition.[31] Systematic studies are, however, necessary to explore this possible explanation. Other factors such as neurocognitive disturbances, speech impairment and loss of insight might contribute to this discrepancy, especially when using self-reported pain scales.

The discrepancy between the prevalence of pain and pain interference versus painful conditions and analgesic use was larger in the RDS compared with the PDS-5. This might partially be explained by regional effects, since the discrepancy was more

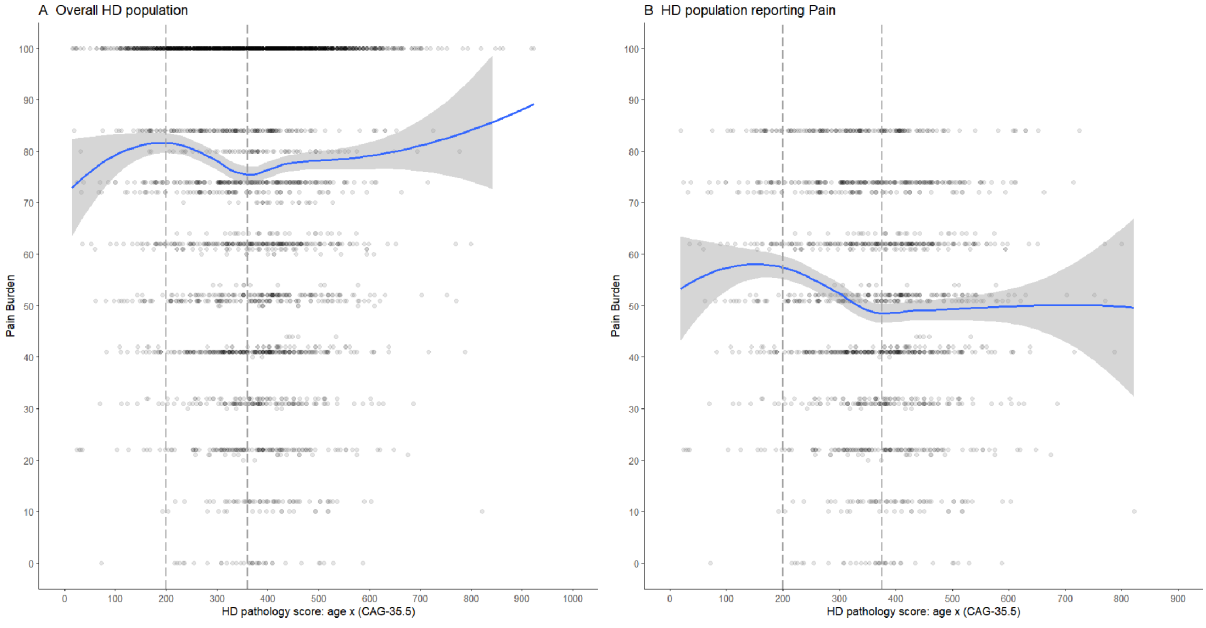

Figure 6 LOESS model for pain burden and HD pathology score. The x-axis includes the transformed score of the pain burden and ranges from 0 to 100. A higher score indicates less and a lower score indicates more pain burden. Blue line is the association between the HD pathology score and the pain burden. Grey area represent the 95% CI ( ). Larger numbers of the HD pathology score represent a higher burden of disease. CAG, cytosine-adenine-guanine; HD, Huntington's disease; LOESS, Locally Estimated Scatterplot Smoother.

or less similar between data sets if only European data from the PDS-5 were used (online supplemental etable 6). As proposed and demonstrated by different studies, national evidence-based guidelines, prescribing culture as well as regulatory policies and costs might contribute to different patterns in analgesic use at global, regional and national level.[32 33]

To our knowledge, this is the first study also assessing the prevalence of different pain outcomes across AO-HD groups including JoHD groups with onset in childhood and adolescence. Our study showed that the overall prevalence of pain at baseline was significantly lower for cJHD (14%), as compared with aJHD, AHD and LoHD: all above 40%. The only available study examining the frequency of pain in JoHD, included caregivers as responders and demonstrated that pain was reported in 69% of the 33 cases. The lower pain prevalence found in JoHD in the RDS cohort might be caused by the fact that in the RDS, pain was self-reported and with a shorter time frame (last 4 weeks). In addition, in the RDS a verbal pain scale was used, which might be interfered with by the severe progression of neurocognitive and speech impairments in JoHD. On the other hand, the 69% reported by caregivers might as well be an overestimation, confusing behavioural changes for an expression of pain. Finally, the divergent results might also be explained by the fact that the sample size, in particular the cJHD, was relatively small, providing less robust data regarding the prevalence of pain and pain interference.

In this study, we demonstrated that the proportions of type of painful conditions and analgesic use differ across the disease stages and AO-HD groups. These differences might be related to the development of the symptoms as HD progresses and due to the specific symptoms across the AO-HD groups. For instance, JoHD is characterised by dystonia and rigidity, as opposed to the hyperkinetic symptoms of AHD and LoHD, thereby increasing the risk of acquired deformities (contractures). In this current study, we indeed demonstrated that pain caused by acquired deformities are the most frequently reported painful conditions in JoHD (figure 4). Based on these findings, it can be proposed that the symptoms of HD influence the causes of pain and subsequently the prescribed analgesics.

Second, this study demonstrated that HD patients experience more *pain burden* compared with the general population (including individuals with and without pain). Remarkably, patients in the early, middle and late stage of HD experience more pain burden compared with normative data of chronic pain patients. A potential explanation of the increase of the pain burden could be due to the massive atrophy of the striatum in HD, consequently diminishing the pain inhibition.[8 26] The third finding of this study, based on a LOESS curving fitted method, demonstrated indeed a significant and positive association between the pain and HD pathology score (disease burden). This is an indirect indicator of striatum pathology. This association should, however, be further studied since the amount of data was not sufficient to assess the association in the more advanced stages of HD. Despite the fact that patients with HD experience more pain burden, current study demonstrated, however, a significantly lower proportion of analgesic use in patients in the late stage of HD compared with NMC (figure 2). Based on this finding, the clinical field should be aware of the potential risk of undertreatment of pain in HD, especially in the later stages.

The retrospective and cross-sectional nature of this study is a limitation to assess potential causal relations between pain and HD. The self-reported verbal pain scales were not part of the core assessment in the RDS and Enroll-HD study. It might be that only patients capable of (reliable) reporting pain were assessed, increasing the risk for selection bias. The included self-reported pain scales are too limited for an adequate pain assessment and interpretation of data (such as the pain burden) should be done with caution. Finally, the HD-Integrated Staging System was not used to determine the different groups, due to the lack of the necessary imaging variables in both databases.[34 35] As a result, in particular, premanifest participants cannot be definitively staged. Future studies may use an initial and promising algorithm to partly bypass this issue,[36] although for further subgroup differentiation, using PIN-HD (or CAG-age product) or TFC scores are still required.

On the other hand, to our knowledge, this study is the first of its kind assessing the prevalence of different pain outcomes and the pain burden across the entire spectrum of HD. To do so, we used two large data sets of high quality including various pain outcomes. The use of these data sets provided an unique opportunity to study pain in HD from different perspectives, consequently improving the generalisability of the findings.

More *prospective* studies, using different and more extended unidimensional and multidimensional self-reported pain scales, are warranted to investigate pain in HD. It is advised for future pain studies, particularly in severely affected patients, to use already validated non-verbal pain scales such as the numerical rating scale, facial pain scales and coloured analogue scales, because these are less cognitive demanding.[37] Studies assessing the validity and reliability of self-reported and observational pain scales in HD are also required. In particular, the validity and reliability of observational pain scales, which play a key role in the pain assessment in the most affected patients. Promising preliminary results are present regarding the reliability of the Pain Assessment in Impaired Cognition scale (PAIC15) in HD, which is a recently developed observational pain scale.[38 39] More studies with different experimental setups are, however, necessary to confirm these findings.

Finally, fundamental knowledge about the effect of HD on pain processing is essential for improving pain management regimens in HD. To our knowledge, the only available studies concerning this topic, demonstrated that pain processing seems to be prolonged in the manifest stage of HD compared with healthy controls.[40 41] In addition, studies assessing the association between clinical symptoms of HD (such as cognitive and mood disturbances), the disease burden and pain can use, for instance, network modelling to expand fundamental knowledge.

Acknowledgements Enroll-HD is a global clinical research platform and observational study (www.Enroll-HD.org) funded, managed and data made available by CHDI Foundation. Registry was a prospective multinational observational study funded by CHDI Foundation that ended in 2017; data from it is made available by the European Huntington's Disease Network (EHDN). Both studies are designed to facilitate clinical research in Huntington's disease. Neither of these studies would have been possible without the vital contribution of the research participants and their families; we thank them unreservedly. Core data sets have been collected annually from all research participants as part of these multicentre longitudinal observational studies. Data have been monitored for quality and accuracy using a risk-based monitoring approach. All sites have been required to obtain and maintain local ethical approval. A list of the many healthcare professionals and researchers involved in data collection is available: Enroll-HD https://enroll-hd.org/enrollhd_documents/ENROLLHD_AcknowledgementsListPDS6_v1.0_20230119.pdf and Registry https://ehdn.org/wp-content/uploads/REGISTRY-contributors-full-list.pdf. Furthermore, we would like to acknowledge L C E Huberts and R H A M Reijntjes for their help and supervision for programming and merging the data sets in R. Finally, we would like to acknowledge Amstelring, a specialised Huntington Center in Amsterdam, for the financial support to conduct this study. Authors Hannah Bakels and STdB are members of the European Reference Network for Rare Neurological Diseases - Project ID No 739510.

Contributors GPS conceived the study and drafted the manuscript. EWvZ//HSB/WPA/RAR/STdB contributed to the conception of study and drafted parts of the

manuscript. EWvZ verified the analytical methods and analysis. STdB/WPA/RAR encouraged GPS for studying pain in Huntington's disease and supervised the findings of this work. STdB acted as guarantor. All authors discussed the results and contributed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests STdB: Leiden University Medical Center receives grants from the European Huntington's Disease Network (EHDN) and Cure HD Initiative (CHDI), participates in an EU Horizon 2020 project: Innovative Medicines Initiative (IMI) 2 (IDEA_FAST), and participates in clinical trials sponsored by PRILENIA, PTC Therapeutics, WAVE and VICO Therapeutics. The aforementioned sponsors had no role in the design, execution, interpretation or writing of this current study. RAR: Member DSMB uniQure 130 study, member DSMB Enroll-HD, Research advisor MIJZO Care centre. The other authors have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Medical Ethics Committee: Leiden -The Hague- The study is registered as: P13.167. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available on request. For the ENROLL-HD study, please sent direct inquiries to info@chdifoundation.org with the words 'ENROLL-HD PDS' in the subject line and for the RDS see: https://www.euro-hd.net/html/projects/proposals/scipro. The data are not publicly available due to privacy or ethical restrictions.

ORCID iD

Gregory P Sprenger http://orcid.org/0000-0001-9822-4536

REFERENCES

1 Macdonald M. A novel gene containing a trinucleotide repeat that is expanded and unstable on huntington's disease chromosomes. *Cell* 1993;72:971–83.
2 Tabrizi SJ, Langbehn DR, Leavitt BR, *et al*. Biological and clinical manifestations of huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol* 2013;8:791–801.
3 Roos RAC. Huntington's disease: a clinical review. *Orphanet J Rare Dis* 2010;5:1–8.
4 Sprenger GP, van derKF, Roos RAC, *et al*. The prevalence and the burden of pain in patients with huntington's disease. *Pain* 2019;160:773–83.
5 Underwood M, Bonas S, Dale M, *et al*. Huntington's disease: prevalence and psychological indicators of pain. *Mov Disord Clin Pract* 2017;4:198–204.
6 Delussi M, Sciruicchio V, Taurisano P, *et al*. Lower prevalence of chronic pain in manifest huntington's disease: a pilot observational study. *Brain Sci* 2022;12:676.
7 Sprenger GP, Roos RAC, van Zwet E, *et al*. The prevalence of pain in Huntington's disease in a large worldwide cohort. *Parkinsonism Relat Disord* 2021;89:73–8.
8 Barceló AC, Filippini B, Pazo JH. The striatum and pain modulation. *Cell Mol Neurobiol* 2012;32:1–12.
9 Hagelberg N, Jääskeläinen SK, Martikainen IK, *et al*. Striatal dopamine D2 receptors in modulation of pain in humans: a review. *Eur J Pharmacol* 2004;500:187–92.
10 Kieburtz K. Unified huntington's disease rating scale: reliability and consistency. *Mov Disord* 1996;11:136–42.
11 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
12 Bjelland I, Dahl AA, Haug TT, *et al*. The validity of the hospital anxiety and depression scale. *J Psychosom Res* 2002;52:69–77.
13 Beck A, Steer RBG. *Beck depression inventory. Second*. San Antonio, TX, E.U: Psychological Corporation, 1996. Available: https://scholar.google.com/scholar_lookup?title=Beck+Depression+Inventory&author=A+Beck&author=R+Steer&author=G+Brown&publication_year=1996&
14 Ware JE, Kosinski M, Keller SD, *et al*. SF-12: how to score the SF-12 physical and mental health summary scales; 1998.
15 Ware JE, Snow KK, Kosinski M, *et al*. SF-36 health survey: manual and interpretation guide. *The Health Institute, New England Medical Center* 1993:1.
16 Ware JE, Snow KK, Kosinski M, *et al*. *SF-36 health survey. Manual and interpretation guide*. 1993: 1–316.
17 The World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/ DDD); 2003. Available: https://www.whocc.no/atc_ddd_index/
18 World Health Organization. International classification of diseases for mortality and morbidity stastics (10th revision); 2014. Available: https://icd.who.int/browse10/2014/en#!/XIV
19 Tabrizi SJ, Scahill RI, Owen G, *et al*. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013;12:637–49.
20 Langbehn DR, Brinkman RR, Falush D, *et al*. A new model for prediction of the age of onset and penetrance for huntington's disease based on CAG length. *Clin Genet* 2004;65:267–77.
21 Long JD, Langbehn DR, Tabrizi SJ, *et al*. Validation of a prognostic index for huntington's disease. *Mov Disord* 2017;32:256–63.
22 Bates GP, Tabreizi SJ, Jones L. *Huntington's disease*. 2014.
23 Bakels HS, Roos RAC, van Roon-Mom WMC, *et al*. Juvenile-onset huntington disease pathophysiology and neurodevelopment: a review. *Mov Disord* 2022;37:16–24.
24 Petracca M, Di Tella S, Solito M, *et al*. Clinical and genetic characteristics of late-onset huntington's disease in a large European cohort. *Eur J Neurol* 2022;29:1940–51.
25 Orth M, Handley OJ, Schwenke C, *et al*. Observing huntington's disease: the European huntington's disease network's REGISTRY. *PLoS Curr* 2010;2:RRN1184.
26 Penney JB Jr, Vonsattel JP, MacDonald ME, *et al*. CAG repeat number governs the development rate of pathology in huntington's disease. *Ann Neurol* 1997;41:689–92.
27 Tabrizi SJ, Scahill RI, Durr A, *et al*. Biological and clinical changes in premanifest and early stage huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol* 2011;10:31–42.
28 Team RC. R: A language and environment for statistical computing. 2022. Available: https://www.r-project.org/
29 Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc* 1979;74:829–36.
30 Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. *J Am Stat Assoc* 1988;83:596–610.
31 Scherder E, Statema M. Huntington's disease. *Lancet* 2010;376:1464.
32 Ju C, Wei L, Man KKC, *et al*. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. *Lancet Public Health* 2022;7:e335–46.
33 Wagemaakers FN, Hollingworth SA, Kreijkamp-Kaspers S, *et al*. Opioid analgesic use in Australia and The Netherlands: a cross-country comparison. *Int J Clin Pharm* 2017;39:874–80.
34 Tabrizi SJ, Schobel S, Gantman EC, *et al*. A biological classification of huntington's disease: the integrated staging system. *Lancet Neurol* 2022;21:632–44.
35 Tabrizi SJ, Schobel S, Gantman EC, *et al*. Huntington's disease integrated staging system (HD-ISS): a novel evidence-based classification system for staging. *medRxiv* 2021:21262503.
36 Long JD, Gantman EC, Mills JA, *et al*. Applying the huntington's disease integrated staging system (HD-ISS) to observational studies. *J Huntingtons Dis* 2023;12:57–69.
37 Birnie KA, Hundert AS, Lalloo C, *et al*. Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. *Pain* 2019;160:5–18.
38 de Waal MWM, van Dalen-Kok AH, de Vet HCW, *et al*. Observational pain assessment in older persons with dementia in four countries: observer agreement of items and factor structure of the pain assessment in impaired cognition. *Eur J Pain* 2020;24:279–96.
39 Kunz M, de Waal MWM, Achterberg WP, *et al*. The pain assessment in impaired cognition scale (PAIC15): a multidisciplinary and international approach to develop and test a meta-tool for pain assessment in impaired cognition, especially dementia. *Eur J Pain* 2020;24:192–208.
40 Perrotta A, Serpino C, Cormio C, *et al*. Abnormal spinal cord pain processing in Huntington's disease. The role of the diffuse noxious inhibitory control. *Clin Neurophysiol* 2012;123:1624–30.
41 de Tommaso M, Franco G, Ricci K, *et al*. Laser evoked potentials in early and presymptomatic huntington's disease. *Behav Neurol* 2016;2016:8613729.