Data Supplement for Zadegan et al., Frequency and Pathophysiology of Apathy in Huntington Disease: A Systematic Review and Meta-Analysis, Journal of Neuropsychiatry and Clinical Neurosciences (doi: 10.1176/appi.neuropsych.20220033).

Appendix 1 – Search strategy

PubMed (Medline)

(("Huntington Disease"[Mesh])
OR "huntington disease"
OR "huntington's disease"
OR "huntington chorea"
OR "huntington's chorea"
OR "huntington's"
OR "huntington")
AND
(("Apathy"[Mesh])
OR "apath*"
OR "blunting of affect"
OR "blunted affect"
OR "emotional* blunt*"
OR "emotional coldness"
OR "emotional detachment"
OR "emotional responsiv*"
OR "amotivat*"
OR "diminished motivation"
OR "lack of motivation"
OR "loss of motivation"
OR "motivation loss"
OR "diminished interest"
OR "lack of interest"
OR "loss of interest"
OR "interest loss"
OR "disinterest*"
OR "diminished initiat*"
OR "lack of initiat*"
OR "loss of initiat*"
OR "abulia"
OR "inertia"
OR "psychic akinesia"
OR "loss of psychic self activation"
OR "athymi*"
OR "avolition"
OR "asocial*"
OR "diminished social"
OR "loss of social"
OR "anhedonia"
OR "diminished pleasure"
OR "lack of pleasure"
OR "loss of pleasure"
OR "diminished enthusiasm"
OR "loss of enthusiasm"
OR "indifference"
OR "diminished drive"

OR "letharg*"
OR "goal directed"
OR "goal oriented"
OR "listless*"
OR "dispassion*")

Ovid

- MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to November 04, 2021
- APA PsycInfo 1967 to November Week 1 2021

1. exp Huntington Disease/
2. huntington* disease.mp.
3. huntington* chorea.mp.
4. huntington*.mp.
5. 1 or 2 or 3 or 4
6. exp Apathy/
7. apath*.mp.
8. emotional* blunt*.mp.
9. emotional coldness.mp.
10. emotional detachment.mp.
11. emotional responsiv*.mp.
12. blunt* affect.mp.
13. amotivat*.mp.
14. diminished motivation.mp.
15. lack of motivation.mp.
16. loss of motivation.mp.
17. motivation loss.mp.
18. diminished interest.mp.
19. lack of interest.mp.
20. loss of interest.mp.
21. interest loss.mp.
22. disinterest*.mp.
23. diminished initiat*.mp.
24. lack of initiat*.mp.
25. loss of initiat*.mp.
26. initiat* loss.mp.
27. abulia.mp.
28. inertia.mp.
29. psychic akinesia.mp.
30. loss of psychic self activation.mp.
31. lack of psychic self activation.mp.
32. loss of self activation.mp.
33. lack of self activation.mp.
34. athymi*.mp.
35. avolition.mp.

36. asocial*.mp.
37. diminished social.mp.
38. loss of social.mp.
39. anhedonia.mp.
40. diminished pleasure.mp.
41. lack of pleasure.mp.
42. loss of pleasure.mp.
43. pleasure loss.mp.
44. diminished enthusiasm.mp.
45. loss of enthusiasm.mp.
46. lack of enthusiasm.mp.
47. indifference.mp.
48. diminished drive.mp.
49. letharg*.mp.
50. goal directed.mp.
51. goal oriented.mp.
52. listless*.mp.
53. dispassion*.mp.
54. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. 5 and 54

Embase (Embase, MEDLINE, Embase Classic, PubMed-not-MEDLINE)

#53 #4 AND #52
#52 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
#51 'dispassion*'
#50 'listless*'
#49 'goal oriented'
#48 'goal directed'
#47 'letharg*'
#46 'diminished drive'
#45 'indifference'
#44 'loss of enthusiasm'
#43 'diminished enthusiasm'
#42 'pleasure loss'
#41 'loss of pleasure'
#40 'lack of pleasure'
#39 'diminished pleasure'
#38 'anhedonia'
#37 'loss of social'
#36 'diminished social'
#35 'asocial*'
#34 'avolition'

#33 'athymi*'
#32 'lack of self activation'
#31 'loss of self activation'
#30 'lack of psychic self activation'
#29 'loss of psychic self activation'
#28 'psychic akinesia'
#27 'inertia'
#26 'abulia'
#25 'initiat* loss'
#24 'loss of initiat*'
#23 'lack of initiat*'
#22 'diminished initiat*'
#21 'disinterest*'
#20 'interest loss'
#19 'loss of interest'
#18 'lack of interest'
#17 'diminished interest'
#16 'motivation loss'
#15 'loss of motivation'
#14 'lack of motivation'
#13 'diminished motivation'
#12 'amotivat*'
#11 'emotional responsiv*'
#10 'emotional* detach*'
#9 'emotional* cold*'
#8 'emotional* blunt*'
#7 'blunt* affect'
#6 'apath*'
#5 'apathy'/exp
#4 #1 OR #2 OR #3
#3 'huntington':ti,ab,kw
#2 'huntington* disease':ti,ab,kw
#1 'huntington chorea'/exp

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Appendix 2. Risk of bias assessment tool

Selection

I. Diagnosis of HD cases

0 – Not explained or not adequately outlined
1 – Clinical diagnosis
2 – Genetic confirmation

II. Sample size calculation

0 – Not explained, or not adequately outlined
1 – At least one justification was given (e.g., saturation), or large-scale database analysis
2 – Predetermined sample size (sample size calculation)

III. Sampling quality

0 – Not adequately described, or the sample is not representative of population (cross sectional and cohort), or the sample is not consecutive or obviously representative series of cases (case-control)
1 – The sample is representative of population (cross sectional and cohort), or the sample is consecutive or obviously representative series of cases (case-control)

IV. Inclusion criteria

0 – Not explained or not adequately outlined
1 – Adequately described

Outcome

V. Apathy measure

0 – Not specified
1 – Binary questionnaire
2 – Validated apathy scale
3 – Interview by a psychiatrist, psychologist, or neurophysiologist to make the diagnosis

VI. Involvement of an informant for apathy measurement

0 – No informant was involved or not clearly specified
1 – An informant was involved

Comparability

VII. Addressing psychiatric history or other overlapping psychiatric diagnoses (e.g., depression)

0 – Not specified or not addressed
1 – Adequately addressed

VIII. Reporting of relevant demographic data (age and disease manifestation)

0 – Both missing
1 – Only one was reported
2 – Both were reported

IX. Controlling for possible confounding

0 – Not specified or not performed
1 – Study controlled for possible confounding factors (e.g., case-control matching, adjustment by regression analysis)

Appendix 3 – Summary of excluded studies with reason

#	Study	Exclusion criterion
1.	Khan et al.[1], 2021	b: modeling study on clinical dataset, apathy was not reported as a score or number of cases
2.	Schultz et al.[2], 2021	a: apathetic patients were excluded from the study, no report of the apathy assessment method
3.	Carlozzi et al.[3], 2019	b: apathy was reported as a Pearson correlation
4.	Trinkler et al. [4], 2019	c: interventional study
5.	Andesron et al.[5], 2018	a: Consensus and guideline development for apathy in HD, no report of the apathy assessment
6.	Gelderblom et al.[6], 2017	c: interventional study
7.	Quaid et al.[7], 2017	b: apathy was reported as hazard ratio
8.	Schobel et al.[8], 2017	b: apathy was reported as signal to noise ratio
9.	Underwood et al.[9], 2017	b: apathy was not reported as a score or number of cases
10.	Keogh et al.[10], 2016	b: associations between medication use and apathy was presented as mean difference using different models
11.	Larsen et al. [11], 2016	a: no report of the apathy assessment
12.	Simpson et al.[12], 2016	a: survey of patients and caregivers to assess patient and caregiver view on HD symptoms, lack of a valid apathy assessment method
13.	Callaghan et al.[13], 2015	b: apathy was not reported for separate groups
14.	McNally et al. [14], 2015	b: a validity assessment study for problem behavior assessment, apathy was not reported as a score or number of cases for separate groups
15.	Thompson et al.[15] , 2012	b: slope of apathy (difference) was reported between different stages of HD
16.	Rickards et al.[16], 2011a	a: loss of interest was reported as a part of Beck depression inventory, lack of a valid apathy assessment method
17.	Rickards et al.[17], 2011b	b: apathy was not reported as a score or number of cases for separate groups
18.	Vaccarino et al. [18], 2011	a: interview questions developed by the Functional Rating Scale Taskforce for pre-Huntington Disease (FuRST-pHD), no report of the apathy assessment method
19.	Williams et al.[19], 2011	a: self-report telephone interview, lack of a valid apathy assessment method
20.	Pflanz et al. [20], 1991	a: lack of a valid apathy assessment method
21.	Cummings et al.[21], 1988	a: lack of a valid apathy assessment method
22.	Dewhurst et al.[22], 1969	a: lack of a valid apathy assessment method

Exclusion criteria: a) studies without a valid scale for apathy scoring or with scales that are not specifically for apathy; b) studies that did not report the number of apathy cases or apathy scores for each group; c) therapeutic/interventional studies.

References

1. Khan W, Alusi S, Tawfik H, Hussain A. The relationship between non-motor features and weight-loss in the premanifest stage of Huntington's disease. *PLoS ONE.* 2021;16(7 July).
2. Schultz JL, Saft C, Nopoulos PC. Association of CAG Repeat Length in the Huntington Gene With Cognitive Performance in Young Adults. *Neurology.* 2021;96(19):e2407-e2413.

3. Carlozzi NE, Goodnight S, Kratz AL, et al. Validation of Neuro-QoL and PROMIS Mental Health Patient Reported Outcome Measures in Persons with Huntington Disease. *J Huntingtons Dis.* 2019;8(4):467-482.
4. Trinkler I, Chéhère P, Salgues J, et al. Contemporary Dance Practice Improves Motor Function and Body Representation in Huntington's Disease: A Pilot Study. *J Huntingtons Dis.* 2019;8(1):97-110.
5. Anderson KE, van Duijn E, Craufurd D, et al. Clinical Management of Neuropsychiatric Symptoms of Huntington Disease: Expert-Based Consensus Guidelines on Agitation, Anxiety, Apathy, Psychosis and Sleep Disorders. *J Huntingtons Dis.* 2018;7(3):355-366.
6. Gelderblom H, Wüstenberg T, McLean T, et al. Bupropion for the treatment of apathy in Huntington's disease: A multicenter, randomised, double-blind, placebo-controlled, prospective crossover trial. *PLoS One.* 2017;12(3):e0173872.
7. Quaid KA, Eberly SW, Kayson-Rubin E, Oakes D, Shoulson I. Factors related to genetic testing in adults at risk for Huntington disease: the prospective Huntington at-risk observational study (PHAROS). *Clin Genet.* 2017;91(6):824-831.
8. Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology.* 2017;89(24):2495-2502.
9. Underwood M, Bonas S, Dale M. Huntington's Disease: Prevalence and Psychological Indicators of Pain. *Mov Disord Clin Pract.* 2017;4(2):198-204.
10. Keogh R, Frost C, Owen G, et al. Medication Use in Early-HD Participants in Track-HD: an Investigation of its Effects on Clinical Performance. *PLoS Curr.* 2016;8.
11. Larsen IU, Vinther-Jensen T, Nielsen JE, Gade A, Vogel A. Social Cognition, Executive Functions and Self-Report of Psychological Distress in Huntington's Disease. *PLoS Curr.* 2016;8.
12. Simpson JA, Lovecky D, Kogan J, Vetter LA, Yohrling GJ. Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. *Journal of Huntington's Disease.* 2016;5(4):395-403.
13. Callaghan J, Stopford C, Arran N, et al. Reliability and factor structure of the Short Problem Behaviors Assessment for Huntington's disease (PBA-s) in the TRACK-HD and REGISTRY studies. *J Neuropsychiatry Clin Neurosci.* 2015;27(1):59-64.
14. McNally G, Rickards H, Horton M, Craufurd D. Exploring the validity of the short version of the Problem Behaviours Assessment (PBA-s) for Huntington's disease: A Rasch analysis. *Journal of Huntington's Disease.* 2015;4(4):347-369.
15. Thompson JC, Harris J, Sollom AC, et al. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2012;24(1):53-60.
16. Rickards H, de Souza J, Crooks J, et al. Discriminant analysis of beck depression inventory and hamilton rating scale for depression in huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences.* 2011;23(4):399-402.
17. Rickards H, De Souza J, Van Walsem M, et al. Factor analysis of behavioural symptoms in Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry.* 2011;82(4):411-412.
18. Vaccarino AL, Sills T, Anderson KE, et al. Assessment of depression, anxiety and apathy in prodromal and early huntington disease. *PLoS Curr.* 2011;3:Rrn1242.
19. Williams J, Downing N, Vaccarino AL, Guttman M, Paulsen JS. Self reports of day-to-day function in a small cohort of people with prodromal and early HD. *PLoS Currents.* 2011(AUG).
20. Pflanz S, Besson JA, Ebmeier KP, Simpson S. The clinical manifestation of mental disorder in Huntington's disease: a retrospective case record study of disease progression. *Acta Psychiatr Scand.* 1991;83(1):53-60.
21. Cummings JL, Benson DF. Psychological dysfunction accompanying subcortical dementias. *Annu Rev Med.* 1988;39:53-61.
22. Dewhurst K, Oliver J, Trick KLK, McKnight AL. Neuro psychiatric aspects of Huntington's disease. *Confin-Neurol.* 1969;31(4):258-268.

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Appendix 4. Included studies in detail

#	Study	Apathy assessment	Sample	Database	Findings
1.	Abreu et al.[1] 2021	- PBA-s	Premanifest and manifest HD* (n=6,614) categorized based on CAP score (an indicator derived from CAG length and age): - CAP 1: 25.69-66.26 (n=682) - CAP 2: 66.56-79.04 (n=650) - CAP 3: 79.51-88.75 (n=656) - CAP 4: 89.06-97.07 (n=723) - CAP 5: 98.00-101.69 (n=526) - CAP 6: 102.16-107.40 (n=701) - CAP 7: 107.86-111.86 (n=586) - CAP 8: 112.17-117.1 (n=702) - CAP 9: 117.87-125.42 (n=688) - CAP 10: 125.73—228.66 (n=700)	Enroll-HD	- Apathy scoring (PBA, severity x frequency)**: CAP 1 (1.2 ±2.6), CAP 2 (1.7 ±3.3), CAP 3 (2.2 ±3.8), CAP 4 (2.5 ±3.8), CAP 5 (2.9 ±4.0), CAP 6 (3.2 ±4.3), CAP 7 (3.8 ±4.7), CAP 8 (4.1 ±4.8), CAP 9 (4.0 ±5.0), CAP 10 (4.5 ±5.3)
2.	Atkins et al.[2] 2021	- DAS - AES	Survey of people (n=238) who self-identified into one of the following groups: - Premanifest HD (n=50) - Manifest HD (n=51) - Healthy controls (n=87) - HD-observers (n=50)	-	- Number of apathy cases (AES>41): higher apathy in manifest (38%) vs. premanifest (18%) and control (6.9%), P<0.001 - Number of apathy cases (Total DAS≥38): manifest (43.1%) was higher than premanifest (10.0%) and control (1.1%), P < 0.001 - Apathy scoring (AES): premanifest (30.96 ±9.24), manifest (36.76 ±12.22), control (28.28 ±6.55) - Apathy scoring (DAS): premanifest (24.18 ±10.85), manifest (35.49), control (22.66 ±6.98) DAS subscales - Premanifest: less executive, compared to Initiation and emotional subscales (P<0.001) - Manifest: similar levels of apathy across all subscales (30.4% executive, 34.8% initiation, 15.2% emotional)

3.	De Paepe et al.[3] 2021	- PBA-s	- Premanifest HD (n=22) - Manifest HD (n=23)	-	- Number of apathy cases (PBA severity >2), baseline: all HD (47.8%) - Number of apathy cases (PBA severity >2), 18 ±6 months F/U: all HD (64.4%) - Apathy scoring (PBA, severity x frequency), baseline: Pre-HD (2.55 ±4.3), manifest HD (5.61 ±5.0), all HD (4.11 ±4.9)
4.	Hentosh et al.[4] 2021	- PBA-s	- Manifest HD (n=2,145), divided into female (n=1097) and male (n=1048)	Enroll-HD	- Number of apathy cases: female (71.5%), male (68.0%), P=0.131
5.	Hergert et al.[5] 2021	- FrSBe	- Manifest HD (n=50) - Informed caregivers (n=50)	Partly from Enroll-HD	- Apathy scoring (FrSBe self-reported): 71.44 ±19.02 (range: 30–120) - Apathy scoring (FrSBe caregiver-reported): 87.96 ±19.36 (range: 44–136) - Apathy correlation with caregiver burden: Self-reported (0.29, $p < 0.05$) vs. caregiver-reported (0.61, $p < .001$), caregiver-report scores were more strongly associated with caregiver burden than self-report scores
6.	Martinez-Horta et al.[6] 2021	- PBA-s	- Early manifest HD (n=31), classified as IAs (score > 2) and non-IAs (n=14) based on irritability and aggression score	-	- Apathy scoring (PBA, severity only): IAs (1.7 ± 1.4), non-IAs (1.6 ± 1.6), P=0.910
7.	McAllister et al.[7] 2021	- HDCC	- Manifest HD (n=6,316)	REGISTRY	- Number of apathy cases (HDCC): male (1456/2715 [53.63%]), female (1495/2869 [52.11%]), P= 0.256 - Apathy tended to occur after motor symptoms in 69.5% individuals
8.	Migliore et al.[8] 2021	- PBA-s	- Manifest HD (n=97) - t0 baseline, t1 after one year, t2 after two years	Enroll-HD	- Apathy score (PBA, severity x frequency): t0 (4.43 ± 4.3), t1 (4.96 ± 4.9), t2 (5.23 ± 4.7); p= 0.13 - Apathy severity was associated with the severity of the cognitive decline regardless of the timepoints (baseline, 1 y, 2 y), p <.0001
9.	Nair et al.[9] 2021	- BAIS (AS)	- Premanifest (n=60) - Early manifest (n=34)	TRACK-ON HD	- Apathy scoring (AS): 10.9 ±6.0
10.	Oosterloo et al.[10] 2021	- PBA-s (or UHDRS-b in case PBA-s data was not available)	- Premanifest non-converters (n = 3276): Premanifest HD who did not convert to manifest - Premanifest convertors (n = 455): Premanifest HD who converted to manifest	Enroll-HD REGISTRY	- Number of apathy cases: non-converters (697/3276 [21.2%]), convertors (149/455 [32.7%]), P <0.001

11.	Ranganathan et al.[11] 2021	- PBA-s	Manifest HD (n=4,469), grouped based on age of onset (AOO): - AOO <30 (n=479) - AOO 30-59 (n=3,478) - AOO >59 (n=512)	Enroll-HD	- Number of apathy cases (PBA severity ≥1): Total (57%), AOO <30 (58%), AOO 30-59 (57%), AOO > 59 (51%) - Number of apathy cases (PBA severity ≥2): Total (45%), AOO <30 (46%), AOO 30-59 (45%), AOO > 59 (41%) - Number of apathy cases (PBA severity ≥ 3): Total (22%), AOO <30 (22%), AOO 30-59 (22%), AOO >59 (22%) - Number of apathy cases (PBA severity ≥ 4); Total (5%), AOO <30 (5%), AOO 30-59 (5%), AOO >59 (5%)
12.	van der Zwaan et al.[12] 2021	- PBA-s	- Gene carriers (n = 1,249) - Healthy controls (n = 1,542)	Enroll-HD	- Apathy scoring (PBA, severity x frequency), median: carriers (0), control (0)
13.	Andrews et al.[13] 2020	- PBA-s	- Premanifest HD (n=111) - Early HD (n=118) - Healthy control (n=118)	TRACK-HD	- Number of apathy cases (PBA severity ≥2), baseline: Premanifest (17/111 [15.3%]), early HD (46/118 [38.9%]), control (8/118 [6.7%]) - Apathy scoring (PBA, severity only), baseline: Premanifest (0.49 ± 0.94), early HD (1.12 ±1.18), control (0.25 ± 0.67) - 2y F/U: Premanifest group was not significantly different from control (p = 0.12); However, severe apathy at baseline predicted more rapid cognitive decline over 2 years. Early HD showed more cognitive decline than control (p = <0.001)
14.	Atkins et al.[14] 2020	- AES - DAS - Effort-based decision-making tasks	- Premanifest HD (n=20) - Healthy Controls (n=20)	-	- Apathy scoring (AES): Premanifest (27.4 ±5.7), control (27.6 ±6.4), P=0.94 - Apathy scoring (Total DAS): Premanifest (19.7 ±8.3), control (22.6 ± 6.7), P = 0.29 - Pre-manifest HD patients were less cognitively motivated than controls, but equally physically motivated.
15.	Ellis et al.[15] 2020	- HDCC	- Manifest HD (n=5854)	REGISTRY Enroll-HD	- Number of apathy cases (HDCC): Total (53.8%), male (1484/2775 [53.4%]), female (1581/2925 [54%]), P= 0.664 - Disease duration significantly increased the odds of apathy
16.	Gunn et al.[16] 2020	- PBA-s	- Manifest HD (n=4,109): Informant present (n=2,845) and participant only (n=1,264) - Premanifest HD (n=1,790): Informant present (n=641)	Enroll-HD	Apathy factor (3-item structure)[◊] - Manifest: Informant present (7.73 ±8.08), Participant only (4.04 ±5.60), P=0.001 - Premanifest: Informant present (2.23 ±4.42), Participant only (1.83 ±3.86), P=0.046

			and Participant only (n=1,149) - Genotype negative with a carrier relative (n=1,041): Informant present (n=188) and participant only (n=853) - Healthy control, family (n=974): Informant present (n=359) and participant only (n=615)		- Genotype negative with a carrier relative: Informant (1.34 ±4.03), Participant only (0.80 ±2.41), P=0.016 - Healthy control, family: Informant (0.87 ±2.61), Participant only (0.76 ±2.24), P=0.52
17.	Isaacs et al.[17] 2020	- PBA-s - FrSBe	- Manifest HD (n=50)	-	- Apathy scoring (PBA): severity 2.1 ±1.3, frequency 2.5 ±1.6 - Apathy scoring (FrSBe): 38.2 ±11.3
18.	Julayanont et al.[18] 2020	- PBA-s	Early motor manifest HD (≤5 y, n= 3,505), classified into - C-HD (n = 1125): Chorea dominant - P-HD (n = 867): Parkinsonism dominant - M-HD (n = 1513): Mixed motor	Enroll-HD	- Apathy scoring (PBA, severity x frequency): C-HD (2.46 ± 0.12), P-HD (3.95 ± 0.13), M-HD (2.89 ± 0.10) - P-HD > M-HD > C-HD (P<0.001)
19.	Martinez-Horta et al.[19] 2020a	- AS - PBA-s	- Premanifest HD (n=16) - Matched healthy controls from relatives (n=16)	-	- Apathy scoring (AS): premanifest (5.2 ± 7), control (0.1 ± 0.3), P= 0.012 - Apathy scoring (PBA, severity x frequency): premanifest (1.8 ± 3.3), control (0), P= 0.045
20.	Martinez-Horta et al.[20] 2020b	- PBA-s	Manifest HD (n=139) - HD-NC (n=36): cognitively preserved - HD-MCI (n=62): mild cognitive impairment - HD-Dem (n=41): demented Matched healthy controls (n=33)	-	- Apathy scoring (PBA, severity x frequency): total manifest HD (3 ±3.7), HD-NC (1.8 ±2.7), HD-MCI (2.8 ±3.6), HD-Dem (4.6 ±4.1), control (0), P<0.005
21.	Aldaz et al.[21] 2019	- NMSQuest	- Manifest HD (n=53) - PD (n=45) - Healthy control (n=25)	Partly from Enroll-HD	- Number of apathy cases: 64% in HD, higher compared to PD (p = 0.03)

22.	Ceccarini et al.[22] 2019	- PBA-HD	- Premanifest HD (n=15, three declined to take the PBA) - Healthy control (n=27): 15 from HD families and 12 from community	-	- Apathy factor (PBA-HD apathy subscale)[Δ]: premanifest (1.4 ± 2.0), control (0.1 ± 0.3), P=0.005
23.	De Paepe et al.[23] 2019	- PBA-s - LARS-s	- Premanifest HD (n=22) - Manifest HD (n=24) - Healthy control (n=35)	-	- Number of apathy cases (PBA severity >2): 45% of all HD - Number of apathy cases (LARS-s > -7): premanifest (29.4%), manifest (52.2%), control (12.9%) - Apathy factor (3-item structure)[◊]: premanifest (4.76 ± 8.6), manifest (8.08 ± 7.6) - Apathy scoring (LARS-s): premanifest (−8.65 ± 4.1), manifest (−6.14 ± 5.4), control (−9.90 ± 3.1)
24.	McLauchlan et al.[24] 2019	- AES - PBA-s - Effort-based decision-making task (BISBAS)	- Premanifest to moderately affected HD (n=51) - Controls (n=26)	-	- Apathy scoring (AES): HD (38.48), control (18.85) - Apathy scoring (PBA, severity x frequency): HD (5.02), control (0.5) - Apathy in HD patients was associated with blunted responses to loss and impaired instrumental learning, but there was no evidence to suggest altered reward-related behavior or effort
25.	Misiura et al.[25] 2019	- FrSBe	- Prodromal/Premanifest HD (n=797) - Healthy control (n=208)	PREDICT-HD	- Apathy scoring (FrSBe): Premanifest (12.4 ±5.54), control (11.0 ±4.29), P<0.001
26.	Osborne-Crowley et al.[26] 2019	- PBA-s	- HD-A: apathetic (n=43) - HD-NA: non-apathetic (n=67) - Healthy control (n=107)	TRACK-HD	- Apathy scoring (PBA, severity x frequency): HD-NA (0.16 ± 0.37), HD-A (6.44 ±3.28), Control (0.08 ±0.23), P<0.001 - HD-A patients were impaired on the recognition of happy facial expressions, compared to other two groups (P=0.002)
27.	Sampedro et al.[27] 2019	- PBA-s	- Premanifest HD (n=21) - Early HD (n=19)	-	- Number of apathy cases (PBA severity ≥2): premanifest (33%), early HD (63%) - Apathy scoring (PBA, severity x frequency): premanifest (2.1 ± 3.4), early HD (5.2 ± 5.1), P=0.03
28.	Andrews et al.[28] 2018	- FrSBe	- Premanifest HD (n=60) - Early HD (n=72) - Healthy controls (n=119)	TRACK-HD	- Apathy scoring (FrSBe self-reported): Premanifest (27.60 ±8.13), early (30.0 ±9.48), control (24.23 ±6.47); early HD was higher than control (P<0.001) and pre-HD (P=0.002) - Apathy scoring (FrSBe informant): Premanifest (25.38 ±8.00), early (33.45 ±10.92); early HD was higher than pre-HD (P<0.001)

					- Impaired executive task performance was related to unawareness of executive dysfunction and apathy
29.	Baake et al.[29] 2018a	- PBA-s	- PreA (n = 52): estimated disease onset > 10.8 y - PreB (n = 39): estimated disease onset < 10.8 y - HD1 (n = 50): Manifest HD, UHDRS-TMS > 5, TFC stage 1 - HD2 (n = 30): Manifest HD, UHDRS-TMS > 5, TFC stage 2	TRACK-HD	- Number of apathy cases (PBA severity ≥2), baseline: PreA (6/52 [11.5%]), PreB (6/39 [15.3%]), HD1 (12/50 [24%]), HD2 (15/30 [50%]), P = 0.001 - Number of apathy cases (PBA severity ≥2), 23-24 months F/U: PreA (9%), PreB (25%), HD1 (36%), HD2 (70%), P < 0.001
30.	Baake et al.[30] 2018b	- AES	Patients (n=109) and their proxies: - Premanifest HD (n=31) - Early manifest HD (n=49) - Late manifest HD (n=29)	REGISTRY	- Apathy scoring (AES patient), extracted†: Premanifest HD (24.93), early manifest HD (32.46), late manifest HD (39.12) - Apathy scoring (AES proxy), extracted†: Premanifest HD (21.92), early manifest HD (28.99), late manifest HD (44.16) - Pre-motor manifest: 10 points lower than late motor manifest (p=0.01) - Early motor manifest: 6 points lower than late motor manifest (p=0.03) - No significant difference was found between the pre- and early motor manifest
31.	Fritz et al.[31] 2018	- PBA-s	- Premanifest HD (n=193) - Early manifest: TFC 7-13 (n=187) - Late manifest: TFC 0-6 (n=91)	PREDICT-HD	- Apathy scoring (PBA, severity x frequency): Premanifest (1.4 ±2.9), early (3.0 ±4.1), late (3.9 ±5.0), across all groups (2.5 ±4.0) - Premanifest stage was lower than other groups (p<.0001), early and late stages did not differ - Apathy was related to physical, cognitive and behavioral dysfunction across disease stages
32.	Jacobs et al.[32] 2018	- PBA-s	HD mutation carriers - Employed (n=114) - Unemployed (n=106)	Enroll-HD	- Apathy scoring (PBA, severity x frequency): employed (0.75 ±1.9), unemployed (2.2 ±3.6), P <0.001
33.	Kempnich et al.[33] 2018	- FrSBe	- Premanifest or manifest HD (n=32): comparison of previously reported data (self-reported) with family ratings (n=32)	-	- Apathy scoring (FrSBe, family ratings): 71.22 ± 23.92
34.	Martinez-Horta et al.[34] 2018	- PBA-s	- Mild HD (n=40): UHDRS TMS >4 and TFC >7	-	- Number of apathy cases (PBA severity >2): 46%

35.	Sousa et al.[35] 2018	- AES	- Manifest HD (n=30) - PD (n=45)	-	- Number of apathy cases (AES>35): HD (15/29 [51.7%]), PD (17/40 [42.5%]), P = 0.474 - Apathy scoring (AES companion): HD (50.60 ±10.8), PD (44.94 ±6.6), P = 0.083
36.	McColgan et al.[36] 2017	- BAIS (AS)	- Main group: fMRI cohort (n=186), including Premanifest HD (n=92), Healthy control (n=94) - Diffusion MRI cohort (n=151): Premanifest HD (n=70), Healthy control (n=81) - Structural replication (n=96): Premanifest HD (n=50), Healthy control (n=46)	TRACK -ON HD TRACK HD	- Apathy scoring (AS self-reported), fMRI cohort: Premanifest HD (11.4 ±7), control (8.8 ±4.8), P=0.004 - Apathy scoring (AS self-reported), diffusion MRI cohort: Premanifest HD (11.3 ±7.3), control (8.3 ±4.1), P=0.0017 - Apathy scoring (AS self-reported), replication: Premanifest HD (10.9 ±6.3), control (9.4 ±3.5), P=0.156
37.	Ruiz-Idiago et al.[37] 2017	- PBA-s	- At risk (n=9) - Asymptomatic carrier (n=12) - Manifest HD (n=77) - Control expansion negative (n=6) - Control without HD family history (n=13)	-	- Number of apathy cases (PBA severity ≥2) in the last year: at risk (2/9 [22.2%]), asymptomatic carrier (3/12 [25%]), manifest (53/77 [68.8%]), control expansion negative (1/6 [16.7%]), Control without HD family history (2/13 [15.4%])
38.	Trinkler et al.[38] 2017	- UHDRS-b	- Manifest HD (n=28) - Matched Healthy control (n=24)	-	- Apathy scoring (UHDRS-b): HD (0.3 ± 0.6)
39.	Bouwens et al.[39] 2016	- AS	- HD mutation carriers (n=124), both premanifest and manifest	-	- Apathy scoring (AS), baseline: 8.6 ± 8.7
40.	Martinez-Horta et al.[40] 2016	- PBA-s	- PreHD-A (n=34): estimated disease onset > 10.8 y - PreHD-B (n=25): estimated disease onset < 10.8 y - Early HD (n=70): UHDRS-TMS ≥5 and TFC 11-13 - Healthy control (n=101)	REGISTRY	- Number of apathy cases (PBA severity ≥2): PreHD-A (23%), PreHD-B (64%), Early HD (63%), Control (<2%) - Apathy scoring (PBA, severity x frequency): PreHD-A (1.5 ±3.2), PreHD-B (4 ±4), Early-HD (4.7 ±4.6), Control (0.1 ±0.9), P=0.000 - Apathy scoring for PreHD-B and Early-HD were significantly higher than PreHD-A and control

41.	Yang et al.[41] 2016	- UHDRS-b	- HD: 25 male, 33 female	-	- Number of apathy cases (UHDRS-b): Total (24/ [41.4%]), male (14/25 [56%]), female (10/33 [30.3%]), P=0.049 - Apathy scoring (UHDRS-b): Total (1.1 ± 1.9), male (1.8 ± 2.1), female (0.6 ± 1.6), P=0.018
42.	Bouwens et al.[42] 2015	- AS	HD mutation carriers (n=90) - No baseline irritability (n=57), no irritability at F/U (I-A; n=44) and incident irritability (I-B; n=13) - With baseline irritability (n=33), no irritability at F/U (II-A; n=10) and incident irritability (II-B;n=23)	-	- Apathy scoring (AS): I-A (5.41 ±1.26), I-B (8.62 ±1.93), P=0.22; II-A (8.00 ±1.76), II-B (13.30 ±2.05), P=0.13
43.	Gregory et al.[43] 2015	- PBA-s	- Premanifest HD (n=39) - Early manifest HD (n=45)	TRACK-HD	- Apathy scoring (PBA, severity x frequency): premanifest (2.45 ±4.08), early (5.53 ±5.66), P= 0.006
44.	Hergert et al.[44] 2015	- FrSBe	- Manifest HD (n=13) and their informants (n=13)	-	- Apathy scoring (FrSBe): patient (76.46 ±17.83), informant (85.38 ±23.19) - Apathy score for patients with severe motor score (median motor score > 23): patient (77.09 ±11.03), informant (101.82 ±16.68)
45.	Mason et al.[45] 2015	- AES	- Baseline (n=108): Pre-HD (n=20), early (n=24), moderate (n=29), late (n=35) - F/U (n=72): Pre-HD (n=15), early (n=15), moderate (n=17), late (n=25)	-	- Number of apathy cases (AES>41 for patient and >39 for companion rated), baseline, all HD: AES participant-reported (29/108 [26.9%]), AES companion-reported (40/79 [50.6%]) - Number of apathy cases (AES>41 for patient and >39 for companion rated), F/U, all HD: AES participant-reported (21/68 [30.9%]), AES Companion-reported (29/51 [56.9%]) - Apathy scoring (AES participant-reported), extracted†: Pre-HD (29), early (30), moderate (40), late (n=41) - Apathy scoring (AES companion-reported), extracted†: Pre-HD (27), early (29), moderate (42), late (n=47) - Lower self-rated apathy in pre-manifest and early HD than late HD (P<0.05) - Self-rated and companion-rated AES were correlated (P<0.001)
46.	Bouwens et al.[46] 2014	- PBA-HD	- HD mutation carriers (n=122) - Controls (n=42)	-	- Apathy factor (4-item structure)$^{\Delta}$, median: carriers (2; IQR: 0–18), controls (0; IQR: 0–0), P<0.001
47.	van Duijn et al.[47] 2014a	- PBA-HD	- Premotor symptomatic (n = 46)	-	- Apathy factor (4-item structure)$^{\Delta}$, median, baseline: Premotor symptomatic (0, IQR: 0-7), Symptomatic (8, IQR: 0-24), P<0.001

			- Symptomatic (n = 75)		- Apathy factor, median, 2-year F/U: Premotor symptomatic (0, IQR: 0-5), Symptomatic (8, IQR: 0-24), P<0.001; No significant change after 2y in premotor (P=0.27) and motor (P=0.84)
48.	van Duijn et al.[48] 2014b	- UHDRS-b	- HD mutation carriers (n=1993)	REGISTRY	- Number of apathy cases (UHDRS-b): mild apathy (2–4 points; 19.3%), moderate to severe apathy (>4 points; 28.1% total; 11.8% stage 1, 54.6% stage 4-5)
49.	Delmaire et al.[49] 2013	- PBA-s	- Early manifest HD (n=27) - Controls (n= 24)	TRACK-HD	- Apathy scoring (PBA, severity x frequency): early (3.9 ±4.7), control (0.8 ±2.3), P=0.004
50.	Eddy et al.[50] 2013	- FrSBe	- Manifest HD (n=20) with mild to moderate motor symptoms	-	- Apathy scoring (FrSBe): 38.2 ±10.75 - Apathy scoring (FrSBe), median: 37.5 (range: 18–60)
51.	Hubers et al.[51] 2013	- UHDRS-b	- HD mutation carriers (n=2,106), divided into non-suicidal (n=1937) and suicidal (n=169)	REGISTRY	- Number of apathy cases (UHDRS-b): non-suicidal (881 [45.7%]), suicidal (123 [73.7%]), P<0.001
52.	Killoran et al.[52] 2013	- UHDRS-b	- Control with CAG ≤26 (n=587) - Intermediate with CAG 27–35 (n=50) - Expanded CAG ≥36 (n=346)	PHAROS	- Apathy scoring (HUDRS-b), extracted†: intermediate (0.72), expanded (0.68), control (0.37); Intermediate vs control (P=0.0381)
53.	Read et al.[53] 2013	- PBA-s	- Pre-A: Premanifest, >10.8 y from predicted onset (n=61) - Pre-B: Premanifest, <10.8 y from predicted onset (n=57) - HD 1: stage I, TFC 11–13 (n=75) - HD 2: stage II, TFC 7–10 (n=42) - Healthy control siblings (n=36) - Healthy control partners (n=84)	TRACK-HD	- Apathy scoring (PBA, severity x frequency): Pre-A (0.9 ±2.2), Pre-B (1.4 ±2.9), HD1 (2.1 ±3.3), HD2 (3.9 ±4.2), control siblings (0.5 ±1.7), control partners (0.3 ±1.1)

54.	Scahill et al.[54] 2013	- PBA-s	- Premanifest HD (n=120) - Early manifest HD (n=119)	TRACK-HD	- Apathy scoring (PBA, severity x frequency, square root of the score): Premanifest (0.5 ±0.9), early (1.1 ±1.2), P < 0.0001
55.	Tabrizi et al.[55] 2013 (Tabrizi et al.[56] 2012, Tabrizi et al.[57] 2011)	- PBA-s	36-month (2013) - PreHD-A: Premanifest, ≥10.8 y from predicted onset (n=58) - PreHD-B: Premanifest, <10.8 y from predicted onset (n=46) - HD1: early HD, TFC score 11–1 (n=66) - HD2: early HD, TFC score 7–10 (n=31) - Control: healthy individuals (n=97) 24-month (2012) - PreHD-A: Premanifest, ≥10·8 y from predicted onset (n=60) - PreHD-B: Premanifest, <10·8 y from predicted onset (n=51) - HD1: early HD, TFC score 11–13 (n=70) - HD2: early HD, TFC score 7–10 (n=41) - Control: healthy individuals (n=110) 12-month (2011) - PreHD-A: Premanifest, ≥10·8 y from predicted onset (n=62)	TRACK-HD	Effect sizes (95% CI) for net change of apathy scores (square root of points on PBA scale) in HD groups compared with control: 36-month - PreHD-A: 0.21 (–0.02 to 0.44), P=0.069 - PreHD-B: 0.34 (0.02 to 0.66), P=0.038 - HD1: 0.60 (0.29 to 0.90), P=0.0002 - HD2: 0.48 (–0.10 to 1.06), P=0.104 - Control: –0.05 (–0.20 to 0.10) - Apathy showed significant increase in PreHD-B (P=0·038) and HD1 (P=0·0002) comparing to control. 24-month - PreHD-A: 0.35 (–0.03 to 0.71) - PreHD-B: 0.16 (–0.18 to 0.49) - All preHD: 0.27 (0.00 to 0.54) - HD1: 0.41 (0.13 to 0.72) - HD2: 0.45 (0.14 to 0.81) - All HD: 0.41 (0.18 to 0.64) - Apathy showed significant increase in PreHD-B (P=0·038) and HD1 (P=0·0002) comparing to control 12-month - All preHD: 0.09 (–0.14 to 0.31), P= 0.47 - PreHD-A: 0.13 (–0.14 to 0.40), P= 0.34 - PreHD-B: 0.03 (–0.28 to 0.33), P=0.86 - All HD: 0.06 (–0.21 to 0.33), P= 0.66 - HD1: 0.10 (–0.23 to 0.43), P= 0.55 - HD2: 0.00 (–0.40 to 0.39), P= 0.98 Apathy scorings (PBA, severity x frequency, square root of score), extracted†: - Baseline: PreHD-A (0.40), PreHD-B (0.62), HD1 (0.88), HD2 (1.5), Control (0.19) - 12 months: PreHD-A (0.48), PreHD-B (0.60), HD1 (1.1), HD2 (1.6), Control (0.16)

			- PreHD-B: Premanifest, <10·8 y from predicted onset (n=55) - HD1: early HD, TFC score 11–13 (n=71) - HD2: early HD, TFC score 7–10 (n=43) - Control: healthy individuals (n=114) Baseline - PreHD-A: Premanifest, ≥10·8 y from predicted onset (n=62) - PreHD-B: Premanifest, <10·8 y from predicted onset (n=58) - HD1: early HD, TFC score 11–13 (n=77) - HD2: early HD, TFC score 7–10 (n=46) - Control: healthy individuals (n=123)		- 24 months: PreHD-A (0.59), PreHD-B (0.74), HD1 (1.3), HD2 (2.1), Control (0.17)
56.	Banaszkiewicz et al.[58] 2012	- UHDRS-b	- Manifest HD patients (n=80)	-	- Apathy scoring (UHDRS-b): 3.6 ±2.4
57.	Hubers et al.[59] 2012	- AS	- Mutation-carriers (n=152) divided to non-suicidal (n=121) and suicidal (n=31) groups - Non carriers (n=56)	-	- Number of apathy cases (AS≥14): non-suicidal (33/121 [27.2%]), suicidal (16/31 [51.6%]), P=0.01
58.	Tabrizi et al.[56] 2012	See Tabrizi et al. 2013			

59.	Reedeker et al.[60] 2011	- AS	- Premanifest HD (n=55) - HD (n=97) - 122 were analyzed	-	- Number of apathy cases (AS ≥14), Baseline: 88/122 (72.1%) without apathy, 34/122 (27.8%) with apathy - 2y F/U: 13/88 (14.7%) showed new apathy, 20/34 (58.8%) had persistent apathy and 14/34 (41.1%) had remission from apathy
60.	Tabrizi et al.[57] 2011	See Tabrizi et al. 2013			
61.	Duff et al.[61] 2010	- FrSBe	- Expansion positive (n=745) - Expansion negative (n=163)	PREDICT-HD	- Apathy scoring (FrSBe participant-reported): Expansion positive (13.7 ±6.1), expansion negative (11.7 ±4.2), P=0.001 - Apathy scoring (FrSBe companion-reported): Expansion positive (12.3 ±5.4), expansion negative (11.0 ±3.9), P=0.001
62.	Reedeker et al.[62] 2010	- AS	- Premanifest HD (n=54) - Manifest HD (n=96)	-	- Number of apathy cases (AS ≥14): Manifest (41/96 [42.7%]) - Apathy scoring (AS), median: Manifest (12 [IQR: 6-18])
63.	van Duijn et al.[63] 2010a	- AS	- HD mutation carriers (n=152) - Healthy control (n=56)	-	- Number of apathy cases (AS ≥14): HD (49/152 [32.2%]), control (0)
64.	van Duijn et al[64] 2010b	- PBA-HD	- HD mutation carriers (n=152) divided into three groups based on DSMIV diagnoses: subjects without DSM-IV diagnosis (n=121), subjects with DSM-IV diagnosis (n=19), subjects in whom interview was not possible (n=12)	-	- Apathy factor (4-item structure)$^{\Delta}$, median (IQR): without diagnosis (1 [0–12]), with diagnoses (15 [6–32]), cognitively impaired (40 [13–56]), P<0.001
65.	Naarding et al.[65] 2009	- AES - PBA-HD	- Mild to moderate HD (n=34)	-	- Number of apathy cases for severe apathy (AES > 40): 18/34 (52.9%) - Apathy scoring (AES): 40.4 ±11.7 - Apathy scoring (PBA, severity x frequency): 2.7 ±2.5
66.	Tabrizi et al.[66] 2009	- PBA-s	- PreHD-A: Premanifest, ≥10·8 y from predicted onset (n=62) - PreHD-B: Premanifest, <10·8 y from predicted onset (n=58) - HD1: early HD, TFC score 11–13 (n=77)	TRACK-HD	- Apathy scoring (PBA, severity x frequency): PreHD-A (0.85 ±2.22), PreHD-B (1.35 ±2.88), HD1 (2.11 ±3.25), HD2 (3.75 ±4.04), control (0.38 ±1.27) - Apathy scoring (PBA, severity x frequency), adjusted with 95% CI: PreHD-A (0.85 [0.41 to 1.66]), PreHD-B (1.40 [0.76 to 2.43]), HD1 (2.08 [1.45 to 2.87]), HD2 (3.87 [2.82 to 5.15]), control (0.38 [0.20 to 0.71])

			- HD2: early HD, TFC score 7–10 (n=46) - Healthy control (n=123)		
67.	Kingma et al.[67] 2008	- PBA-HD	- Premanifest HD (n=55) - Early HD (n=47) - Advanced HD (n=50) - Noncarriers (n=56)	-	- Apathy factor (4-item structure)[Δ], the mean of the 4 items (range 0-16): Premanifest (1.01 ±1.86), early (2.07 ±3.07), advanced (5.76 ±5.10), noncarriers (0.11 ±0.40); noncarriers vs carriers P<0.001; noncarriers vs premanifest P<0.001; premanifest vs early P=0.01; early vs advanced P <0.001
68.	Baudic et al.[68] 2006	- IAS	- Early manifest HD, diagnosed by clinical criteria and family history (n=36)	-	- Number of apathy cases (IAS>13): 20/36 (55.5%) - Apathy scoring (IAS): Non-apathetic (8.9 ±1.8), apathetic (17.3 ±3.5), P<0.0001
69.	Chatterjee et al.[69] 2005	- BAIS (AS)	- Manifest HD, diagnosed by clinical criteria and family history or genetic testing (n=53) - Informed caregivers (n=53)	-	- Apathy scoring (AS): patient (15.4 ±8.4), informant (18.3 ±9.3) - Agreement between two groups (apathy was defined as score > 15 for patient and > 19 for informant) was poor for patients with low cognition and good for the high cognition.
70.	Hamilton et al.[70] 2003	- FLOPS (FrSBe)	- Manifest HD, diagnosed clinically or genetically (n=22)	-	- Apathy scoring (FrSBe): 1.2 ±0.7
71.	Stout et al. [71] 2003	- FrSBe	- Manifest HD, diagnosed by clinical criteria and family history (n=91)	-	- Apathy scoring (FrSBe): 39.0 ±11.8
72.	Leroi et al.[72] 2002	- AS	- Early- to mid-stage HD (n=21) - Healthy control (n=29)	-	- Apathy scoring (AS): informant (13.57 ±7.00), control (4.58 ±5)
73.	Thompson et al.[73] 2002	- PBA-HD	- Manifest HD (n=82)	-	- Apathy factor (PBA-HD apathy subscale) [Δ], median: 8 - Apathy was significantly correlated (P<0.0001) with functional, motor and cognitive decline
74.	Craufurd et al.[74] 2001	- PBA-HD	- Manifest HD (n=134; 78 cases included in the factor analysis)	-	- Number of apathy cases (PBA severity ≥2): 76% (lack of initiative item from PBA-HD apathy subscale) - Apathy showed linear relationship, increasing in severity with duration (p < 0.0005)
75.	Paulsen et al.[75] 2001	- NPI	- Manifest HD (n=52)	-	- Number of apathy cases (NPI): 55.8% - Apathy scoring: 2.79 ±4.02
76.	Kulisevsky et al.[76]	See Litvan et al.			

	2001				
77.	Litvan et al. [77] 1998 (Kulisevsky et al.[76] 2001)	- NPI	- Manifest HD (n=29)	-	- Number of apathy cases (NPI): 34% - Apathy scoring: 2.28 ± 0.7
78.	Levy et al.[78] 1998	- NPI	- Manifest HD, diagnosed by clinical criteria and family history (n=34)	-	- Number of apathy cases (NPI): 58.8% (7 apathy, 13 apathy + depression) - Apathy scoring: 2.5 ±3.5 - Apathy did not correlate with depression; apathy but not depression, correlated with lower cognitive function (P<0.0001)
79.	Paulsen et al.[79] 1996	- FLOPS (FrSBe)	- Manifest HD, diagnosed by clinical criteria, family history, and imaging (n=24)	-	- Apathy scoring (FrSBe): 44.28 ±12.05
80.	Burns et al.[80] 1990	- IAS	- Manifest HD, diagnosed by clinical criteria and family history (n=26)	-	- Apathy scoring (IAS): 17.8

AES, Apathy Evaluation Scale; AS, Apathy Scale; BAIS, Baltimore apathy/irritability scale; BISBAS, Behavioral Inhibition Behavioral Activation Scale; CI, Confidence Interval; DAS, Dimensional Apathy Scale; FLOPS, Frontal Lobe Personality Scale; FrSBe, Frontal Systems Behavior Scale; F/U, follow-up; HDCC, HD Clinical Characteristics; IQR, Interquartile Range; LARS, Lille Apathy Rating Scale; NMSQuest, Non-Motor Symptoms Questionnaire; NPI, Neuropsychiatric Inventory; PBA, Problem Behaviors Assessment; TFC, Total Functional Capacity; UHDRS-b, Unified HD Rating Scale behavioral; UHDRS-TMS, Unified HD Rating Scale Total Motor Score.

* HD diagnosis was based on genetic testing, unless stated otherwise.
** Apathy scores are mean ±standard deviation, unless stated otherwise.
† These scores were extracted from a plot by WebPlotDigitizer.
◊ In PBA-s, apathy as a factor is different from apathy score and includes 3 items: apathy, perseveration, and disorientation. The factor ranges from 0 to 48.
Δ In PBA-HD, apathy factor may refer to a 4-item factor (including lack of perseverance, poor quality of work, lack of initiative, and poor self-care), or the 7-item apathy subscale of the PBA-HD which was primarily defined by Craufurd et al.[74] The scoring of 4-item factor ranges from 0 to 64 (summation of items) and the 7-item apathy subscale ranges from 0-16 (mean of items).

References

1. Abreu D, Ware J, Georgiou-Karistianis N, et al. Utility of Huntington's Disease Assessments by Disease Stage: Floor/Ceiling Effects. *Front Neurol.* 2021;12:595679.
2. Atkins KJ, Andrews SC, Chong TT, Stout JC. Multidimensional Apathy: The Utility of the Dimensional Apathy Scale in Huntington's Disease. *Mov Disord Clin Pract.* 2021;8(3):361-370.
3. De Paepe AE, Ara A, Garcia-Gorro C, et al. Gray Matter Vulnerabilities Predict Longitudinal Development of Apathy in Huntington's Disease. *Mov Disord.* 2021;36(9):2162-2172.
4. Hentosh S, Zhu L, Patino J, Furr JW, Rocha NP, Furr Stimming E. Sex Differences in Huntington's Disease: Evaluating the Enroll-HD Database. *Movement Disorders Clinical Practice.* 2021;8(3):420-426.
5. Hergert DC, Cimino CR. Predictors of Caregiver Burden in Huntington's Disease. *Arch Clin Neuropsychol.* 2021.
6. Martinez-Horta S, Sampedro F, Horta-Barba A, et al. Structural brain correlates of irritability and aggression in early manifest Huntington's disease. *Brain Imaging Behav.* 2021;15(1):107-113.
7. McAllister B, Gusella JF, Landwehrmeyer GB, et al. Timing and Impact of Psychiatric, Cognitive, and Motor Abnormalities in Huntington Disease. *Neurology.* 2021;96(19):e2395-e2406.
8. Migliore S, D'Aurizio G, Maffi S, et al. Cognitive and behavioral associated changes in manifest Huntington disease: A retrospective cross-sectional study. *Brain Behav.* 2021;11(7):e02151.
9. Nair A, Razi A, Gregory S, Rutledge RR, Rees G, Tabrizi SJ. Imbalanced basal ganglia connectivity is associated with motor deficits and apathy in Huntington's disease. *Brain.* 2021.
10. Oosterloo M, de Greef BTA, Bijlsma EK, et al. Disease Onset in Huntington's Disease: When Is the Conversion? *Movement Disorders Clinical Practice.* 2021;8(3):352-360.
11. Ranganathan M, Kostyk SK, Allain DC, Race JA, Daley AM. Age of onset and behavioral manifestations in Huntington's disease: An Enroll-HD cohort analysis. *Clinical Genetics.* 2021;99(1):133-142.
12. van der Zwaan KF, Jacobs M, van Zwet EW, Roos RAC, de Bot ST. Predictors of Working Capacity Changes Related to Huntington's Disease: A Longitudinal Study. *J Huntingtons Dis.* 2021;10(2):269-276.
13. Andrews SC, Langbehn DR, Craufurd D, et al. Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychol Med.* 2020:1-7.
14. Atkins KJ, Andrews SC, Stout JC, Chong TT. Dissociable Motivational Deficits in Pre-manifest Huntington's Disease. *Cell Rep Med.* 2020;1(9):100152.
15. Ellis N, Tee A, McAllister B, et al. Genetic Risk Underlying Psychiatric and Cognitive Symptoms in Huntington's Disease. *Biol Psychiatry.* 2020;87(9):857-865.
16. Gunn S, Maltby J, Dale M. Assessing Mental Health Difficulties of Persons With Huntington's Disease: Does Informant Presence Make a Difference? *J Neuropsychiatry Clin Neurosci.* 2020;32(3):244-251.
17. Isaacs D, Gibson JS, Stovall J, Claassen DO. The Impact of Anosognosia on Clinical and Patient-Reported Assessments of Psychiatric Symptoms in Huntington's Disease. *Journal of Huntington's Disease.* 2020;9(3):291-302.

18. Julayanont P, Heilman KM, McFarland NR. Early-Motor Phenotype Relates to Neuropsychiatric and Cognitive Disorders in Huntington's Disease. *Mov Disord.* 2020;35(5):781-788.
19. Martínez-Horta S, Horta-Barba A, Perez-Perez J, et al. Impaired face-like object recognition in premanifest Huntington's disease. *Cortex.* 2020;123:162-172.
20. Martinez-Horta S, Horta-Barba A, Perez-Perez J, et al. Utility of the Parkinson's disease-Cognitive Rating Scale for the screening of global cognitive status in Huntington's disease. *Journal of Neurology.* 2020;267(5):1527-1535.
21. Aldaz T, Nigro P, Sánchez-Gómez A, et al. Non-motor symptoms in Huntington's disease: a comparative study with Parkinson's disease. *J Neurol.* 2019;266(6):1340-1350.
22. Ceccarini J, Ahmad R, Van de Vliet L, et al. Behavioral Symptoms in Premanifest Huntington Disease Correlate with Reduced Frontal CB(1)R Levels. *J Nucl Med.* 2019;60(1):115-121.
23. De Paepe AE, Sierpowska J, Garcia-Gorro C, et al. White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *Neuroimage Clin.* 2019;24:101965.
24. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Insensitivity to loss predicts apathy in huntington's disease. *Mov Disord.* 2019;34(9):1381-1391.
25. Misiura MB, Ciarochi J, Vaidya J, et al. Apathy Is Related to Cognitive Control and Striatum Volumes in Prodromal Huntington's Disease. *J Int Neuropsychol Soc.* 2019;25(5):462-469.
26. Osborne-Crowley K, Andrews SC, Labuschagne I, et al. Apathy Associated With Impaired Recognition of Happy Facial Expressions in Huntington's Disease. *J Int Neuropsychol Soc.* 2019;25(5):453-461.
27. Sampedro F, Martínez-Horta S, Perez-Perez J, et al. Cortical atrophic-hypometabolic dissociation in the transition from premanifest to early-stage Huntington's disease. *Eur J Nucl Med Mol Imaging.* 2019;46(5):1111-1116.
28. Andrews SC, Craufurd D, Durr A, et al. Executive impairment is associated with unawareness of neuropsychiatric symptoms in premanifest and early Huntington's disease. *Neuropsychology.* 2018;32(8):958-965.
29. Baake V, Coppen EM, van Duijn E, et al. Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study. *Neuroimage Clin.* 2018;19:66-70.
30. Baake V, van Duijn E, Roos RAC. Huntington's Disease Gene Expansion Carriers Are Aware of Their Degree of Apathy. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):183-187.
31. Fritz NE, Boileau NR, Stout JC, et al. Relationships Among Apathy, Health-Related Quality of Life, and Function in Huntington's Disease. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):194-201.
32. Jacobs M, Hart EP, Roos RAC. Cognitive Performance and Apathy Predict Unemployment in Huntington's Disease Mutation Carriers. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):188-193.
33. Kempnich CL, Andrews SC, Fisher F, Wong D, Georgiou-Karistianis N, Stout JC. Emotion Recognition Correlates With Social-Neuropsychiatric Dysfunction in Huntington's Disease. *J Int Neuropsychol Soc.* 2018;24(5):417-423.

34. Martinez-Horta S, Perez-Perez J, Sampedro F, et al. Structural and metabolic brain correlates of apathy in Huntington's disease. *Mov Disord.* 2018;33(7):1151-1159.
35. Sousa M, Moreira F, Jesus-Ribeiro J, et al. Apathy Profile in Parkinson's and Huntington's Disease: A Comparative Cross-Sectional Study. *Eur Neurol.* 2018;79(1-2):13-20.
36. McColgan P, Razi A, Gregory S, et al. Structural and functional brain network correlates of depressive symptoms in premanifest Huntington's disease. *Hum Brain Mapp.* 2017;38(6):2819-2829.
37. Ruiz-Idiago JM, Floriach M, Mareca C, et al. Spanish Validation of the Problem Behaviors Assessment-Short (PBA-s) for Huntington's Disease. *J Neuropsychiatry Clin Neurosci.* 2017;29(1):31-38.
38. Trinkler I, Devignevielle S, Achaibou A, et al. Embodied emotion impairment in Huntington's Disease. *Cortex.* 2017;92:44-56.
39. Bouwens JA, van Duijn E, Cobbaert CM, Roos RA, van der Mast RC, Giltay EJ. Plasma Cytokine Levels in Relation to Neuropsychiatric Symptoms and Cognitive Dysfunction in Huntington's disease. *J Huntingtons Dis.* 2016;5(4):369-377.
40. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. *Parkinsonism Relat Disord.* 2016;25:58-64.
41. Yang J, Chen K, Wei Q, et al. Clinical and genetic characteristics in patients with Huntington's disease from China. *Neurol Res.* 2016;38(10):916-920.
42. Bouwens JA, van Duijn E, van der Mast RC, Roos RA, Giltay EJ. Irritability in a Prospective Cohort of Huntington's Disease Mutation Carriers. *J Neuropsychiatry Clin Neurosci.* 2015;27(3):206-212.
43. Gregory S, Scahill RI, Seunarine KK, et al. Neuropsychiatry and White Matter Microstructure in Huntington's Disease. *J Huntingtons Dis.* 2015;4(3):239-249.
44. Hergert DC, Sanchez-Ramos J, Cimino CR. Examining Huntington's disease patient and informant concordance on frontally mediated behaviors. *J Clin Exp Neuropsychol.* 2015;37(9):981-987.
45. Mason S, Barker RA. Rating Apathy in Huntington's Disease: Patients and Companions Agree. *J Huntingtons Dis.* 2015;4(1):49-59.
46. Bouwens JA, Hubers AA, van Duijn E, et al. Acute-phase proteins in relation to neuropsychiatric symptoms and use of psychotropic medication in Huntington's disease. *Eur Neuropsychopharmacol.* 2014;24(8):1248-1256.
47. van Duijn E, Reedeker N, Giltay EJ, Eindhoven D, Roos RA, van der Mast RC. Course of irritability, depression and apathy in Huntington's disease in relation to motor symptoms during a two-year follow-up period. *Neurodegener Dis.* 2014;13(1):9-16.
48. van Duijn E, Craufurd D, Hubers AA, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J Neurol Neurosurg Psychiatry.* 2014;85(12):1411-1418.
49. Delmaire C, Dumas EM, Sharman MA, et al. The structural correlates of functional deficits in early huntington's disease. *Hum Brain Mapp.* 2013;34(9):2141-2153.
50. Eddy CM, Rickards HE. Impact of cognitive and behavioural changes on quality of life in Huntington's disease. *Basal Ganglia.* 2013;3(2):123-126.
51. Hubers AAM, Duijn EV, Roos RAC, et al. Suicidal ideation in a European Huntington's disease population. *Journal of Affective Disorders.* 2013;151(1):248-258.

52. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. *Neurology.* 2013;80(22):2022-2027.
53. Read J, Jones R, Owen G, et al. Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. *J Huntingtons Dis.* 2013;2(2):159-175.
54. Scahill RI, Hobbs NZ, Say MJ, et al. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. *Hum Brain Mapp.* 2013;34(3):519-529.
55. 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(7):637-649.
56. Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. *The Lancet Neurology.* 2012;11(1):42-53.
57. 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(1):31-42.
58. Banaszkiewicz K, Sitek EJ, Rudzińska M, Sołtan W, Sławek J, Szczudlik A. Huntington's disease from the patient, caregiver and physician's perspectives: three sides of the same coin? *J Neural Transm (Vienna).* 2012;119(11):1361-1365.
59. Hubers AA, Reedeker N, Giltay EJ, Roos RA, van Duijn E, van der Mast RC. Suicidality in Huntington's disease. *J Affect Disord.* 2012;136(3):550-557.
60. Reedeker N, Bouwens JA, van Duijn E, Giltay EJ, Roos RA, van der Mast RC. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. *J Neuropsychiatry Clin Neurosci.* 2011;23(4):434-441.
61. Duff K, Paulsen JS, Beglinger LJ, et al. "Frontal" behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: evidence of early lack of awareness. *J Neuropsychiatry Clin Neurosci.* 2010;22(2):196-207.
62. Reedeker N, Van Der Mast RC, Giltay EJ, Van Duijn E, Roos RA. Hypokinesia in Huntington's disease co-occurs with cognitive and global dysfunctioning. *Mov Disord.* 2010;25(11):1612-1618.
63. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2010;22(3):287-294.
64. van Duijn E, Giltay EJ, Zitman FG, Roos RA, van der Mast RC. Measurement of psychopathology in Huntington's disease: the critical role of caregivers. *J Nerv Ment Dis.* 2010;198(5):329-333.
65. Naarding P, Janzing JG, Eling P, van der Werf S, Kremer B. Apathy is not depression in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2009;21(3):266-270.
66. 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.* 2009;8(9):791-801.
67. Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *Gen Hosp Psychiatry.* 2008;30(2):155-161.

68. Baudic S, Maison P, Dolbeau G, et al. Cognitive impairment related to apathy in early Huntington's disease. *Dement Geriatr Cogn Disord.* 2006;21(5-6):316-321.
69. Chatterjee A, Anderson KE, Moskowitz CB, Hauser WA, Marder KS. A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2005;17(3):378-383.
70. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. *J Neurol Neurosurg Psychiatry.* 2003;74(1):120-122.
71. Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS. Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment.* 2003;10(1):79-85.
72. Leroi I, O'Hearn E, Marsh L, et al. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. *Am J Psychiatry.* 2002;159(8):1306-1314.
73. Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci.* 2002;14(1):37-43.
74. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. *Neuropsychiatry Neuropsychol Behav Neurol.* 2001;14(4):219-226.
75. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry.* 2001;71(3):310-314.
76. Kulisevsky J, Litvan I, Berthier ML, Pascual-Sedano B, Paulsen JS, Cummings JL. Neuropsychiatric assessment of Gilles de la Tourette patients: comparative study with other hyperkinetic and hypokinetic movement disorders. *Mov Disord.* 2001;16(6):1098-1104.
77. Litvan I, Paulsen JS, Mega MS, Cummings JL. Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Arch Neurol.* 1998;55(10):1313-1319.
78. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci.* 1998;10(3):314-319.
79. Paulsen JS, Stout JC, DeLaPena J, et al. Frontal Behavioral Syndromes in Cortical and Subcortical Dementia. *Assessment.* 1996;3(3):327-337.
80. Burns A, Folstein S, Brandt J, Folstein M. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis.* 1990;178(1):20-26.

Data Supplement for Zadegan et al., Frequency and Pathophysiology of Apathy in Huntington Disease: A Systematic Review and Meta-Analysis, Journal of Neuropsychiatry and Clinical Neurosciences (doi: 10.1176/appi.neuropsych.20220033).

Appendix 5. Risk of bias assessment

	Study	**Year**	I*	II	III	IV	V	VI	VII	VIII	IX	Total (Max 14)
1.	Abreu et al.[1]	2021	2	1	1	1	2	0	1	2	0	10
2.	Atkins et al.[2]	2021	2	0	0	1	2	0	1	2	1	9
3.	De Paepe et al.[3]	2021	2	0	0	1	2	1	1	2	1	10
4.	Hentosh et al.[4]	2021	2	1	1	1	2	0	1	2	0	10
5.	Hergert et al.[5]	2021	1	0	1	1	2	1	0	2	1	9
6.	Martinez-Horta et al.[6]	2021	2	0	0	1	2	0	1	2	1	9
7.	McAllister et al.[7]	2021	2	1	1	1	1	0	1	2	1	10
8.	Migliore et al.[8]	2021	2	0	1	1	2	1	1	2	0	10
9.	Nair et al.[9]	2021	2	0	1	1	2	0	1	2	1	10
10.	Oosterloo et al.[10]	2021	2	1	1	1	2	0	1	2	0	10
11.	Ranganathan et al.[11]	2021	2	1	1	1	2	0	1	2	1	11
12.	van der Zwaan et al.[12]	2021	2	1	1	1	2	0	1	2	1	11
13.	Andrews et al.[13]	2020	2	1	1	1	2	1	1	2	1	12
14.	Atkins et al.[14]	2020	2	0	0	1	2	0	1	2	1	9
15.	Ellis et al.[15]	2020	2	1	1	1	1	0	1	2	1	10
16.	Gunn et al.[16]	2020	2	1	1	1	2	1	1	2	1	12
17.	Isaacs et al.[17]	2020	2	0	1	1	3	1	1	2	0	11
18.	Julayanont et al.[18]	2020	2	1	1	1	2	1	1	2	1	12
19.	Martinez-Horta et al.[19] a	2020	2	1	1	1	2	0	1	2	1	11
20.	Martinez-Horta et al.[20] b	2020	2	0	1	1	2	0	1	2	1	10
21.	Aldaz et al.[21]	2019	2	0	1	1	1	1	1	2	1	10
22.	Ceccarini et al.[22]	2019	2	0	0	1	2	0	1	2	1	9
23.	De Paepe et al.[23]	2019	2	0	0	1	3	0	1	2	1	10
24.	McLauchlan et al.[24]	2019	2	0	0	1	2	0	1	1	1	8
25.	Misiura et al.[25]	2019	2	1	1	1	2	1	1	2	1	12
26.	Osborne-Crowley et al.[26]	2019	2	1	1	1	2	1	1	2	1	12
27.	Sampedro et al.[27]	2019	2	0	0	1	2	0	0	2	1	8
28.	Andrews et al.[28]	2018	2	1	1	1	2	1	1	2	1	12
29.	Baake et al.[29] a	2018	2	1	1	1	2	0	1	2	1	11
30.	Baake et al.[30] b	2018	2	0	1	1	2	0	0	2	1	9
31.	Fritz et al.[31]	2018	2	0	1	1	2	1	1	2	1	11
32.	Jacobs et al.[32]	2018	2	0	1	1	2	0	1	2	1	10
33.	Kempnich et al.[33]	2018	2	0	0	1	2	1	0	1	1	8
34.	Martinez-Horta et al.[34]	2018	2	0	0	1	2	1	1	2	1	10
35.	Sousa et al.[35]	2018	2	0	1	1	2	0	1	2	1	10
36.	McColgan et al.[36]	2017	2	1	1	1	3	0	1	2	1	12
37.	Ruiz-Idiago et al.[37]	2017	2	0	1	1	3	1	1	2	0	11
38.	Trinkler et al.[38]	2017	2	0	0	1	2	0	1	2	1	9
39.	Bouwens et al.[39]	2016	2	0	1	1	2	1	1	2	1	11
40.	Martinez-Horta et al.[40]	2016	2	1	1	1	2	1	1	2	1	12
41.	Yang et al.[41]	2016	2	0	1	1	2	0	1	1	0	8
42.	Bouwens et al.[42]	2015	2	0	1	1	2	1	1	2	1	11
43.	Gregory et al.[43]	2015	2	0	1	1	2	0	1	2	1	10
44.	Hergert et al.[44]	2015	1	0	0	1	2	1	0	2	0	7

45.	Mason et al.[45]	2015	2	0	1	1	2	1	1	2	0	10
46.	Bouwens et al.[46]	2014	2	0	1	1	2	0	1	2	1	10
47.	van Duijn et al.[47] a	2014	2	0	1	1	2	1	1	2	1	11
48.	van Duijn et al.[48] b	2014	2	1	1	1	2	0	1	1	1	10
49.	Delmaire et al.[49]	2013	2	0	1	1	2	0	1	2	1	10
50.	Eddy et al.[50]	2013	2	0	0	1	2	0	1	2	0	8
51.	Hubers et al.[51]	2013	2	1	1	1	2	0	1	2	1	11
52.	Killoran et al.[52]	2013	2	1	1	1	2	0	1	2	1	11
53.	Read et al.[53]	2013	2	1	1	1	2	0	1	2	1	11
54.	Scahill et al.[54]	2013	2	1	1	1	2	0	1	2	1	11
55.	Tabrizi et al.[55]	2013	2	2	1	1	2	0	1	2	1	12
56.	Banaszkiewicz et al.[56]	2012	2	0	1	1	2	0	1	2	1	10
57.	Hubers et al.[57]	2012	2	0	1	1	2	0	1	2	1	10
58.	Tabrizi et al.[58]	2012	2	2	1	1	2	0	1	2	1	12
59.	Reedeker et al.[59]	2011	2	0	1	1	2	1	1	2	1	11
60.	Tabrizi et al.[60]	2011	2	2	1	1	2	0	1	2	1	12
61.	Duff et al.[61]	2010	2	1	1	1	2	1	0	2	1	11
62.	Reedeker et al.[62]	2010	2	0	1	1	2	1	1	2	1	11
63.	van Duijn et al.[63] a	2010	2	0	1	1	3	1	1	2	1	12
64.	van Duijn et al[64] b	2010	2	0	1	1	2	1	1	1	0	9
65.	Naarding et al.[65]	2009	2	0	1	1	2	1	1	2	0	10
66.	Tabrizi et al.[66]	2009	2	2	1	1	2	0	1	2	1	12
67.	Kingma et al.[67]	2008	2	0	1	1	2	1	1	2	0	10
68.	Baudic et al.[68]	2006	2	0	1	1	2	1	1	2	1	11
69.	Chatterjee et al.[69]	2005	1	0	1	1	2	1	1	2	0	9
70.	Hamilton et al.[70]	2003	2	0	0	1	2	1	1	2	1	10
71.	Stout et al. [71]	2003	1	1	1	1	2	1	0	2	0	9
72.	Leroi et al.[72]	2002	2	0	1	1	3	1	1	2	1	12
73.	Thompson et al.[73]	2002	2	0	0	1	2	1	1	2	0	9
74.	Craufurd et al.[74]	2001	2	0	1	1	2	1	1	2	0	10
75.	Paulsen et al.[75]	2001	2	0	1	1	2	1	1	2	0	10
76.	Kulisevsky et al.[76]	2001	2	0	0	1	2	1	1	2	1	10
77.	Litvan et al. [77]	1998	1	0	0	1	2	1	1	2	1	9
78.	Levy et al.[78]	1998	1	0	0	1	2	1	1	2	0	8
79.	Paulsen et al.[79]	1996	1	0	0	1	2	1	0	2	1	8
80.	Burns et al.[80]	1990	1	0	0	1	2	1	0	2	1	8

* See appendix 2 for risk of bias assessment tool.

References

1. Abreu D, Ware J, Georgiou-Karistianis N, et al. Utility of Huntington's Disease Assessments by Disease Stage: Floor/Ceiling Effects. *Front Neurol.* 2021;12:595679.
2. Atkins KJ, Andrews SC, Chong TT, Stout JC. Multidimensional Apathy: The Utility of the Dimensional Apathy Scale in Huntington's Disease. *Mov Disord Clin Pract.* 2021;8(3):361-370.
3. De Paepe AE, Ara A, Garcia-Gorro C, et al. Gray Matter Vulnerabilities Predict Longitudinal Development of Apathy in Huntington's Disease. *Mov Disord.* 2021;36(9):2162-2172.
4. Hentosh S, Zhu L, Patino J, Furr JW, Rocha NP, Furr Stimming E. Sex Differences in Huntington's Disease: Evaluating the Enroll-HD Database. *Movement Disorders Clinical Practice.* 2021;8(3):420-426.
5. Hergert DC, Cimino CR. Predictors of Caregiver Burden in Huntington's Disease. *Arch Clin Neuropsychol.* 2021.
6. Martinez-Horta S, Sampedro F, Horta-Barba A, et al. Structural brain correlates of irritability and aggression in early manifest Huntington's disease. *Brain Imaging Behav.* 2021;15(1):107-113.
7. McAllister B, Gusella JF, Landwehrmeyer GB, et al. Timing and Impact of Psychiatric, Cognitive, and Motor Abnormalities in Huntington Disease. *Neurology.* 2021;96(19):e2395-e2406.
8. Migliore S, D'Aurizio G, Maffi S, et al. Cognitive and behavioral associated changes in manifest Huntington disease: A retrospective cross-sectional study. *Brain Behav.* 2021;11(7):e02151.
9. Nair A, Razi A, Gregory S, Rutledge RR, Rees G, Tabrizi SJ. Imbalanced basal ganglia connectivity is associated with motor deficits and apathy in Huntington's disease. *Brain.* 2021.
10. Oosterloo M, de Greef BTA, Bijlsma EK, et al. Disease Onset in Huntington's Disease: When Is the Conversion? *Movement Disorders Clinical Practice.* 2021;8(3):352-360.
11. Ranganathan M, Kostyk SK, Allain DC, Race JA, Daley AM. Age of onset and behavioral manifestations in Huntington's disease: An Enroll-HD cohort analysis. *Clinical Genetics.* 2021;99(1):133-142.
12. van der Zwaan KF, Jacobs M, van Zwet EW, Roos RAC, de Bot ST. Predictors of Working Capacity Changes Related to Huntington's Disease: A Longitudinal Study. *J Huntingtons Dis.* 2021;10(2):269-276.
13. Andrews SC, Langbehn DR, Craufurd D, et al. Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychol Med.* 2020:1-7.
14. Atkins KJ, Andrews SC, Stout JC, Chong TT. Dissociable Motivational Deficits in Pre-manifest Huntington's Disease. *Cell Rep Med.* 2020;1(9):100152.
15. Ellis N, Tee A, McAllister B, et al. Genetic Risk Underlying Psychiatric and Cognitive Symptoms in Huntington's Disease. *Biol Psychiatry.* 2020;87(9):857-865.
16. Gunn S, Maltby J, Dale M. Assessing Mental Health Difficulties of Persons With Huntington's Disease: Does Informant Presence Make a Difference? *J Neuropsychiatry Clin Neurosci.* 2020;32(3):244-251.
17. Isaacs D, Gibson JS, Stovall J, Claassen DO. The Impact of Anosognosia on Clinical and Patient-Reported Assessments of Psychiatric Symptoms in Huntington's Disease. *Journal of Huntington's Disease.* 2020;9(3):291-302.
18. Julayanont P, Heilman KM, McFarland NR. Early-Motor Phenotype Relates to Neuropsychiatric and Cognitive Disorders in Huntington's Disease. *Mov Disord.* 2020;35(5):781-788.
19. Martínez-Horta S, Horta-Barba A, Perez-Perez J, et al. Impaired face-like object recognition in premanifest Huntington's disease. *Cortex.* 2020;123:162-172.
20. Martinez-Horta S, Horta-Barba A, Perez-Perez J, et al. Utility of the Parkinson's disease-Cognitive Rating Scale for the screening of global cognitive status in Huntington's disease. *Journal of Neurology.* 2020;267(5):1527-1535.

21. Aldaz T, Nigro P, Sánchez-Gómez A, et al. Non-motor symptoms in Huntington's disease: a comparative study with Parkinson's disease. *J Neurol.* 2019;266(6):1340-1350.
22. Ceccarini J, Ahmad R, Van de Vliet L, et al. Behavioral Symptoms in Premanifest Huntington Disease Correlate with Reduced Frontal CB(1)R Levels. *J Nucl Med.* 2019;60(1):115-121.
23. De Paepe AE, Sierpowska J, Garcia-Gorro C, et al. White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *Neuroimage Clin.* 2019;24:101965.
24. McLauchlan DJ, Lancaster T, Craufurd D, Linden DEJ, Rosser AE. Insensitivity to loss predicts apathy in huntington's disease. *Mov Disord.* 2019;34(9):1381-1391.
25. Misiura MB, Ciarochi J, Vaidya J, et al. Apathy Is Related to Cognitive Control and Striatum Volumes in Prodromal Huntington's Disease. *J Int Neuropsychol Soc.* 2019;25(5):462-469.
26. Osborne-Crowley K, Andrews SC, Labuschagne I, et al. Apathy Associated With Impaired Recognition of Happy Facial Expressions in Huntington's Disease. *J Int Neuropsychol Soc.* 2019;25(5):453-461.
27. Sampedro F, Martínez-Horta S, Perez-Perez J, et al. Cortical atrophic-hypometabolic dissociation in the transition from premanifest to early-stage Huntington's disease. *Eur J Nucl Med Mol Imaging.* 2019;46(5):1111-1116.
28. Andrews SC, Craufurd D, Durr A, et al. Executive impairment is associated with unawareness of neuropsychiatric symptoms in premanifest and early Huntington's disease. *Neuropsychology.* 2018;32(8):958-965.
29. Baake V, Coppen EM, van Duijn E, et al. Apathy and atrophy of subcortical brain structures in Huntington's disease: A two-year follow-up study. *Neuroimage Clin.* 2018;19:66-70.
30. Baake V, van Duijn E, Roos RAC. Huntington's Disease Gene Expansion Carriers Are Aware of Their Degree of Apathy. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):183-187.
31. Fritz NE, Boileau NR, Stout JC, et al. Relationships Among Apathy, Health-Related Quality of Life, and Function in Huntington's Disease. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):194-201.
32. Jacobs M, Hart EP, Roos RAC. Cognitive Performance and Apathy Predict Unemployment in Huntington's Disease Mutation Carriers. *J Neuropsychiatry Clin Neurosci.* 2018;30(3):188-193.
33. Kempnich CL, Andrews SC, Fisher F, Wong D, Georgiou-Karistianis N, Stout JC. Emotion Recognition Correlates With Social-Neuropsychiatric Dysfunction in Huntington's Disease. *J Int Neuropsychol Soc.* 2018;24(5):417-423.
34. Martinez-Horta S, Perez-Perez J, Sampedro F, et al. Structural and metabolic brain correlates of apathy in Huntington's disease. *Mov Disord.* 2018;33(7):1151-1159.
35. Sousa M, Moreira F, Jesus-Ribeiro J, et al. Apathy Profile in Parkinson's and Huntington's Disease: A Comparative Cross-Sectional Study. *Eur Neurol.* 2018;79(1-2):13-20.
36. McColgan P, Razi A, Gregory S, et al. Structural and functional brain network correlates of depressive symptoms in premanifest Huntington's disease. *Hum Brain Mapp.* 2017;38(6):2819-2829.
37. Ruiz-Idiago JM, Floriach M, Mareca C, et al. Spanish Validation of the Problem Behaviors Assessment-Short (PBA-s) for Huntington's Disease. *J Neuropsychiatry Clin Neurosci.* 2017;29(1):31-38.
38. Trinkler I, Devignevielle S, Achaibou A, et al. Embodied emotion impairment in Huntington's Disease. *Cortex.* 2017;92:44-56.
39. Bouwens JA, van Duijn E, Cobbaert CM, Roos RA, van der Mast RC, Giltay EJ. Plasma Cytokine Levels in Relation to Neuropsychiatric Symptoms and Cognitive Dysfunction in Huntington's disease. *J Huntingtons Dis.* 2016;5(4):369-377.
40. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. *Parkinsonism Relat Disord.* 2016;25:58-64.

41. Yang J, Chen K, Wei Q, et al. Clinical and genetic characteristics in patients with Huntington's disease from China. *Neurol Res.* 2016;38(10):916-920.
42. Bouwens JA, van Duijn E, van der Mast RC, Roos RA, Giltay EJ. Irritability in a Prospective Cohort of Huntington's Disease Mutation Carriers. *J Neuropsychiatry Clin Neurosci.* 2015;27(3):206-212.
43. Gregory S, Scahill RI, Seunarine KK, et al. Neuropsychiatry and White Matter Microstructure in Huntington's Disease. *J Huntingtons Dis.* 2015;4(3):239-249.
44. Hergert DC, Sanchez-Ramos J, Cimino CR. Examining Huntington's disease patient and informant concordance on frontally mediated behaviors. *J Clin Exp Neuropsychol.* 2015;37(9):981-987.
45. Mason S, Barker RA. Rating Apathy in Huntington's Disease: Patients and Companions Agree. *J Huntingtons Dis.* 2015;4(1):49-59.
46. Bouwens JA, Hubers AA, van Duijn E, et al. Acute-phase proteins in relation to neuropsychiatric symptoms and use of psychotropic medication in Huntington's disease. *Eur Neuropsychopharmacol.* 2014;24(8):1248-1256.
47. van Duijn E, Reedeker N, Giltay EJ, Eindhoven D, Roos RA, van der Mast RC. Course of irritability, depression and apathy in Huntington's disease in relation to motor symptoms during a two-year follow-up period. *Neurodegener Dis.* 2014;13(1):9-16.
48. van Duijn E, Craufurd D, Hubers AA, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J Neurol Neurosurg Psychiatry.* 2014;85(12):1411-1418.
49. Delmaire C, Dumas EM, Sharman MA, et al. The structural correlates of functional deficits in early huntington's disease. *Hum Brain Mapp.* 2013;34(9):2141-2153.
50. Eddy CM, Rickards HE. Impact of cognitive and behavioural changes on quality of life in Huntington's disease. *Basal Ganglia.* 2013;3(2):123-126.
51. Hubers AAM, Duijn EV, Roos RAC, et al. Suicidal ideation in a European Huntington's disease population. *Journal of Affective Disorders.* 2013;151(1):248-258.
52. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. *Neurology.* 2013;80(22):2022-2027.
53. Read J, Jones R, Owen G, et al. Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. *J Huntingtons Dis.* 2013;2(2):159-175.
54. Scahill RI, Hobbs NZ, Say MJ, et al. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. *Hum Brain Mapp.* 2013;34(3):519-529.
55. 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(7):637-649.
56. Banaszkiewicz K, Sitek EJ, Rudzińska M, Sołtan W, Sławek J, Szczudlik A. Huntington's disease from the patient, caregiver and physician's perspectives: three sides of the same coin? *J Neural Transm (Vienna).* 2012;119(11):1361-1365.
57. Hubers AA, Reedeker N, Giltay EJ, Roos RA, van Duijn E, van der Mast RC. Suicidality in Huntington's disease. *J Affect Disord.* 2012;136(3):550-557.
58. Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. *The Lancet Neurology.* 2012;11(1):42-53.
59. Reedeker N, Bouwens JA, van Duijn E, Giltay EJ, Roos RA, van der Mast RC. Incidence, course, and predictors of apathy in Huntington's disease: a two-year prospective study. *J Neuropsychiatry Clin Neurosci.* 2011;23(4):434-441.

60. 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(1):31-42.
61. Duff K, Paulsen JS, Beglinger LJ, et al. "Frontal" behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: evidence of early lack of awareness. *J Neuropsychiatry Clin Neurosci.* 2010;22(2):196-207.
62. Reedeker N, Van Der Mast RC, Giltay EJ, Van Duijn E, Roos RA. Hypokinesia in Huntington's disease co-occurs with cognitive and global dysfunctioning. *Mov Disord.* 2010;25(11):1612-1618.
63. van Duijn E, Reedeker N, Giltay EJ, Roos RA, van der Mast RC. Correlates of apathy in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2010;22(3):287-294.
64. van Duijn E, Giltay EJ, Zitman FG, Roos RA, van der Mast RC. Measurement of psychopathology in Huntington's disease: the critical role of caregivers. *J Nerv Ment Dis.* 2010;198(5):329-333.
65. Naarding P, Janzing JG, Eling P, van der Werf S, Kremer B. Apathy is not depression in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2009;21(3):266-270.
66. 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.* 2009;8(9):791-801.
67. Kingma EM, van Duijn E, Timman R, van der Mast RC, Roos RA. Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *Gen Hosp Psychiatry.* 2008;30(2):155-161.
68. Baudic S, Maison P, Dolbeau G, et al. Cognitive impairment related to apathy in early Huntington's disease. *Dement Geriatr Cogn Disord.* 2006;21(5-6):316-321.
69. Chatterjee A, Anderson KE, Moskowitz CB, Hauser WA, Marder KS. A comparison of self-report and caregiver assessment of depression, apathy, and irritability in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2005;17(3):378-383.
70. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. *J Neurol Neurosurg Psychiatry.* 2003;74(1):120-122.
71. Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS. Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment.* 2003;10(1):79-85.
72. Leroi I, O'Hearn E, Marsh L, et al. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. *Am J Psychiatry.* 2002;159(8):1306-1314.
73. Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci.* 2002;14(1):37-43.
74. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. *Neuropsychiatry Neuropsychol Behav Neurol.* 2001;14(4):219-226.
75. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry.* 2001;71(3):310-314.
76. Kulisevsky J, Litvan I, Berthier ML, Pascual-Sedano B, Paulsen JS, Cummings JL. Neuropsychiatric assessment of Gilles de la Tourette patients: comparative study with other hyperkinetic and hypokinetic movement disorders. *Mov Disord.* 2001;16(6):1098-1104.
77. Litvan I, Paulsen JS, Mega MS, Cummings JL. Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. *Arch Neurol.* 1998;55(10):1313-1319.
78. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci.* 1998;10(3):314-319.
79. Paulsen JS, Stout JC, DeLaPena J, et al. Frontal Behavioral Syndromes in Cortical and Subcortical Dementia. *Assessment.* 1996;3(3):327-337.
80. Burns A, Folstein S, Brandt J, Folstein M. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis.* 1990;178(1):20-26.