Prevalence and burden of pain in Huntington's disease

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CHAPTER 2

The prevalence and the burden of pain in patients with Huntington's disease: A systematic review and meta-analysis.

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Abstract

It is remarkable that studies focusing on the prevalence and the burden of pain in patients with Huntington's disease (HD) are scarce. This may lead to inadequate recognition of pain and hence lack of treatment, eventually affecting the quality of life. The aim of this review is to investigate the prevalence of pain and its burden in HD by performing a systematic literature search. In February 2018, a systematic search was performed in the electronic databases of Pubmed, Embase, Cinahl, Cochrane, and PsycINFO. Studies focusing on patients with juvenile HD were excluded. All other types of study were included without language restrictions. In total, 2234 articles were identified, 15 of which met the inclusion criteria and provided information on 2578 patients with HD. The sample-weighted prevalence of pain was 41.3 % (95% confidence interval: 36% - 46%). The pain burden, which was measured with the SF-36, is significantly less compared with that in the general population. The sample-weighted mean score on the SF-36 was 84 (95% confidence interval: 81 - 86), where a score of 100 represents the lowest symptom burden. The results demonstrate that pain could be an important non-motor symptom in patients with HD and there are indications that the pain burden could be diminished because of HD. Larger and high quality prospective cohort and clinical studies are required to confirm these findings. In the meantime, awareness about pain and its burden in patients with HD is warranted in clinical practice.

Key words: Huntington's disease, pain, pain burden, prevalence of pain.

1. Introduction

Huntington's disease (HD) is a devastating autosomal-dominant inherited neurodegenerative disease, causing characteristic motor (eg chorea), cognitive, emotional, and behavioral disturbances. Secondary symptoms are weight loss, sleep disorders, and autonomic symptoms.[1] In the brain, HD leads to massive atrophy of especially the GABAergic medium spine neurons of the striatum.[2] The striatal atrophy is already present in the premanifest stage, even 10 to 15 years before clinical diagnosis.[3,4] In the manifest stage, atrophy of the striatum correlates with disease severity,[5,6] total functional capacity (TFC)[7] and cognitive disturbances (eg, memory, executive function and processing speed). [8–10]

The striatum belongs to the "pain matrix", which is a network of brain regions concerned with different functions of pain, such as processing the different dimensions of pain (eg, sensory-discriminative, affective-emotional and cognitive-evaluative).[11–13] The striatum does not seem to encode the sensory-discriminative dimension of pain, which consists of the location, timing, and physical characteristics (eg, mechanical, chemical, and heat) of the noxious stimuli. The striatum is predominantly concerned with the affective-motivational and cognitive-evaluative dimension of pain.[11,14–16] These dimensions are important for the burden, the degree of suffering, feelings of unpleasantness of pain and remembering, interpreting and responding adequately to pain.[13] Besides involvement in these dimensions of pain, the striatum also has an analgesic function.[17,18] For instance, microinjection of morphine directly into the marginal divisions of the striatum resulted in a dose-dependent, naloxone-reversible hypoalgesia.[19,20] Furthermore, a high concentration of endogenous opiates and their receptors are found in the striatum.[21,22] The other brain regions of the 'pain matrix' and their proposed dimensions of pain include the anterior cingulate cortex (affective and cognitive), insula (affective and cognitive), thalamus (sensory-discriminative and affective), amygdala (affective), prefrontal cortex (affective and cognitive) and the primary and secondary somatosensory cortices (sensory-discriminative).[12,13,23] Based on magnetic resonance imaging studies, atrophy of these areas has been found in (pre) manifest HD. Disease progression is correlated with an increase in atrophy of these areas.[2,24–26]

Studies focusing on pain in patients with HD demonstrate conflicting results. For instance, in a study of 19 patients with HD, 11 patients reported a maximum score on pain, but only 3 received analgesics.[27] In a case report, 2 patients with HD were described with intense, intermittent sharp, shooting pain; one of them eventually committed suicide.[28] In a more recent HD case-report, a marathon runner complained

about severe exercise-induced muscle pain after running, which hampered his running.[29] In a preliminary study in 90 patients with premanifest HD, 49% of the participants used analgesics, compared with 14% in the general population.[30] However, experimental studies with laser-evoked potentials and somatosensory-evoked potentials in patients with HD demonstrate a slowing of pain processing.[31–33] Slowing of pain processing may interfere with sensory-motor integration and may cause an inadequate motor response in reaction to painful events. The authors proposed that these findings were in line with the clinical observations that patients do not complain about pain.

Considering the devastating effect of HD on the different brain areas of the "pain matrix" and the conflicting findings about pain in patients with HD, it is remarkable that attention is seldom paid to pain. The lack of systematic studies on this matter could consequently lead to an underestimation of the prevalence of pain, and, when untreated, it could potentially cause secondary symptoms such as decreased mobility, impaired sleep, chronic pain, and an affect on quality of life (QoL).[34] Furthermore, identifying pain in patients may be particularly challenging due to the cognitive disturbances in HD. It is well-known that, in patients with cognitive disturbances, pain can manifest atypically (eg, agitation, increased confusion and depression).[35–37] The aim of this review is, therefore, to investigate the prevalence of pain and its burden (unpleasantness) in HD by performing a systematic literature search. The pain burden will be compared with that in the general population. The hypothesis is that the pain burden in patients with HD is less than in the general population, due to an affected affective-emotional and cognitive-evaluative dimension of pain.

2. Methods

2.1 Search strategy

We used Pubmed, Embase, Cinahl, Cochrane and PsycINFO as an electronic bibliographic database. The systematic search was carried out on February 15, 2018. The search strategy consisted of medical subject headings (*eg*, MESH) and free terms relating to pain and HD (Table 1 and supplementary material: Appendix A). In addition, we identified articles through hand searching from reference lists of previously published articles.

Table 1. The search strategy which was used in Pubmed.

Search	Query	Items found
#3	#1 AND #2	641
#2	"Pain"[Mesh] OR "Pain Measurement"[Mesh] OR "Hyperalgesia"[Mesh] OR "Pain Perception"[Mesh] OR pain*[tiab] OR ache*[tiab] OR nocicepti*[tiab] OR neuralgia*[tiab] OR hyperalgesi*[tiab] OR analgesi*[tiab] OR allodyni*[tiab] OR vas[tiab] OR visual analog scale*[tiab] OR formalin[tiab] OR "Quality of Life"[Mesh] OR "Health Status Indicators"[Mesh] OR SF-36*[tiab] OR SF36[tiab] OR SF-12[tiab] OR SF12[tiab] OR SF-20[tiab] OR SF20[tiab] OR RAND-36[tiab] OR RAND36[tiab] OR EQ-5D*[tiab] OR EQ5D*[tiab] OR Health related Quality of Life[tiab] OR Qol[tiab] OR Hrql[tiab] OR hrqol[tiab] OR medical outcome stud*[tiab] OR MOS[tiab] OR health utilities index[tiab] OR health utility index[tiab] OR hui[tiab] OR hui2[tiab] OR hui3[tiab] OR hui-2[tiab] or hui-3[tiab] OR health status indicator*[tiab] OR health status inde*[-tiab] OR Nottingham Health Profile*[tiab] OR Health Status Questionnaire[tiab] OR HSQ [tiab] OR Duke Health Profile[tiab]	1,245,397
#1	"Huntington Disease"[Mesh] OR huntington*[tiab] OR chronic progressive hereditary chorea[tiab]	17,148

2.2 Selection of studies

For inclusion, studies had to meet the following criteria: present primary (percentage) data, including the prevalence of pain in patients with HD and the pain burden (mean and SD). There was no restriction in terms of the type of pain or pain measurements. All languages and the following types of study were included: cross-sectional, (non)-randomized controlled trial, prospective, and retrospective study. Excluded were case series ($n < 6$), poster presentations, studies in which pain was an exclusion criterion, and juvenile HD. The titles and abstracts of studies were independently screened for eligibility by two reviewers (G.P.S. and K.F.v.d.Z.). After reaching consensus, they reviewed the full text of the selected articles. If the 2 reviewers failed to reach a consensus, a third reviewer (W.P.A.) was available. The protocol of this review has been published in Prospero, number: CRD42018090961.

2.3 Assessment of risk of bias

The literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[38] Bias assessment was performed using the modified and enhanced version (13-items) of the Research Triangle Institute item bank, developed by the Agency for Healthcare Research and Quality.[39] This is a tool for evaluating the quality of observational studies with a focus on bias and confounding.[40] The Research Triangle Institute bank was found to provide a more complete quality assessment than the Newcastle Ottawa Scale.[40] The selection bias, detection bias, attrition bias, selective outcome performance and confounding variables were evaluated with the grading system advised by Cochrane.[41] For each

question, three options were possible: "+" = low risk of bias, "-" possible risk of bias, and "?" risk of bias unclear (due to poor reporting). As advised by the Agency for Healthcare Research and Quality, the 13-item tool has been slightly modified in order to assess the risk of bias of the studies included in this review. The advice stated by the Agency for Healthcare and Research Quality was used through the modification procedure (Supplementary material: Appendix B). To improve the inter-rater reliability in assessing and grading the biases, two reviewers (K.F.v.d.Z. and G.P.S.) applied the tool to 5 different studies to calibrate the evaluation procedure.

2.4 Data extraction and synthesis

The following data were extracted: study design, setting, sample size, age, sex, Unified Huntington Disease Rating Score (UHDRS)- Motor score[42], UHDRS-TFC[42], stage of disease, depression/ anxiety, type of pain tool, prevalence of pain, and pain burden. The prevalence had to be reported in percentages or it had to be possible to calculate this based on the data presented. The pain burden had to be reported as a mean (SD) score. The pain burden was stated as the sum score of the severity and the interference of pain in daily life. This was calculated using the sum score of the bodily pain items of the 36-item Short Form Health Survey (SF-36).

2.5 Analysis

A comprehensive meta-analysis program (3.0) was used to conduct the meta-analysis.[43] The prevalence (eg, %) of pain in patients with HD was analysed as well as the pain burden which was compared with that in the general population. To calculate the prevalence of pain, any type of pain was included without any consideration for the severity of type of pain. The pain burden was based on the bodily pain domain of the SF-36. The SF-36 contains 36 items grouped in 8 domains: physical functioning, role limitations (physical problems), bodily pain, general health, vitality, social functioning, role limitations (emotional problems), and mental health. The bodily pain domain comprises 2 items: pain intensity and pain interference during the last 4 weeks. There are 5 possible answer categories (eg, score from 1 [none at all] to 5 [extremely]). Every domain is scored on a 0 to 100 range, where 100 represents the lowest symptom burden.[44] The norms of the SF-36 were used to compare the symptom burden with that of the general population.[44] Heterogeneity was assessed with the Q statistic and the I^2 index.

3. Results

3.1 Study selection and characteristics

The electronic systematic search yielded 2234 eligible citations: Pubmed (641), Embase (1404), PsycINFO (97), Cinahl (70) and Cochrane Library (22). After removing duplicates, 1810 were screened for eligibility based on title and abstract. In total, 361 studies underwent full-text scanning, producing 15 studies which met the criteria for inclusion in the review (Table 2). Reasons for exclusion are reported in the PRISMA flowchart (Figure 1). Of the 15 studies (Table 2), 8 reported the prevalence of pain[32,33,45–50] and 7 reported the pain burden in patients with HD[51–57](Tables 4 and 5, respectively). Overall, the data were based on 11 cross-sectional studies[45,46,57,47–52,54,55], 2 randomized controlled trials[53,56] and 2 interrupted time series designs[32,33]. Participant selection was through a registry in 5 studies[46,48,51,52,57], an HD clinic in 4 studies[53–56], a neurological science department in 2 studies[32,33], a collaboration of academic centers in one study[50], a general neurological department in one study[49] and one study collected the participant from a hospice[47]. Different instruments for pain measurement were reported; 8 studies used the SF-36[48,51–57], 4 studies the EQ-5D-3L[45,46,49,50], one study a web-based survey with a pain item[47] and in 2 studies the physician assessed pain with the Visual Analogue Scale (VAS)[32] or Brief Pain Inventory (BPI).[33]

Table 2. Summary of the characteristics of the included studies (n = 15).

Source: First Author (refs) Country	Study Design	Setting/ Register	N	Pain measurement
Arran et al.[51] United Kingdom	Cross-sectional study	European HD Network Registry	87	SF-36
Brugger et al.[52] Germany	Cross-sectional study	European HD Network Registry; University department for neurology and psychiatry	80	SF-36
Busse et al.[53] United Kingdom	Randomized controlled trial	HD clinic	HD Exercise: 16 HD Control: 15	SF-36
Calvert et al.[45] United Kingdom	Cross-sectional study	HD association	53	EQ-5D-3L
Dorey et al.[46] France	Cross-sectional study	Euro-HDB Registry	55	EQ-5D-3L
Ho et al. [54] United Kingdom	Cross-sectional study	HD clinic	70	SF-36
Ho et al.[55] United Kingdom	Cross-sectional study	HD clinic	79	SF-36

Table 2. Summary of the characteristics of the included studies (n = 15). (continued)

Source: First Author (refs) Country	Study Design	Setting/ Register	N	Pain measurement
Johnson et al.[47] USA	Cross-sectional study	Hospice	101	Suncoast Solutions Electronic Health Record Software
Khalil et al.[56] United Kingdom	Randomized controlled trial	HD clinic	HD Exercise:11	SF-36
			HD Control: 10	
Read et al.[57] United Kingdom	Cross-sectional study	TRACK-HD Registry	HD Stage I: 75	SF-36
			HD Stage II: 42	
			HD Pre-A*: 61	
			HD Pre-B**: 57	
			Siblings: 36	
			Partners: 84	
Tommaso et al.[32] Italy	Interrupted time series (without comparison group)	Neurological science department	28	VAS
Tommaso et al.[33] Italy	Interrupted time series (with comparison group)	Neurological science department	HD: 44	BPI
			PHD: 10	
			Healthy Control: 64	
Underwood et al.[48] United Kingdom	Cross-sectional study	EHDN- registry	PHD: 263	SF-36
			HD Stage I: 296	
			HD Stage II: 327	
			HD Stage III: 359	
			HD Stage IV/V: 139	
Varda et al.[49] Cyprus	Cross-sectional study	Neurology Clinic	32	EQ-5D-3L
Van Walsem et al.[50] Norway	Cross-sectional study	Academic medical centers and Center for Rare Disorders	HD Stage I: 12	EQ-5D-3L
			HD Stage II: 22	
			HD Stage III: 19	
			HD Stage IV: 14	
			HD Stage V: 17	

*Premanifest group A (Pre-A): predicted years of onset > 10.8 years; **Premanifest group B (Pre-B): predicted years of onset < 10.8 years; BPI, Brief Pain Inventory; C, control group; EHDN, European Huntington's Disease Network; Euro-HDB, European Huntington's Diseases Burden survey; EQ-5D-3L, EuroQoL-5D-3L; N, number of participants; HD, Huntington's disease; PHD, premanifest Huntington's disease; SF-36, Short-Form Health Survey; Shoulsen Stage of disease progression (I, II, III, IV or V), VAS, Visual Analogue Scale.

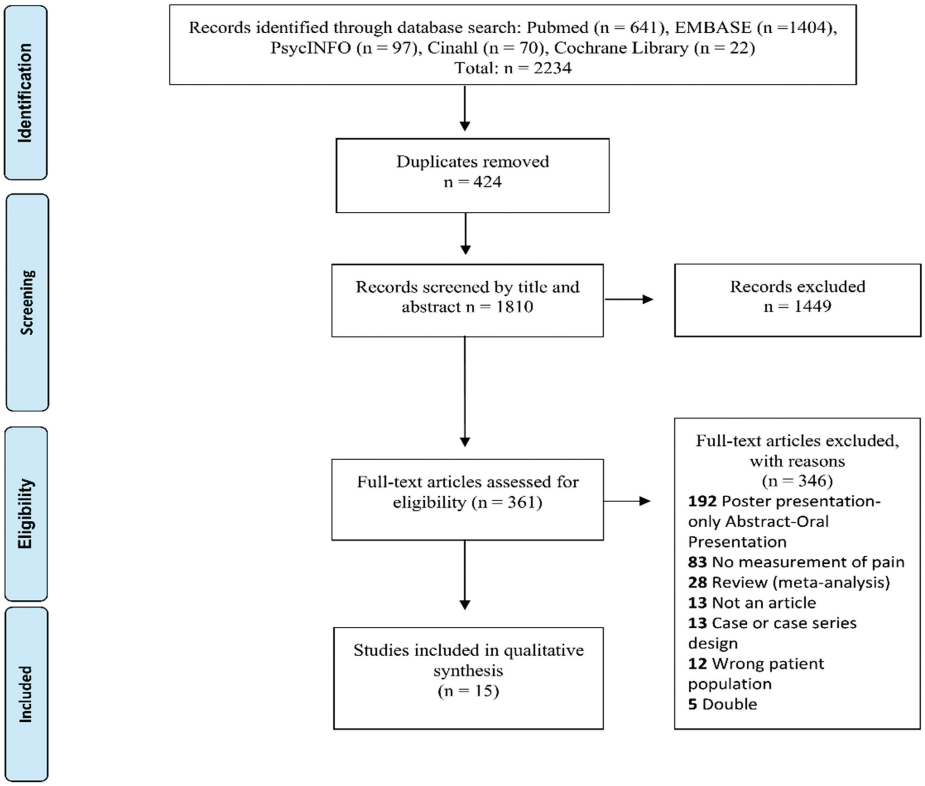

Figure 1. PRISMA flowchart showing the process of selection of studies for the review.

3.2 Quality assessment

The quality assessment was conducted on the 15 included studies (Table 3), possible risk of selection bias, and confounding variables being present in the majority. Selection bias was mostly caused by unclear inclusion and exclusion criteria and selective recruiting of participants. Confounding variables were due to lack of clarity about whether or not the included patients were genetically diagnosed with HD, the stage of disease, the years of onset of disease, separate data concerning sex, psychiatric disturbances, or drug treatment. One of the 15 studies scored the lowest possible risks of biases.[56] They only reported the pain burden. Most studies reporting the prevalence of pain in HD did have a possible risk regarding the selection bias, attrition bias, detection bias, and confounding variables.[32,33,45–50] Moreover, 3 studies did not describe whether the scores on the pain measurements were dichotomized or categorized.[32,33,47] The same risks of biases were found in the 6 studies reporting

the pain burden.[51–55,57] Despite the different shortcomings of the 15 studies, they were all included for further analysis.

Table 3. Quality assessment of the included studies (n = 15).

Study	Selection bias			Detection bias	Attrition bias		Selective outcome performing	Confounding		Overall Assessment
	Inclusion/ exclusion criteria formulated	Selective recruiting participants	Selection control group inappropriate	Valid and reliable measurements	Length follow-up	Impact missing data	Primary outcome missing	Balance allocation between groups	Confounding variables	Overall assessment
Arran et al.[51]	-	-	N/A	-	N/A	-	+	N/A	-	+
Brugger et al.[52]	-	-	N/A	+	N/A	?	+	N/A	-	+
Busse et al.[53]	+	-	+	+	+	+	+	-	+	+
Calvert et al.[45]	-	-	N/A	-	N/A	-	+	N/A	-	+
Tommaso et al.[32]	+	-	N/A	+	N/A	?	+	N/A	+	+
Tommaso et al. [33]	+	-	+	+	N/A	?	+	-	-	+
Dorey et al.[46]	-	-	N/A	-	N/A	-	+	N/A	-	+
Ho et al.[54]	-	-	N/A	-	N/A	?	+	N/A	-	+
Ho et al.[55]	-	-	N/A	+	N/A	+	+	N/A	-	+
Khalil et. al[56]	+	-	+	+	+	+	+	+	+	+
Johnson et al.[47]	-	-	N/A	?	N/A	?	?	N/A	-	+
Read et al.[57]	-	-	+	+	N/A	?	+	N/A	+	+
Underwood et al.[48]	-	-	N/A	+	N/A	?	+	N/A	+	+
Van Walsem et al.[50]	-	-	N/A	+	N/A	+	+	N/A	-	+
Varda et al.[49]	-	-	N/A	+	N/A	+	+	N/A	-	+

Low risk of bias (+); Possible risk of bias (-); Risk of bias unclear (due to poor reporting) (?); Not available (N/A).

3.3 Overall sample

The 15 published reports provided information on 2578 patients with HD. The sample size ranged from 10 to 1474, the proportion female/ male was equal, and the mean age of the participants was 50 (range 36-64; SD 6.3) years. In 7 studies, the UHDRS-motor score[33,52–57] was reported, and in 6 studies, the UHDRS-TFC score[33,46,52,53,56,57] was described (Tables 4 and 5). The mean UHDRS-motor score and UHDRS-TFC score were respectively, 27.3 (SD 16.5) and 10.7 (SD 3.7). The UHDRS-motor and UHDRS-TCF of patients with manifest HD were respectively, 34.6 (SD 10.4) and 9.8 (SD 4.0).

3.4 Prevalence of pain

In total, 8 studies, representing a sample size of 1861 patients with HD, age range 36 - 57 years, reported the prevalence of pain (Table 4). A random-effect meta-analysis demonstrated a sample-weighted prevalence of pain of 41.3 % (95% confidence interval: 36% - 46%, Figure 2) with substantial heterogeneity (I^2 = 75.3%). The prevalence ranged from 10% to 75% (Table 4). Four studies measured the prevalence of pain with the EQ-5D-3L[45,46,49,50] and the other studies used the SF-36[48], VAS[32], BPI[33] or a specific software system.[47] In only 4 studies was pain severity a consideration in the reporting of pain prevalence.[45,46,49,50] Furthermore, 6 studies evaluated the presence of pain in the last 24-hours,[32,33,45,46,49,50], one study in the last 4 weeks[48] and in one study, it was not clear which question(s) was asked regarding the presence of pain.[47]

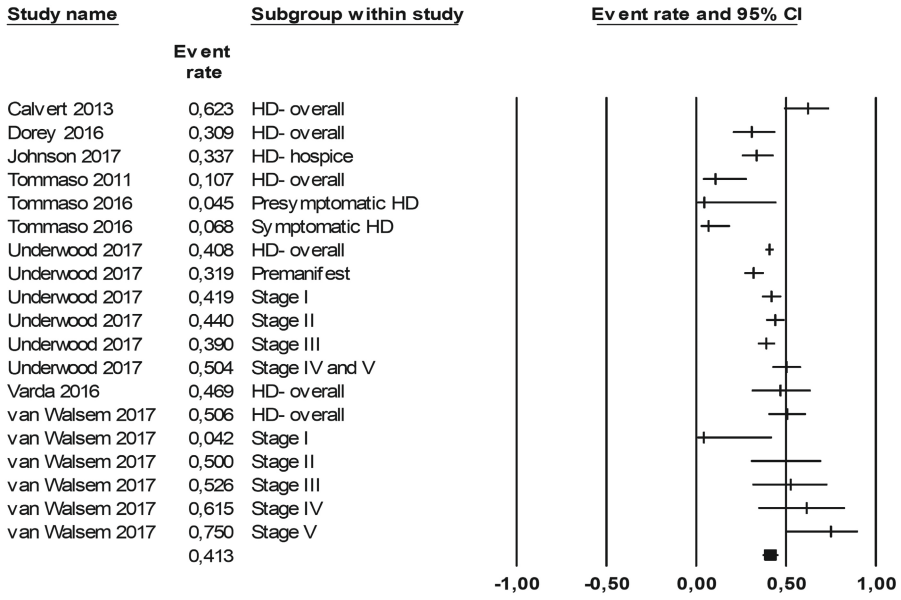

Figure 2. Random effects meta-analysis of studies that examined the prevalence of pain in patients with Huntington's Disease

Table 4. Summary of study findings (Prevalence of pain, n = 8).

Author	Mean age in years (SD), range	Female/ Male	UHDRS-TMS Mean (SD)	UHDRS-TFC Mean (SD)	Depression Mean (SD) or percentage	Anxiety Mean (SD) or percentage	Stage of Disease (N)	Prevalence of Pain (%)
Calvert et al.[45]	57.1 (15.4)	24/ 29	N/A	N/A	*EQ-5D-3L:* No: 13.21%; Moderate: 67.92% Extreme: 18.87%		N/A	No: 37.74% Moderate: 50.94% Severe: 11.32%
Dorey et al.[46]	49.66 (13.66)	28/ 27	N/A	3.06 (2.53)	*H-CSRI*: 9.12 (5.01) *EQ-5D-3L*: No: 37%; Moderate: 44%; Extreme: 19%		N/A	No: 69% Moderate: 24% Severe: 7%
Johnson et al.[47]	57 (IQR 48-65)	53/ 48	N/A	N/A	N/A	29.7%	N/A	33.7%
Tommaso et al.[32]	50.32 (10.36)	14/ 14	N/A	N/A	N/A	N/A	N/A	10.7%
Tommaso et al.[33]	HD: 54 (11.50)	HD: 20/ 22	HD: 32.93 (18.97)	HD: 8.92 (3.33)	N/A	N/A	N/A	13.6%
	PHD: 36.62 (8.61)	PHD: 5/ 5	PHD: 4.1 (4.33)	PHD: 13 (0)				0%
Underwood et al.[48]	49 (13.8)	787/ 687	N/A	N/A	N/A	N/A	PHD: 263	32%
							I: 296	42%
							II:327	44%
							III: 359	39%
							IV/V: 139	50%
							Overall: 1474	40.8%

Table 4. Summary of study findings (Prevalence of pain, n = 8).

Author	Mean age in years (SD), range	Female/ Male	UHDRS-TMS Mean (SD)	UHDRS-TFC Mean (SD)	Depression Mean (SD) or percentage	Anxiety Mean (SD) or percentage	Stage of Disease (N)	Prevalence of Pain (%)
Varda et al.[49]	52.5 (N/A) Median IQR:20.5	20/ 12	N/A	N/A		EQ-5D-3L: No: 25% Moderate: 59.38% Severe: 15.63%	N/A	No: 53.13% Moderate: 40.63% Severe: 6.25%
Van Walsem et al. [50]	56.7 (11.4)	37/47	N/A	N/A		EQ-5D-3L: No: 75% Moderate: 25% Severe: 0%	I: 12	No: 92% Moderate: N/A Severe: N/A
						No: 23% Moderate: 73% Severe: 5%	II: 22	No: 50% Moderate: 45% Severe: 5%
						No: 37% Moderate: 53% Severe: 10%	III: 19	No: 47% Moderate: 47% Severe: 6%
						No: 21.5% Moderate: 57% Severe: 21.5%	IV: 14	No: 38.5% Moderate: 54% Severe: 7.5%
						No: 17.5% Moderate: 65% Severe: 17.5%	V: 17	No: 24% Moderate: 71% Severe: N/A
						Overall: 68.2%	Overall: 84	Overall: 51.2%

Ass. I or II, Assessment one or two; C, Control group; E, Experimental Group; EQ-5D, EuroQoL-5D; H-CSRI, Huntington Clinical Self-Reported Instrument; IQR, Interquartile range; M, mean; N/A, not available; N, number of participants; PHD, premanifest Huntington's disease; SF-36, study 36-item Short Form Health Survey; TFC, Total Functional Capacity scale; UHDRS-TMS, Unified Huntington's Disease Rating scale- Total Motor Score; Shoulsen Stage of disease progression (I, II, III, IV or V).

3.5 Pain burden in Huntington's disease

Seven of the included studies reported the pain burden, measured with the SF-36 (Table 5). Despite contacting the authors, one study could not be included in the analysis due to missing data.[55] The sample size consisted of 603 patients with HD with an age range of 40 to 64 years. A random-effect meta-analysis on the SF-36 of 6 studies, showed a sample-weighted mean score of 84 (95% confidence interval: 81-86, Figure 3) with a substantial heterogeneity (I^2 = 52,64%). In the general population, the mean score of the pain burden is 70.8 (SD 25.5), a score of 100 representing the lowest symptom burden.[58] Based on these results, there is a significantly reduced pain burden in the HD population compared with the general population (p< 0.001).

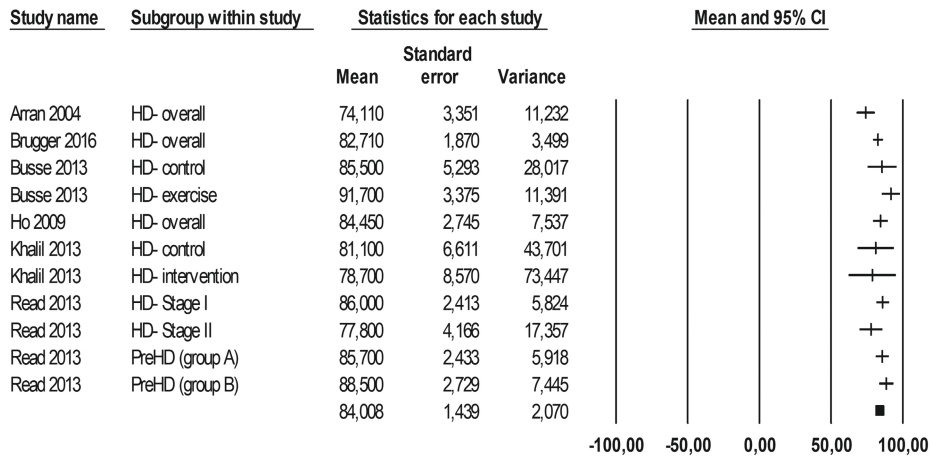

Figure 3. Random effects meta-analysis of studies that examined the mean score on Short-Form health survey-36 in patients with Huntington's disease.

Table 5. Summary of findings (pain burden, n = 7).

	Mean age in years (SD), range	Female/ Male	UHDRS-TMS, mean (SD)	UHDRS-TFC, mean (SD)	Depression mean (SD), or percentage	Anxiety mean (SD), or percentage	Stage of Disease (N)	SF-36 mean (SD)
Arran et al.[51]	Range 55-64	49/ 38	N/A	N/A	HADS: 8.25 (5.23)	HADS: 7.23 (4.94)	N/A	74.11 (31.26)
Brugger et al.[52]	49.6 (13.4)	37/ 43	28.67 (19.60)	18.78 (6.26)	BDI: 6.44 (5.82) HRS: 6.03 (5.36)	N/A	N/A	82.71 (16.73)
Busse et al.[53]	HD Exercise: 53.5 (12.5)	8/ 8	32.4 (15.5)	8.4 (2.6)	N/A	N/A	N/A	91.7 (13.5)
	HD Control: 47.4 (9.5)	7/ 8	35.2 (20.5)	8.9 (3.1)				85.5 (20.5)
Ho et al.[54]	50.13 (11.91)	35/35	24.37 (18.26)	N/A	BDI: 7.60 (7.11)	N/A	N/A	84.45 (22.97)
Ho et al.[55]	55.24 (11.92)	31/48	40.68 (20.68)	N/A	BDI: 10.65 (7.95)	N/A	N/A	88.3 (N/A)
Khalil et al.[56]	HD Exercise: 54.2 (9.9)	N/A	51.6 (15.9)	6.9 (2.8)	N/A	N/A	N/A	78.8 (30.9)
	HD Control: 51.3 (16.9)	N/A	50.5 (19.3)	6.0 (1.8)				81.1 (22.9)
Read et al.[57]	Stage I: 47.2 (10.3)	46/ 29	19.5 (9.3)	12.03 (0.9)	PBA-s: 2.5 (3.3)	PBA-s: 3.1 (3.2)	75	86.0 (20.9)
	Stage II: 51.2 (8.8)	19/23	30.2 (10.0)	8.6 (1.1)	PBA-s: 2.5 (3.1)	PBA-s: 4.1 (4.1)	42	77.8 (27.9)
	Pre-A*: 41.1 (8.7)	33/ 28	2.2 (1.4)	12.9 (0.4)	PBA-s: 2.4 (3.1)	PBA-s: 3.0 (3.2)	61	85.7 (19.0)
	Pre-B**: 40.2 (8.8)	32/ 29	2.8 (1.9)	12.8 (0.7)	PBA-s: 2.3 (2.8)	PBA-s: 2.8 (3.2)	57	88.5 (20.6)

BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; HD, Huntington's disease; HRS, Hamilton Rating Scale; N/A, not available; N, number of participants; PBA-s, Problem Behavior Assessments; Shoulsen Stage of disease progression (eg, Stage I, II, III, IV or V); TFC, Total Functional Capacity; UHDRS-TMS, Unified Huntington's Disease Rating Scale - Total Motor Score.

*Premanifest group A (Pre-A): predicted years of onset > 10.8 years **Premanifest group B (Pre-B): predicted years of onset < 10.8 years

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to provide a comprehensive overview of the prevalence of pain and the pain burden in patients with HD. The sample-weighted prevalence of pain in patients with HD was 41.3%, which is comparable to the prevalence in another neurodegenerative disease (Parkinson's disease [PD]: 40% - 60%).[59] Besides the prevalence, this meta-analysis demonstrates that the pain burden is significantly lower than that in the general population.

The findings could, however, be influenced by a variety of confounding variables such as age, sex, drug treatment, motor functions, cognitive, emotional and behavioral disturbances, co-morbidity, severity and duration of the disease, and site and types of pain (eg, nociceptive versus neuropathic and acute versus chronic pain). Of the studies included in this review, only one demonstrated a significant association between pain and age, sex, analgesic medication, motor functions, comorbid conditions, and severity of disease in HD.[48] Moreover, a higher score of depression and anxiety, taking analgesic medication, and having comorbid conditions were associated with an increase in the odds of greater pain severity in HD. However, behavioral disturbances (such as irritability) in HD were not associated with an increased chance of greater pain severity.[48] Other studies have demonstrated that pain could be a significant predictor for anxiety in HD[51,60], but the association between pain and depression in HD seems to be less clear.[55] It is worthwhile mentioning that the prevalence of depression in HD is around 40% and twice as high compared to the general population.[61,62] In Parkinson's disease, however, pain and depression have repeatedly been demonstrated as being inversely correlated.[63–65] It is likely that the same inverse correlation could be found in patients with HD. Besides the use of analgesics, the use of psychoactive drug could be an important variable influencing the pain prevalence and its burden. More specifically, neuroleptics (dopamine receptor blocking)[66,67] and antidepressants[68–70] frequently do have an analgesic effect. None of the studies in this review demonstrates the prevalence and the burden of pain in relation to the use of neuroleptics or antidepressants. It is worthwhile mentioning that only one study demonstrated no difference in laser-evoked pain between the HD group using neuroleptics and the group using no medication.[32] The findings concerning the prevalence of pain and its burden in this study could also be influenced by the fact that none of the included studies controlled for the different pain types (nociceptive versus neuropathic and acute versus chronic pain). Finally, cognitive disturbances in patients with HD could be a variable influencing the findings. For instance, one-third of the patients with HD are unaware of deficits (anosognosia).[71–74] Lack of awareness of impairments in memory, behavioral, executive, and motor functions has been described in HD.[75] It is

plausible that patients with HD may be unaware of pain. Furthermore, other cognitive disturbances, such as general slowing of thought processes, memory problems, and executive dysfunctions (problems in planning, initiating actions, and mental flexibility), have been demonstrated in HD.[76] These cognitive disturbances could (negatively) interfere with the capacity to understand the questions posed in pain tools and to communicate about the history of the experienced pain. It is important to note that the cognitive disturbance can occur 15 years before diagnosable motor onset, and so, early attention to choosing the right pain tool is advisable.[3,77–81]

Despite the potential confounding variables, it is striking that the meta-analysis demonstrates a significantly lower pain burden in HD compared with that in the general population. Firstly, this could be explained by an affected sensory-discriminative, emotional-affective, and cognitive-evaluative dimension of pain, causing an inadequate reaction to pain stimuli. As already mentioned, the striatum is involved in avoidance of pain or aversive stimuli[14,82,83], in minimizing physical harm[84], the subjective experience/salience of pain[85], motor response to pain[86] and the evaluation of painful stimuli.[87] In line with these results, one animal study demonstrated that pre-onset HD mice exhibited less pain behavior compared with a control group.[83] In addition, an impairment of painful stimuli transmission has been demonstrated in patients with HD, which may cause an impaired pain expression.[31–33] Furthermore, atrophy of other brain areas belonging to the pain matrix such as the anterior cingulate cortex, insula, thalamus, amygdala, prefrontal cortex, and the primary and secondary somatosensory cortices, has been demonstrated in (pre) manifest patients with HD.[2,24–26] Based on these findings, one might presume that all the dimensions of pain in patients with HD could be affected, resulting in a diminished pain burden.

The symptom burden and concerns of patients with HD vary during the different stages of the disease. In pre-manifest HD, most patients report problems in the social domain (eg, complicated family relationship and lack of support from environment), whereas in the manifest stage, physical themes are more frequently reported (swallowing food, driving performance, and walking).[88] It is understandable that due to the severity and extensiveness of HD in the different health domains, pain could be a minor problem affecting the QoL and is, therefore, less frequently reported.[89]

4.1 Strengths and limitations of this review

The strengths of this systematic review are the inclusion of 5 electronic databases, applying a standard study design according to the PRISMA guidelines, and having a standardized research protocol published in Prospero. In addition, the included studies are evaluated on the basis of different risks of bias with a validated tool.

This review does, however, have some limitations. The inclusion and exclusion criteria were broad, resulting in the inclusion of a wide variety of studies. The heterogeneity is, therefore, considerable. Furthermore, the included studies have several methodological shortcomings that could influence the reliability of the findings. Regarding the prevalence of pain, any type of pain was included in the analysis, without any consideration of the severity or type of pain. Furthermore, no specific inclusion criteria were set in the review about predefining the definition of pain (e.g. a cut-off score on a pain tool) or about the pain tool. Investigating the prevalence of pain was the main objective in only one study.[48] Confounding variables affecting the prevalence of pain and its burden are insufficiently controlled for and the findings are, therefore, mainly based on low quality studies. Furthermore, none of the included studies investigated the prevalence of pain, pain burden, and QoL in the same cohort. Nor did any of the studies include a control group to compare the findings. Most of the included studies were cross-sectional, and so, causality of the affected pain dimensions could not be determined. In this review, the pain burden has been compared with that in the general population; the norms could, however, be outdated.

4.2 Recommendations for future research

As well as taking into account the different confounding variables that could potentially affect the prevalence and the burden of pain, future research should investigate the prevalence of pain, pain burden, and QoL in the same cohort and compare the findings with a control group or updated norms. Furthermore, it is recommended that future studies predefine the definition of pain, according the International Association for the Study of Pain (IASP).[90] Reliable and validated pain tools should also be adopted. The gold standard for investigating pain is to use unidimensional patient's self-reported scales (such as the Numeric Rating Scale, VAS and Verbal Rating/ Descriptor Scale) in cognitively intact adults.[91] Multidimensional pain tools (for instance, short-form McGill Pain Questionnaire and the BPI) are recommended for assessing factors such as the quality and temporal sequence of pain, the affective contribution, and the patient's belief system.[92] As already mentioned, both unidimensional and multidimensional self-reported pain measurements require the capacity to understand the questions and to communicate about the pain experienced, which could be challenging in patients with HD because of cognitive disturbances.

4.3 Conclusions

This study revealed that the average prevalence of pain in HD is approximately 40%. In addition, patients with HD seem to have less of a pain burden compared with the general population. The results demonstrate that pain could be an important nonmotor symptom in patients with HD. It is, however, premature to generalize

these findings for the whole HD population. The lack of studies on this matter could consequently lead to an underestimation of pain or potential secondary symptoms, eventually resulting in lack of treatment and QoL. Larger and high-quality prospective cohort and clinical studies are, therefore, necessary to confirm these findings. Until then, awareness of pain and its burden in patients with HD is warranted in clinical practice.

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Chapter 2: Supplementary material

Appendix A: The search strategy which was used for the different electronic bibliographic databases:

Pubmed

Search	Query	Items found
#3	#1 AND #2	641
#2	"Pain"[Mesh] OR "Pain Measurement"[Mesh] OR "Hyperalgesia"[Mesh] OR "Pain Perception"[Mesh] OR pain*[tiab] OR ache*[tiab] OR nocicepti*[tiab] OR neuralgia*[tiab] OR hyperalgesi*[tiab] OR analgesi*[tiab] OR allodyni*[tiab] OR vas[tiab] OR visual analog scale*[tiab] OR formalin[tiab] OR "Quality of Life"[Mesh] OR "Health Status Indicators"[Mesh] OR SF-36*[tiab] OR SF36[tiab] OR SF-12[tiab] OR SF12[tiab] OR SF-20[tiab] OR SF20[tiab] OR RAND-36[tiab] OR RAND36[tiab] OR EQ-5D*[tiab] OR EQ5D*[tiab] OR Health related Quality of Life[tiab] OR Qol[tiab] OR Hrql[tiab] OR hrqol[tiab] OR medical outcome stud*[-tiab] OR MOS[tiab] OR health utilities index[tiab] OR health utility index[tiab] OR hui[tiab] OR hui2[tiab] OR hui3[tiab] OR hui-2[tiab] or hui-3[tiab] OR health status indicator*[tiab] OR health status inde*[tiab] OR Nottingham Health Profile*[tiab] OR Health Status Questionnaire[tiab] OR HSQ [tiab] OR Duke Health Profile[tiab]	1,245,397
#1	"Huntington Disease"[Mesh] OR huntington*[tiab] OR chronic progressive hereditary chorea[tiab]	17,148

Embase

Search	Query	Items found
#3	#1 AND #2	1,404
#2	'pain'/exp OR 'pain measurement'/exp OR 'pain assessment'/exp OR 'hyperalgesia'/exp OR 'nociception'/exp OR pain*:ab,ti,kw OR ache*:ab,ti,kw OR hyperalgesi*:ab,ti,kw OR allodyni*:ab,ti,kw OR nocicepti*:ab,ti,kw OR vas:ab,ti,kw OR 'visual analog scale*':ab,ti,kw OR formalin:ab,ti,kw OR 'quality of life'/exp OR 'health status indicator'/exp OR 'sf-36*':ab,ti,kw OR sf36:ab,ti,kw OR 'sf-12':ab,ti,kw OR sf12:ab,ti,kw OR 'sf-20':ab,ti,kw OR sf20:ab,ti,kw OR 'rand-36':ab,ti,kw OR rand36:ab,ti,kw OR 'eq-5d*':ab,ti,kw OR eq5d*:ab,ti,kw OR 'health related quality of life':ab,ti,kw OR qol:ab,ti,kw OR hrql:ab,ti,kw OR hrqol:ab,ti,kw OR 'medical outcome stud*':ab,ti,kw OR mos:ab,ti,kw OR 'health utilit* index':ab,ti,kw OR hui:ab,ti,kw OR hui2:ab,ti,kw OR hui3:ab,ti,kw OR 'hui 2':ab,ti,kw OR 'hui 3':ab,ti,kw OR 'health status indicator*':ab,ti,kw OR 'health status inde*':ab,ti,kw OR 'nottingham health profile':ab,ti,kw OR 'health status questionnaire':ab,ti,kw OR 'duke health profile':ab,ti,kw	1,928,255
#1	'huntington chorea'/exp OR huntington*:ab,ti,kw OR 'chronic progressive hereditary chorea':ab,ti,kw	27,920

PsycINFO

Search	Query	Items found
#3	S1 AND S2	97
2	DE ("Pain" OR "Aphagia" OR "Back Pain" OR "Chronic Pain" OR "Headache" OR "Myofascial Pain" OR "Neuralgia" OR "Neuropathic Pain" OR "Somatoform Pain Disorder" OR "Migraine Headache" OR "Muscle Contraction Headache" OR "Peripheral Neuropathy" OR "Trigeminal Neuralgia" OR "Complex Regional Pain Syndrome (Type I)" OR "Pain Management" OR "Pain Measurement" OR "Pain Perception" OR "Analgesia" OR "Pain Thresholds" OR "Somatosensory Disorders" OR "Nociceptors") OR ZM (pain OR "Quality of Life" OR "health status") OR TI (pain* OR ache* OR nocicepti* OR neuralgia* OR hyperalgesi* OR analgesi* OR allodyni* OR vas OR visual analog scale* OR formalin OR "SF-36*" OR SF36 OR "SF-12" OR SF12 OR "SF-20" OR SF20 OR "RAND-36" OR RAND36 OR "EQ-5D*" OR EQ5D* OR "Health related Quality of Life" OR Qol OR Hrql OR hrqol OR "medical outcome stud*" OR MOS OR "health utilit* index" OR hui OR hui2 OR hui3 OR hui-2 OR hui-3 OR "health status indicator*" OR "health status inde*" OR "Nottingham Health Profile*" OR "Health Status Questionnaire" OR "Duke Health Profile") OR AB (pain* OR ache* OR nocicepti* OR neuralgia* OR hyperalgesi* OR analgesi* OR allodyni* OR vas OR visual analog scale* OR formalin OR "SF-36*" OR SF36 OR "SF-12" OR SF12 OR "SF-20" OR SF20 OR "RAND-36" OR RAND36 OR "EQ-5D*" OR EQ5D* OR "Health related Quality of Life" OR Qol OR Hrql OR hrqol OR "medical outcome stud*" OR MOS OR "health utilit* index" OR hui OR hui2 OR hui3 OR hui-2 OR hui-3 OR "health status indicator*" OR "health status inde*" OR "Nottingham Health Profile*" OR "Health Status Questionnaire" OR "Duke Health Profile")	148,673
#1	DE "Huntingtons Disease" OR TI (huntington* OR chronic progressive hereditary chorea) OR AB (huntington* OR chronic progressive hereditary chorea)	4,498

CINAHL

Search	Query	Items found
S3	S1 AND S2	70
S2	MH (“Pain+” OR “Pain Measurement” OR “Pain Management” OR “Hyperalgesia” OR “Nociceptive Pain” OR “Allodynia” OR “Somatosensory Disorders+” OR “Visual Analog Scaling” OR “Quality of Life+” OR “Health Status Indicators” OR “Short Form-36 Health Survey (SF-36)”) OR TI (pain* OR ache* OR nocicepti* OR neuralgia* OR hyperalgesi* OR analgesi* OR allodyni* OR vas OR “isual analog scale*” OR formalin OR “SF-36*” OR SF36 OR “SF-12” OR SF12 OR “SF-20” OR SF20 OR “RAND-36” OR RAND36 OR “EQ-5D*” OR EQ5D* OR “Health related Quality of Life” OR Qol OR Hrql OR hrqol OR “medical outcome stud*” OR MOS OR “health utilit* index” OR hui OR hui2 OR hui3 OR hui-2 OR hui-3 OR “health status indicator*” OR “health status inde*” OR “Nottingham Health Profile*” OR “Health Status Questionnaire” OR “Duke Health Profile”) OR AB (pain* OR ache* OR nocicepti* OR neuralgia* OR hyperalgesi* OR analgesi* OR allodyni* OR vas OR “visual analog scale*” OR formalin OR “SF-36*” OR SF36 OR “SF-12” OR SF12 OR “SF-20” OR SF20 OR “RAND-36” OR RAND36 OR “EQ-5D*” OR EQ5D* OR “Health related Quality of Life” OR Qol OR Hrql OR hrqol OR “medical outcome stud*” OR MOS OR “health utilit* index” OR hui OR hui2 OR hui3 OR hui-2 OR hui-3 OR “health status indicator*” OR “health status inde*” OR “Nottingham Health Profile*” OR “Health Status Questionnaire” OR “Duke Health Profile”)	257,947
S1	(MH “Huntington’s Disease”) OR TI (huntington* OR “chronic progressive hereditary chorea”) OR AB (huntington* OR “chronic progressive hereditary chorea”)	1,152

Cochrane Library

Search	Query	Items found
#3	#1 AND #2	22
#2	pain* OR ache* OR nocicepti* OR neuralgia* OR hyperalgesi* OR analgesi* OR allodyni* OR vas OR visual analog scale* OR formalin OR “SF-36*” OR SF36 OR “SF-12” OR SF12 OR “SF-20” OR SF20 OR “RAND-36” OR RAND36 OR “EQ-5D*” OR EQ5D* OR “Health related Quality of Life” OR Qol OR Hrql OR hrqol OR “medical outcome stud*” OR MOS OR “health utilit* index” OR hui OR hui2 OR hui3 OR “hui-2” OR “hui-3” OR “health status indicator*” OR “health status inde*” OR “Nottingham Health Profile*” OR “Health Status Questionnaire” OR “Duke Health Profile”:ti,ab,kw (Word variations have been searched)	150,260
#1	huntington* OR “chronic progressive hereditary chorea”:ti,ab,kw (Word variations have been searched)	471

Chapter 2: Supplementary material

Appendix B: The enhanced version (13-items) of the Research Triangle Institute (RTI) item bank, to assess the risk of biases.

Question	***Formulation question*** *Instructions for principal investigator (PI) and/or abstractor*	***Modified version***	***Type of bias***
Q1	**Do the inclusion/exclusion criteria vary across the comparison groups of the study?** [*PI: Drop question if not relevant to all included studies. To use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals.]*	**Are the inclusion and exclusion criteria clearly formulated?**	**Selection bias**
Q2	**Does the strategy for recruiting participants into the study differ across groups?** *[PI: Drop question if not relevant to all included studies. If the recruitment strategy results in pre-intervention differences in prognostic factors that could explain the selection of the intervention and the outcome, confounding can occur. If the strategy results in the selective and differential inclusion of patients (such as prevalent rather than new users), selection bias can occur. To use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals.]*	**Does the strategy for recruiting participants into the study differ across individuals? (For example from registry, hospital, specialized clinical setting).**	**Selection bias, Confounding**

Question	*Formulation question* *Instructions for principal investigator (PI) and/or abstractor*	*Modified version*	*Type of bias*
Q3	**Is the selection of the comparison group inappropriate?** *[PI: Provide instruction to the abstractor based on the type of study. Interventions with community components are likely to have contamination if all groups are drawn from the same community. Interventions without community components should select groups from the same source (e.g., community or hospital) to reduce baseline differences across groups. For case-control studies, controls should represent the population from which cases arose; that is, controls should have met the case definition if they had the outcome.]*	**Is the selection of the comparison group inappropriate? (Only applicable if control group present)** Consider HD-clinic versus population based	**Selection bias, confounding**
Q4	**Does the study fail to account for important variations in the execution of the study from the proposed protocol?** *[PI: Consider intensity, duration, frequency, route, setting, and timing of intervention/exposures. Drop if not relevant for body of literature.]*	**Not relevant for the included studies**	**Performance bias**
Q5	**Was the assessor not blinded to the outcome, exposure, or intervention status of the participants?** *[PI: Clinical assessors may not always be blinded to exposure/intervention as well as outcome status. For studies where patients are selected based on outcome (e.g., casecontrol), blinding to exposure or intervention status is particularly important. For designs where patients are selected based on exposure status (e.g., cohorts), blinding to outcomes is particularly important. Drop if not relevant to the body of literature.]*	**Not relevant for the included studies**	**Detection bias**

Question	*Formulation question* *Instructions for principal investigator (PI) and/or abstractor*	*Modified version*	*Type of bias*
Q6	**Were valid and reliable measures not used or not implemented consistently across all study participants to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant benefits and harms, and potential confounders?** *[PI: Important measures should be identified for abstractors and if there is more than one, they should be listed separately. PI may need to establish a threshold for what would constitute acceptable measures based on study topic. When subjective or objective measures could be collected, the PI will need to consider if subjective measures based on self-report should be considered as being less reliable and valid than objective measures such as clinical reports and lab findings. Some characteristics may require that sources for establishing their validity and/or reliability be described or referenced. If so, provide instruction to abstractors.]*	**Are valid and reliable measures implemented?** - Reliable and conventional ascertainment of HD? - Reliable and conventional ascertainment of pain, depression and anxiety?	**Detecion bias, confoudnding**

<table>
<tr><th>Question</th><th>Formulation question
Instructions for principal investigator (PI) and/or abstractor</th><th>Modified version</th><th>Type of bias</th></tr>
<tr><td>Q7</td><td>Was the length of followup different across study groups?
[Abstractor: When followup was the same for all study participants, the answer is no. If different lengths of followup were adjusted by statistical techniques, (e.g., survival analysis), the answer is no. Studies in which differences in followup were ignored should be answered yes.]</td><td>Is the length of follow-up the same across individuals or study group?
Only applicable in a follow-up study.</td><td>Attrition bias</td></tr>
<tr><td>Q8</td><td>In cases of missing data (e.g., overall or differential loss to followup for cohort studies or missing exposure data for case-control studies), was the impact not assessed (e.g., through sensitivity analysis or other adjustment method)?
[PI: For cohort studies, attrition is measured in relation to the time between baseline (allocation in some instances) and outcome measurement for both retrospective and prospective studies and could include data loss from switching. Attrition rates may vary by outcome and time of measurement. Specify the criterion to meet relevant standards for the topic. Specify measurement period of interest, if repeated measures. For case-control studies, evaluate missing data in relation to exposure status.]</td><td>In case of missing data, was the impact not assessed?
<table><tr><td colspan="2"></td><td>Present</td><td></td></tr><tr><td rowspan="3">Described</td><td></td><td>Yes</td><td>No</td></tr><tr><td>Yes</td><td>+</td><td></td></tr><tr><td>No</td><td>-</td><td>?</td></tr></table></td><td>Attrition bias, detection bias</td></tr>
</table>

Question	*Formulation question* *Instructions for principal investigator (PI) and/or abstractor*	*Modified version*	*Type of bias*
Q9	**Are any important primary outcomes missing from the results?** *[PI: Identify all primary outcomes that one would expect to be reported in the study,* *including timing of measurement.]*	**Are any important primary outcomes missing from the results?** The dependent variable has been mentioned in the introduction and presented in the result section (Table or text).	**Selective outcome reporting**
Q10	**Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?** *[PI: Identify all important harms that one would expect be reported in the study,* *including timing of measurement. Drop if not relevant to body of literature.]*	**Not relevant for the included studies**	**Selective outcome reporting**
Q11	**Did the study fail to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)?** *[PI: Drop if not relevant to the body of evidence.]*	**Did the study fail to balance the allocation between groups or match group?** Only applicable if control group present**.**	**Confounding**
Q12	**Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?** *[PI: Provide instruction to abstractors on known confounding variables and inadequate* *adjustment for confounding for each outcome.]*	**Were important confounding variables not taken into account in the design and/or analysis?** **Stratified by importance:** **1.** Genetic diagnosis HD, Stage of Disease, Years of onset disease, Gender **2.** Psychiatric disturbances, drug treatment. **3.** Calculation of group differences has been done.	**Confounding**

Question	*Formulation question* *Instructions for principal investigator (PI) and/or abstractor*	*Modified version*	*Type of bias*
Q13	**Are results believable taking study limitations into consideration?** *[Abstractor: This question is intended to capture the overall quality of the study.Consider issues that may limit your ability to interpret the results of the study. Review responses to earlier questions for specific criteria.]*	**Are the result believable taking study limitations into consideration?**	**Overall assessment**