Juvenile Huntington Disease: towards better understanding its unique disease characteristics

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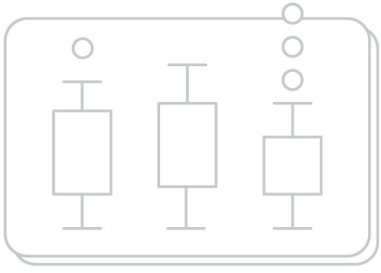

CHAPTER 4

Comparison of the clinical spectrum of juvenile- and adult-onset Huntington Disease: a national cohort and Enroll-HD observational study

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This chapter is an adjusted version of the published article, Bakels HS, van der Zwaan KF, Van Zwet E, Reijntjes R, Sprenger GP, Knecht TA, Roos RAC, de Bot ST. Comparison of the Clinical Spectrum of Juvenile- and Adult-Onset Huntington Disease: A National Cohort and Enroll-HD Observational Study. Neurology. 2025 May 27;104(10):e213525.

ABSTRACT

Background and Objectives: Differences in clinical characteristics between juvenile-onset Huntington Disease (JHD) and adult-onset HD (AHD) are hypothesized but not directly compared. This study compares clinical characteristics occurrence and severity across the age-at-onset (AO) subtypes.

Methods: Using the national juvenile-onset HD patient cohort and the international Enroll-HD registry (NCT01574053), we compared childhood-onset JHD (cJHD; AO 0-10), adolescent-onset JHD (aJHD; AO 11-20), and adult-onset HD (AHD; AO 21-65) on proportions of clinical characteristics at onset and psychiatric characteristics in pooled datasets. Additionally, mixed models were applied to longitudinal data from ENROLL-HD to compare fitted severity and annual progression in motor and neurocognitive domains 5 years post-onset across the 3 AO-HD subtypes.

Results: The combined datasets provided clinical data from 46 patients with cJHD (mean AO 6.7, 45% female), 243 patients with aJHD (mean AO 16.7, 46% female), and 9 504 patients with AHD (mean AO 44.7, 51% female). At onset, neurocognitive symptoms occurred in 47.5% of patients with cJHD (n=46; 95% CI 31.8-63.7%), significantly more often compared to 24.9% of patients with aJHD (n=209; 19.3-31.4%) and 15% of patients with AHD (n=8 177; 14.3-15.8%). Psychiatric symptoms occurred in 47.1% of patients with aJHD (95% CI 40.2-54.1%), significantly more compared to 31% of patients with AHD (30.1-32%). Throughout the disease, aggressive behavior occurred in 73.9% of patients with cJHD (n=46; 95% CI 58.6-85.2%) and 55.9% of patients with aJHD (n=238; 49.3-62.3%), significantly more compared with 40.7% of patients with AHD (n=9 501; 39.7-41.7%). Psychosis occurred in 23.5% of patients with aJHD (95% CI 18.4-29.5%), significantly more compared with 12.8% of those with AHD (12.1-13.5%). Linear regression revealed significantly higher predicted mean UHDRS-TMS scores for dysarthria (1.38, 95% CI 1.08-1.69), parkinsonism (9.85, 8.43-11.27), dystonia (6.47, 4.98-7.96), and oculomotor disturbances (9.86, 7.75-11.97), along with higher predicted annual changes in dysarthria (0.25, 0.16-0.34), oculomotor (1.53, 0.99-2.07) and gait and balance (0.79, 0.55-1.03) in earlier onset phenotypes.

Discussion: This study highlights distinct clinical patterns in JHD subtypes compared with AHD. Stratification by age at onset–defined HD subtypes is needed in future studies. Our use of regression models should not be interpreted as prediction model or to infer causality.

INTRODUCTION

Huntington Disease (HD) is an autosomal dominant brain disorder caused by a pathologically-expanded CAG-repeat (≥36) in the Huntingtin gene.[1]Age at clinical onset is inversely correlated with CAG-repeat length, explaining up to 84% of variability.[2] The mean age at symptom onset is between 30-50 years (range 1.5-87).[3] The term juvenile-onset HD (JHD) is arbitrarily defined for HD patients with symptom onset <21 years, which is seen in approximately 0.5-5% of HD patients.[4,5] Importantly, clinical differences exist between JHD patients with disease onset in childhood (cJHD; onset ≤10 years) and in adolescence (aJHD; onset between 11-20 years).[6] cJHD, mostly associated with CAG-repeats ≥80, represents a different and more aggressive HD subtype.[7]

Over the years, various retrospective JHD case reports and series aided our understanding of this subtype of HD.[6] Patients with JHD often present with a combination of neurocognitive impairments (decline in attention, memory or school performance), psychiatric (e.g. irritability and depression) and behavioral disturbances, early onset of gait, speech and swallowing disturbances, and a hypokinetic-rigid syndrome. In addition, other HD symptoms such as sleep disturbances, epileptic seizures, pain and weight loss are commonly described. Furthermore, systemic disease manifestations in cardiovascular, respiratory and gastrointestinal domains are frequently observed in HD and in some instances correlate with age at disease onset or CAG-repeat length.[8-11] The comparison of clinical characteristics between patients with cJHD, aJHD and adult-onset HD (AHD) becomes more relevant when considering pathophysiologic differences between these Age at Onset-defined HD (AO-HD) subtypes.[12] However, comparative studies between patiens with JHD subtypes and AHD are rarely performed. One such study revealed faster progression of motor symptoms and shorter survival of patients with cJHD patients compared to those with aJHD and AHD.[7] Other studies highlighted differences between patients with JHD and AHD regarding neurocognitive and psychiatric changes at the onset of disease,[13,14] and epilepsy,[15] however, they did not differentiate between childhood-onset and adolescent-onset of disease.

To address JHD subtype differences and to ensure participation of patients with JHD in future interventional studies, quantification of expected clinical differences between AO-HD subtypes is essential.

The major limitation of studying the JHD phenotype is its low prevalence. To allocate as much JHD cases as possible, we started in 2020 a national Dutch registry for

juvenile-onset HD patients (HD-JUNIOR). By the combined use of HD-JUNIOR and the international Enroll-HD platform,[16] the objective of this study was to describe and compare JHD subtypes with AHD in the occurrence of clinical characteristics at onset and during the disease course. In addition, by use of linear mixed models we aimed to compare the fitted severity and annual change for 3 reference patients (cJHD, aJHD and AHD) based on longitudinal clinical data of Enroll-HD. Compared with AHD, we hypothesize that JHD subtypes will have a higher proportion of psychiatric and neurocognitive disease characteristics at onset and a higher occurrence of behavioral changes, epilepsy and pain during the course of the disease. We also hypothesize that cJHD will have more severe and faster progression of motor disease characteristics related to hypokinetic-rigid syndrome, dystonia and dysarthria and less severe chorea compared with aJHD and AHD.

METHODS

Study Design and Population

To analyze JHD patient data from as many patients as possible and to allow for the comparison of JHD with typical disease onset in adulthood, data from 2 (J) HD datasets were used: the HD-JUNIOR and Enroll-HD registries. HD-JUNIOR was started in 2020 and retrospectively collects clinical data of both alive and deceased patients with JHD in the Netherlands (n=28). Enroll-HD[16] is an international (183 sites in 23 countries) prospective observational study since 2012 in which clinical data from (J)HD gene carriers, - patients and controls are gathered. Core Unified Huntington's Disease Rating Scale (UHDRS) datasets were collected annually from all research participants as part of this multicenter longitudinal observational study. Data were monitored for quality and accuracy using a risk-based monitoring approach. Data were generously provided by the participants in the Enroll-HD study and made available by Cure Huntington's Disease Initiative (CHDI) Foundation, Inc. For this study, the 5th periodic dataset was used (PDS5; release 18-DEC-2020; n=21 116 participants), including a specified dataset with deaggregated data for AO and enrolment younger than 17 years and CAG-repeat length of 70 and higher.

Selection and stratification criteria for this study consisted of a clinical diagnosis of HD and AO-HD subtypes (as defined below). Based on a higher suggested occurrence of psychiatric and neurocognitive disease characteristics in with JHD

at onset,[6] a JHD phenotype was primarily defined by any HD-related first symptom below 21 years of age and, subsequently, occurrence of motor symptoms within 15 years of first symptoms. Subsequently, patients with JHD were subdivided into childhood-onset JHD (cJHD: primary onset ≤10 years) and adolescent-onset JHD phenotype (aJHD: primary onset between 11 and 20 years). For the comparison of clinical characteristics in JHD subtypes with typical disease-onset in adulthood, inclusion criteria for an AHD phenotype were any HD-related first symptom between age 21 and 65 years and a CAG-repeat ≥40. In HD-JUNIOR, primary assessment of eligibility was performed by H.S.B and T.A.K. based on all available information in the medical records. In case of a questionable relationship of first symptom with JHD phenotype, S.T.B was consulted for confirmation or withdrawal of the patient with JHD in the registry. In Enroll-HD, participants were selected from the PDS5 by using of the retrospective HD Clinical Characteristics (HDCC) questionnaire, including: raters' estimate of age at first symptom onset; age at first motor symptom onset; and clinical HD diagnosis. Based on this selection H.S.B., R.A.C.R and S.T.B. then further analyzed clinical outliers of the JHD groups based on raters' confidence of AO estimation and time between age onset and enrolment. Patients who we classified as outliers were removed from further analyses and are listed in Supplementary Table 1. See the STROBE- flow diagram for the number of eligible AO-HD defined patients in the HD-JUNIOR and ENROLL-HD datasets (Figure 1). Five patients with aJHD were part of both datasets and therefore excluded from the HD-JUNIOR dataset in case of pooled analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

Local ethical approval for the conduct of assessments on human participants (Enroll-HD, NCT01574053) and use of pseudonymized clinical data (HD-JUNIOR) was provided by the medical research ethical committee of Leiden-The Hague-Delft (MREC-LDD). In addition, all participating sites in Enroll-HD were required to obtain and maintain local ethical approval. Written informed consent was obtained from all participants (or guardians of participants) in the Enroll-HD registry and from all alive participants in the HD-JUNIOR registry. In the case of clinical data from deceased patients with JHD in the HD-JUNIOR registry, the MREC-LDD determined that consent was not required and pseudonymized data were shared by the last treating physician.

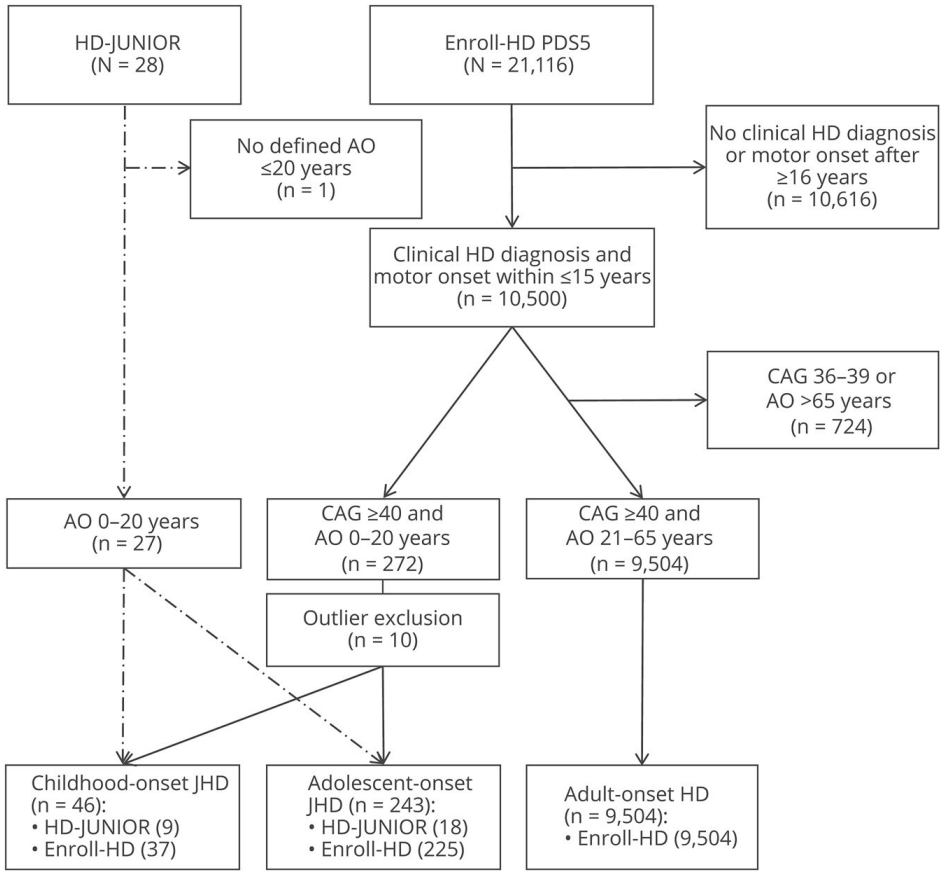

Figure 1. Participant Selection in HD-JUNIOR and Enroll-HD PDS5.

The STROBE flow diagram illustrates the selection and stratification criteria for participants from the HD-JUNIOR (long dashed dot line) and Enroll-HD (solid line) datasets, detailing the number of patients who contributed data for 1 or more outcome measures in this study. Selected patients were stratified into 3 AO-HD subtypes: childhood-onset JHD, adolescent-onset JHD, and adult-onset HD.

AO = age at onset; CAG = cytosine-adenine-guanine repeats in the Huntingtin gene; HD = Huntington disease; n = number of participants; PDS5 = periodic dataset 5; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology.

Outcome Variables

Our aim was to analyze and compare clinical characteristics at disease onset and throughout the disease course across the 3 key neurologic domains in HD: (1) motor, (2) neurocognitive, and (3) psychiatric, as well as (4) other domains.

For the cross-sectional analysis of the prevalence of HD clinical characteristics at onset and occurrence of psychiatric characteristics during the disease course,

retrospective data of both datasets were pooled (HD-JUNIOR: patient/caretaker answer retrieved from medical records; Enroll-HD: patient answer in the HDCC questionnaire) because of comparable outcome and assessment method. For the analysis of disease characteristics at onset, we defined 3 outcome variables:(1) (mixed) motor onset, (2) (mixed) neurocognitive onset, and (3) (mixed) psychiatric onset. For the occurrence of psychiatric disease characteristics, we specified 6 subclusters of which comparable data were available in both datasets: (1) irritability, (2) violent/aggressive behavior, (3) depression, (4) apathy, (5) perseverative and obsessive-compulsive behavior and (6) psychosis. For both outcomes, patients were omitted from analyses in case of missing data.

To perform a cross-sectional analysis of the occurrence of HD motor characteristics during the disease course we used retrospective data from HD-JUNIOR alone (patient/caretaker answer and neurological examination).

To assess the severity of neurocognitive disease characteristics during the disease course in the HD-JUNIOR dataset we used neurocognitive measures (full, verbal and performance IQ) based on neuropsychological assessments obtained from 7 patients with cJHD and 9 patients with aJHD.

In the 'other' domain we performed cross-sectional analysis on the occurrence of epilepsy and pain during the disease course. Regarding epilepsy, in HD-JUNIOR epileptic seizures were recorded in case it was mentioned by the patient, caretaker or medical expert and confirmatory EEG data or summary were available. In the Enroll-HD dataset, we used the comorbidity information to select all patients with an ICD-10 registration "G40": epilepsy and recurrent seizures. For both datasets, the occurrence of epilepsy was recorded as not present in case of no specified data on the outcome. The occurrence of epilepsy was pooled between datasets because the assessment method for epilepsy in both relate to a clinical diagnosis of epileptic seizures. Regarding the assessment of pain, we specified the occurrence of pain in case it was mentioned by the patient or caretaker in the medical file. The occurrence of pain was recorded as not present in case of no specified data on the outcome. Different from the retrospective assessment of pain in the HD-JUNIOR dataset, we used the prospective Short Form health-survey (SF12) at baseline from the Enroll-HD dataset to assess pain interference during daily activities in the past week and to compare it between AO-HD subtypes.[17]

Prospective measurements from the UHDRS-Total-Motor-Score (UHDRS-TMS; motor symptoms), the Symbol-Digit-Modalities-Test (UHDRS-SDMT; psychomotor processing speed) and Stroop-Interference-Test (UHDRS-SIT; executive functioning) of the Enroll-HD dataset were used to predict the severity and annual progression of motor and neurocognitive symptoms for 3 hypothetical patients referring to the AO-HD subtypes as measured 5 years after onset. Regarding the UHDRS-TMS, 6 outcome subclusters were defined based on neuroanatomical and - physiological origin: (1) oculomotor, (2) dysarthria, (3) chorea, (4) dystonia, (5) parkinsonism (hypo- , bradykinesia and rigidity), and (6) gait and balance (see legend Figure 3 for more details). For the assessment of severity (mean score), data from all available visits of the participants in the defined AO-HD subgroups was used (cJHD *n*=60 visits from *n*=37 participants, aJHD *n*=465 visits from *n*=225 participants, AHD *n*=23 225 visits from *n*=9 504 participants). For the assessment of annual progression (mean annual change), data from all participants in the defined AO-HD subgroups, with more than 1 visit, was used (cJHD *n*=35 visits from *n*=13 participants, aJHD *n*=265 from *n*=125 participants, AHD *n*=14 291 visits from *n*=6 075 participants).

Statistics

All analyses were performed using R Statistical Software (v4.3.2; R Core Team 2020).[18] The tidyverse (v2.0.0; 2019) package was used for statistical analyses.[19]

Pairwise comparisons for proportions (Z-test) were performed to compare AO-HD subtypes of the pooled datasets on the occurrence(yes/no) of (1) motor, neurocognitive or psychiatric disease features at onset, (2) specified psychiatric disease characteristics during the disease course (3) epileptic seizures during the disease course and (4) pain interference during the disease course. Adjustment of p-values for 3x multiple testing (1: cJHD vs aJHD, 2: cJHD vs AHD and 3: aJHD vs AHD) was done by Holm's method. Fisher's exact test was performed to compare JHD subtypes of the HD-JUNIOR dataset (too small sample size to assume normality) on (1) the occurrence of specified disease characteristics at onset and (2) on specified motor disease characteristics during the disease course. P-values $<.05$ (2-tailed) were considered statistically significant.

We want to compare the progression of motor and neurocognitive symptoms after onset between the AO-HD subtypes. This is particularly challenging because age at measurement is an important determinant, but there is very little age overlap between the subtypes. To overcome this challenge, we fitted multivariable linear

mixed regression models to the observed motor and neurocognitive symptoms taking into account the patients' sex, age at onset and age at measurement for the 3 different AO-HD subtypes. We do not intend to use the models to predict the disease course for a new patient. Rather, we use the fitted values from the model to describe the "typical" disease progression among the patients from the 3 subtypes, and to make tentative comparisons. To allow for a flexible description of disease severity and progression, we included the following independent variables: sex, age at onset (AO), AO^2, age at measurement (AM), AM^2 and the interactions between (1) AO and AM, (2) AO^2 and AM, (3) AO and AM^2 and (4) AO^2 and AM^2. Finally, we used a random intercept per patient to account for the correlation between repeated measurements on the same individual. This model has 10 regression coefficients which are difficult to interpret in isolation. Therefore, we graph the fitted severity scores during the first 20 years after disease onset for 3 reference patients representing the AO-HD subtypes: A female with AO=6 (cJHD), a female with AO=17 (aJHD) and a female with AO=45 (AHD). We then compare the fitted severity scores of the different outcomes at 5 years since the primary onset of the disease. To compare the annual rate of progression (mean annual change) at 5 years after disease onset, we simplified our model to include only sex, AO, AM and their interaction. In this model, the rate of annual progression is a simple slope. P-values were adjusted by Tukey's method to account for the 3 comparisons of AHD versus aJHD, AHD versus cJHD and cJHD versus aJHD.

Data availability

Enroll-HD anonymized data are available upon request through the CHDI Foundation, Inc. For additional information regarding HD-JUNIOR data for research purposes, the principal investigator S.T. de Bot MD PhD may be contacted.

RESULTS

1.0 Demographic characteristics of the AO-HD subtypes per dataset.

The number of included patients of the HD-JUNIOR and Enroll-HD datasets and stratified by AO-HD subtype are provided in Table 1. No clinically meaningful difference was observed between the JHD samples of the 2 different datasets regarding CAG-repeat length and age at primary onset. Owing to missing values and made selections (as described in methods), the number of participants for the specified outcome measures may slightly differ from the number given in Table 1 and is therefore explicitly stated per outcome measure.

Table 1. Patient Sample Characteristics per AO-HD Subtype and Dataset

	Childhood-onset JHD		Adolescent-onset JHD		Adult-onset HD
	HD-JUNIOR (n = 9)	**Enroll-HD (n = 37)**	**HD-JUNIOR (n = 18)**	**Enroll-HD (n = 225)**	**Enroll-HD (n = 9,504)**
Age at primary onset, mean ± SD	6.70 ± 2.10	6.50 ± 2.60	16.60 ± 2.40	16.80 ± 2.50	44.70 ± 10.40
Age at enrollment, mean ± SD (range)	17.90 ± 3.00 (15.00–23.00)	16.60 ± 6.50 (7.00–29.00)	28.00 ± 5.50 (20.00–39.00)	26.80 ± 5.80 (13.00–47.00)	51.70 ± 11.40 (19.00–92.00)
Years between primary and motor onset mean ± SD (range)	1.00 ± 2.10 (0.00–6.00)	2.90 ± 3.60 (0.00–12.00)	0.90 ± 1.30 (0.00–4.00)	3.20 ± 4.00 (0.00–15.00)	1.20 ± 2.50 (0.00–15.00)
Years between primary onset and enrollment mean ± SD (range)	11.30 ± 3.00 (7.00–17.00)	10.10 ± 5.50 (1.00–17.00)	11.40 ± 5.30 (4.00–23.00)	10.00 ± 5.40 (0.00–19.00)	7.00 ± 5.60 (–7.00—47.00)
Follow-up time since enrollment in y mean ± SD (range)	n/a	1.50 ± 1.70 (0.00–6.20)	n/a	1.80 ± 1.70 (0–7.10)	1.90 ± 1.70 (0–7.60)
Sex					
M/F %	56.00/44.00	54.00/46.00	61.00/39.00	51.00/49.00	49.00/51.00
CAG-repeat mean ± SD (range)	77.00 ± 9.00 (66.00–92.00)	75.00 ± 17.00 (48.00–110.00)	58.00 ± 6.00 (49.00–68.00)	57.00 ± 8.00 (41.00–81.00)	44.00 ± 3.00 (40.00–65.00)
Inheritance paternal/maternal %	89.00/11.00	80.00/20.00	76.00/24.00	67.00/32.00	48.00/52.00

Abbreviations: CAG-repeat = cytosine-adenine-guanine repeats in the Huntingtin gene; F = female; M = male; n/a = not applicable; OC = outlier criterion; SC = selection criterium.

AO-HD sample characteristics related to age at primary symptom onset (SC), age at enrollment in the dataset (for HD-JUNIOR, this corresponds to age at death if medical records were obtained posthumously), years between primary symptom and first motor symptom onset (SC), years between primary symptom onset and enrollment in the dataset (OC for Enroll-HD), and follow-up time since enrollment (not applicable for HD-JUNIOR, because data are collected retrospectively). Additional characteristics include sex, CAG-repeat length (SC for patients with adult-onset HD in Enroll-HD), and inheritance.

2.0 Disease characteristics at onset

The prevalence of disease characteristics at onset were analyzed and compared between AO-HD subtypes in pooled data from the 2 datasets (Figure 2). Stratified counts and proportions per dataset are listed in Supplementary Table 2.

In the cJHD subtype, 47.5% of patients (n=46, 95% CI 31.8-63.7) presented with a neurocognitive phenotype, significantly more often than 24.9% of patients with aJHD (n=209, 95% CI 19.3-31.4, p=<.01) and 15% of patients with AHD (n=8 177, 95% CI 14.3-15.8, p=<.001) (Figure 2A). The prevalence of neurocognitive signs at onset in

patients with aJHD was also significantly higher compared to AHD patients (p=<.001). Specified initial disease characteristics were further analyzed in patients with JHD of the HD-JUNIOR dataset (Supplementary Table 3; cJHD n=9, aJHD n=17), because these types of data were not available in the Enroll-HD dataset. Initial neurocognitive changes were most often encountered as learning difficulties (cJHD 3 of 9; aJHD 2 of 18) and attention deficit (cJHD 2 of 9; aJHD 1 of 18). Furthermore, 5 of 9 patients with cJHD presented with developmental regression and 1 of 9 with developmental delay, which were not mentioned in patients with aJHD (Fisher's exact p=.027). Of these 6 of 9 patients with cJHD with changes in development, 4 were related to initial changes in motor development (fine motor skills and walking pattern) and 2 to initial changes in neurocognitive development (repeating class and need for special education).

In the aJHD subtype 47.1% of patients (n=208, 95% CI 40.2-54.1) presented with psychiatric signs and complaints, significantly more often when compared to 31% of patients with AHD (n=8 472, 95% CI 30.1-32.0, p=<.001) (Fig. 2B). Furthermore, the aJHD subtype had in 45.8% of patients (n=212, 95% CI 39.0-52.7) motor signs and symptoms at onset (Fig. 2C), significantly less often when compared with 70% of patients with AHD (n=8 630, 95% CI 69.0-71.0, p=<.001). The most prevalent initial psychiatric change of patients with aJHD within the HD-JUNIOR dataset (Supplementary Table 3) was irritable and aggressive behavior (7 of 16 patients), which was not observed in 9 patients with cJHD at onset (Fisher's exact p=.002).

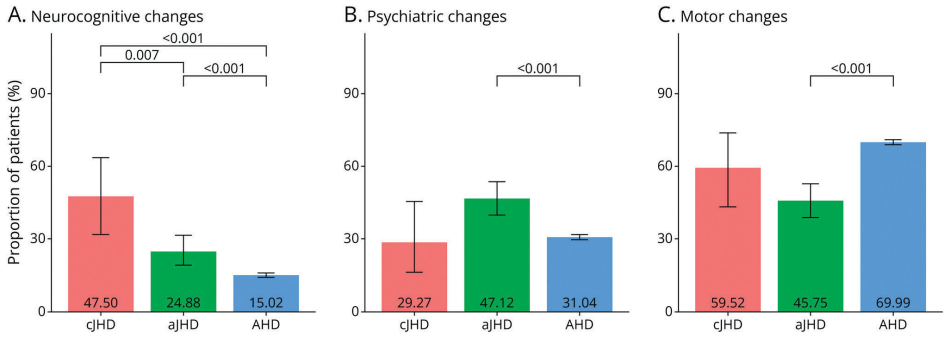

Figure 2. Prevalence and Comparison of HD Disease Characteristics at Onset.

Proportion of patients, 95% CI, and significant p values* per AO-HD subtype (cJHD = red bar; aJHD = green bar; AHD = blue bar) having (A) neurocognitive, (B) psychiatric, and (C) motor changes, whether combined or isolated, at disease onset (pooled datasets). For disease duration and follow-up time, refer to Table 1, and for stratified outcomes per dataset, see Supplementary Table 2. *p Values <0.050 are considered statistically significant and were adjusted for 3 comparisons (cJHD vs aJHD, cJHD vs AHD, and aJHD vs AHD) using the Holm method (inflated p values).

AHD = adult-onset Huntington disease; aJHD = adolescent-onset (juvenile) Huntington disease; AO-HD = AO-defined HD subtype; cJHD = childhood-onset (juvenile) Huntington disease.

3.0 Occurrence of disease characteristics during the disease course

In the next part, the occurrence and severity of changes during the course of the disease will be discussed within the 3 main HD domains, psychiatric, motor, and neurocognitive and in the 'other' domain.

3.1 Psychiatric disease characteristics during the disease course

The occurrence of psychiatric disease characteristics during the disease course was analyzed and compared between AO-HD subtypes in pooled data from the 2 datasets (Figure 3; for disease duration see Table 1). The stratified numbers of patients and proportions per dataset are listed in Supplementary Table 4.

Ever since primary onset, irritability occurred in 91.3% of patients with cJHD (*n*=46, 78.3-97.2), and violence and aggressive behaviour in 73.9% of patients with cJHD (*n*=46, 95% CI 58.6-85.2), significantly more often when compared to 71.4% (*n*=238, 95% CI 65.2-77.0, *p*=<.02) and 55.9% (*n*=238, 95% CI 49.3-62.3, *p*=<.04) of patients with aJHD and 71.0% (*n*=9 501, 95% CI 70.0-71.9, *p*=<.02) and 40.7% (*n*=9 502, 95% CI 39.7-41.7, *p*=<.001) of patients with AHD for irritability and aggressive behaviour respectively (Figure 3A-B). In contrast, depressive complaints occurred in 45.7%of patients with cJHD (*n*=46, 95% CI 31.2-60.8), significantly less often compared to 74.4% of patients with aJHD (*n*=238, 95% CI 68.2-79.7, *p*=<.001) and 74.1% of those with AHD (*n*=9 503, 95% CI 73.2-74.9%, *p*=<.001) (Fig. 3C).

Also, in patients with aJHD violence and aggressive behaviour occurred more often than in patients with AHD (*p*=<.001). Furthermore, apathy occurred in 74.8% of patients with aJHD (*n*=238, 95% CI 68.7-80.1), significantly more often when compared to 52.2% (*n*=46, 95% CI 37.1-66.9, *p*=.01) of patients with cJHD and 65.4% (*n*=9 502, 95% CI 64.4-66.3, *p*=.01) of patients with AHD (Fig. 3D). In addition, psychosis occurred in 23.5% of patients with aJHD (*n*=238, 95% CI 18.4-29.5), which was significantly more often compared to 12.8% (*n*=9 502, 95% CI 12.1-13.5, *p*=<.001) of patients with AHD (Fig. 3E). Perseverative and obsessive behavior occurred in 65.1% of patients with aJHD (*n*=238, 95% CI 58.7-71.2), 69.6% of patients with cJHD (*n*=46, 95% CI 54.3-82.3) and 57.0% of patients with AHD (*n*=9 502, 95% CI 56.0-58.0). No statistically significant differences (p>.05) were observed between patients with cJHD, aJHD and AHD in the occurrence of perseverative and obsessive behavior.

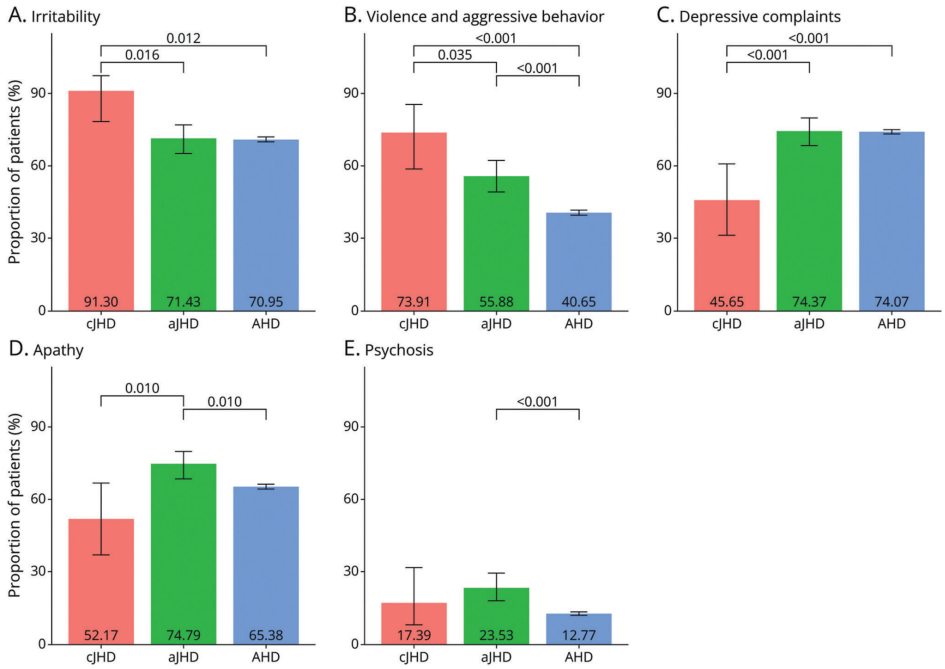

Figure 3. Occurrence and Comparison of Psychiatric HD Disease Characteristics During the Disease Course.

Proportion of patients, 95% CI, and significant p values* per AO-HD subtype (cJHD = red bar; aJHD = green bar; AHD = blue bar) experiencing (A) irritability, (B) violent and aggressive behavior, (C) depressive complaints, (D) apathy, and (E) psychosis as psychiatric disease characteristics (pooled datasets) during the course of the disease. For disease duration and follow-up time, refer to Table 1, and for stratified outcomes per dataset, see Supplementary Table 4. *p Values <0.05 are considered statistically significant and were adjusted for 3 comparisons (cJHD vs aJHD, cJHD vs AHD, and aJHD vs AHD) using the Holm method (inflated p values).

AHD = adult-onset Huntington disease; aJHD = adolescent-onset (juvenile) Huntington disease; AO-HD = AO-defined HD subtype; cJHD = childhood-onset (juvenile) Huntington disease.

3.2 Motor disease characteristics during the disease course

The occurrence of motor disease characteristics during the disease course were analysed and compared between JHD subtypes of the HD-JUNIOR dataset (Table 2; for disease duration see Table 1).

Ever since primary onset, a gait disorder occurred in all cJHD (n=9) and 13 of 18 patients with aJHD. In comparison with aJHD, patients with cJHD more often suffered parkinsonian gait disorder (6/9 vs. 2/18, p=.008) and spastic gait disorder (3/9 vs. 0/17, p=.032). In the motor subdomain ‘speech and swallowing’ dysarthria

occurred in all patients with cJHD (n=9) and 14 of 17 those with aJHD. Patients with cJHD more often suffered from sialorrhea in comparison with patients with aJHD (3/9 vs. 0/18, Fisher's exact p =.029). Also parkinsonism (other than parkinsonian gait disorder) and dystonia occurred often in both JHD subtypes of the HD-JUNIOR dataset. Within this subdomain, patients with cJHD more often experienced loss of fine motor skills (8/9 vs. 8/18, p=.042) and oral dyskinesias (4/9 vs. 1/17, p=.034) in comparison with patients with aJHD. Furthermore, oculomotor disturbances were highly present in both JHD subtypes of the HD-JUNIOR dataset. Between JHD group differences were not observed within this subdomain. In contrast with the higher occurrence of above-mentioned motor symptoms, chorea occurred in 5 of 9 patients with cJHD =, significantly less often when compared to 16 of 17 patients with aJHD (p=.034).

Table 2. The occurrence of motor HD disease characteristics during the disease course and comparison between JHD subtypes of the HD-JUNIOR dataset

			cJHD	aJHD	Fisher's exact p-value
Speech and Swallowing	Anamnesis	Difficulty speech	7/9 (78%)	17/18 (94%)	.250
		Difficulty swallowing	8/9 (89%)	16/18 (89%)	1.000
		Sialorrhea	3/9 (33%)	0/18 (0%)	**.029**
	NE	Dysarthria	9/9 (100%)	14/17 (82.4%)	.529
		Aphasia	1/9 (11.1%)	1/17 (5.9%)	1.000
Walking and Balance	Anamnesis	Difficulty walking	8/9 (89%)	14/18 (78%)	.636
		Difficulty keeping balance	6/9 (67%)	11/18 (61%)	1.000
	NE	Gait disorder;	9/9 (100%)	13/18 (72.2%)	.136
		Parkinsonian gait disorder	6/9 (66.7%)	2/17 (11.8%)	**.008**
		Dystonic gait disorder	2/9 (22.2%)	3/17 (17.6%)	1.000
		Ataxic gait disorder	3/9 (33.3%)	1/17 (5.9%)	.104
		Spastic gait disorder	3/9 (33.3%)	0/17 (0%)	**.032**
		Balance disorder NOS	8/9 (88.9%)	13/17 (76.5%)	.628
Parkinsonism	Anamnesis	Loss of fine motor skills	8/9 (89%)	8/18 (44%)	**.042**
		Stiffness	1/9 (11%)	1/18 (6%)	1.000
	NE	Rigidity	8/9 (88.9%)	15/17 (88.2%)	1.000
		Hypokinesia	6/9 (66.7%)	6/17 (35.3%)	.218
		Bradykinesia	8/9 (88.9%)	14/17 (82.4%)	1.000
		Micrography	2/9 (22.2%)	0/17 (0%)	.111
		Mask face	5/9 (55.6%)	6/17 (35.3%)	.419

Table 2. Continued

			cJHD	aJHD	Fisher's exact p-value
Excessive movement	Anamnesis	Excessive movements extremities	5/9 (56%)	16/18 (89%)	.136
		Excessive movements face	3/9 (33%)	3/18 (17%)	.367
		Tics (vocal or motor)	5/9 (56%)	5/18 (28%)	.219
	NE	Chorea	5/9 (55.6%)	16/17 (94.1%)	**.034**
		Dystonia	6/9 (66.7%)	10/17 (58.8%)	1.000
		Oral dyskinesia	4/9 (44.4%)	1/17 (5.9%)	**.034**
		Motor impersistence	3/9 (33.3%)	9/17 (52.9%)	.429
		Tics vocal	1/9 (11.1%)	1/17 (5.9%)	1.000
		Tics motor	3/9 (33.3%)	2/17 (11.8%)	.302
		Tremor rest	1/9 (11.1%)	0/17 (0%)	.346
		Tremor action	2/9 (22.2%)	2/17 (11.8%)	.591
		Tremor intention	0/9 (0%)	2/17 (11.8%)	.529
		Tremor postural	0/7 (0%)	1/14 (7.1%)	1.000
		Myoclonus	3/9 (33.3%)	2/17 (11.8%)	.302
Oculomotor	NE	Ocular gaze abnormalities	5/9 (55.6%)	9/17 (52.9%)	1.000
		Ocular saccade abnormalities	7/9 (77.8%)	13/17 (76.5%)	1.000
Other	NE	Dysdiadochokinesia	6/9 (66.7%)	7/17 (41.2%)	.411
		Dysmetria	2/9 (22.2%)	1/17 (5.9%)	.268
		Coordination disorder NOS	2/9 (22.2%)	6/17 (35.3%)	.667
		Hyperreflexia	7/9 (77.8%)	4/17 (23.5%)	**.014**
		Scoliosis	2/9 (22.2%)	0/17 (0%)	.111
		Apraxia	1/9 (11.1%)	2/17 (11.8%)	1.000

Results are categorized by neuroanatomical and physiological origin, as well as by source (complaints or signs reported by patients or caregivers during anamnesis, or symptoms identified during neurological examination). The number of participants with each specified sign, symptom, or complaint is presented as a proportion of the total number of participants. Fisher's exact test (two-tailed) was employed to assess the association between JHD subtype and the occurrence of specific motor characteristics. P-values < 0.05 are considered statistically significant and are indicated in bold.

Abbreviations: cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease; NE = Neurological Examination; NOS = Not Otherwise Specified

3.3 Neurocognitive disease characteristics during the disease course

The severity of neurocognitive disease characteristics during the disease course were analysed in JHD subtypes of the HD-JUNIOR dataset (Supplementary Table 5).

Patients with JHD often had a lower-than-average IQ as determined by the primary assessor (cJHD 4 of 7 vs. aJHD 4 of 9). The mean total IQ score in the cJHD group was 80.8±19.4 (years after onset: 3.7±3.1) vs. 75.8±5 (years after onset: 5.4±4.0) in the aJHD group. In general, performance IQ was lower than verbal IQ. This difference was largest in the aJHD group. An executive function disorder was specified in 1 patient with cJHD and 3 patients with aJHD, and an encoding deficit was specified in 4 patients with aJHD.

3.4 Other disease characteristics during the disease course

The occurrence of epileptic seizures during the disease course was analyzed and compared between AO-HD subtypes in pooled data from the 2 datasets. Recurrent epileptic seizures occurred in 23.91% of patients with cJHD (*n*=46, 95% CI 13.10-39.10), significantly more often when compared to 6.33% of patients with aJHD (*n*=237, 95% CI 3.70-10.40, *p*=<.001) and 0.90% of those with AHD (*n*=9472, 95% CI 0.70-1.10, *p*=<.001).

The occurrence of pain during the disease course was analyzed and compared between AO-HD subtypes for the separate datasets. Based on the HD-JUNIOR dataset, 5 of 9 patients with cJHD reported pain throughout their disease. In patients with aJHD, this was 12 of 18 cases. Based on the Enroll-HD dataset, the occurrence of pain interference at baseline was with 42.60% in patients with aJHD (*n*=129, 95% CI 33.70-51.50) significantly higher when compared to 11.80% of patients with cJHD (*n*=17; 95% CI -2.50-26.10, *p* =.014) and 36.60% of patients with AHD (*n*=4262; 95% CI 36.20-37.00, *p*=.040).

4.0 Fitted longitudinal severity and annual progression of motor and neurocognitive disease characteristics

The predicted severity and annual progression of motor and neurocognitive disease characteristics were analysed using longitudinal data from the UHDRS-TMS, UHDRS-SDMT and UHDRS-SIT of the Enroll-HD dataset. We report fitted values from our multivariable regression models for 3 reference patients (Figure 4, Table 3).

By analyzing 6 UHDRS-TMS subclusters, we found distinct patterns in the predicted severity (mean score) and progression (annual change rate) of specified motor symptoms in the 3 AO-HD subtypes. With regard to subcluster ‘dysarthria’, we

found both an increased predicted severity and annual change in the cJHD subtype, followed by aJHD, and in comparison with the AHD subtype, as demonstrated by significantly higher mean scores and annual change rates 5-years after onset (Figure 4A, Table 3). For the subclusters 'parkinsonism' and 'dystonia', we found an increased predicted severity in the cJHD subtype, followed by aJHD, and in comparison with the AHD subtype, as demonstrated by significantly higher mean scores 5-years after onset (Figure 4B-C, Table 3). No between group differences were observed in the predicted annual progression of parkinsonism and dystonia as measured 5-years after onset (Table 3). Alternatively, in the subclusters 'oculomotor' and 'gait & balance', we found an increased predicted annual progression in both JHD subtypes compared to the AHD subtype, as demonstrated by significantly higher annual change scores 5 years after onset (Table 3), but no between group difference was observed in the severity (mean score) of these outcomes (Figure 4D-E, Table 3) Lastly, For the subcluster 'chorea', we found a reduced predicted severity in the cJHD subtype, followed by aJHD, as compared to the AHD subtype, as demonstrated by significantly lower mean scores 5 years after onset (Figure 4G, Table 3). There were no between-group differences in the annual progression of chorea (Table 3).

Apart from motor subclusters, we analyzed differences in the predicted severity and progression of neurocognitive disease characteristics by applying the same models to the UHDRS-SIT (executive functioning) and UHDRS-SDMT (psychomotor speed). Regarding the UHDRS-SDMT, we found an increased predicted annual deterioration in psychomotor processing speed for both JHD subtypes compared to the AHD subtype, as demonstrated by significantly higher mean annual change rates 5 years after onset (Table 3). No between group differences were observed in the predicted annual deterioration of executive functioning, as measured by the SIT assessment (Table 3). In contrast to annual deterioration, the predicted general performance on neurocognitive assessment 5 years after onset was significantly better in the aJHD subtype compared to the AHD subtype, as demonstrated by higher mean SDMT and SIT scores (Table 3).

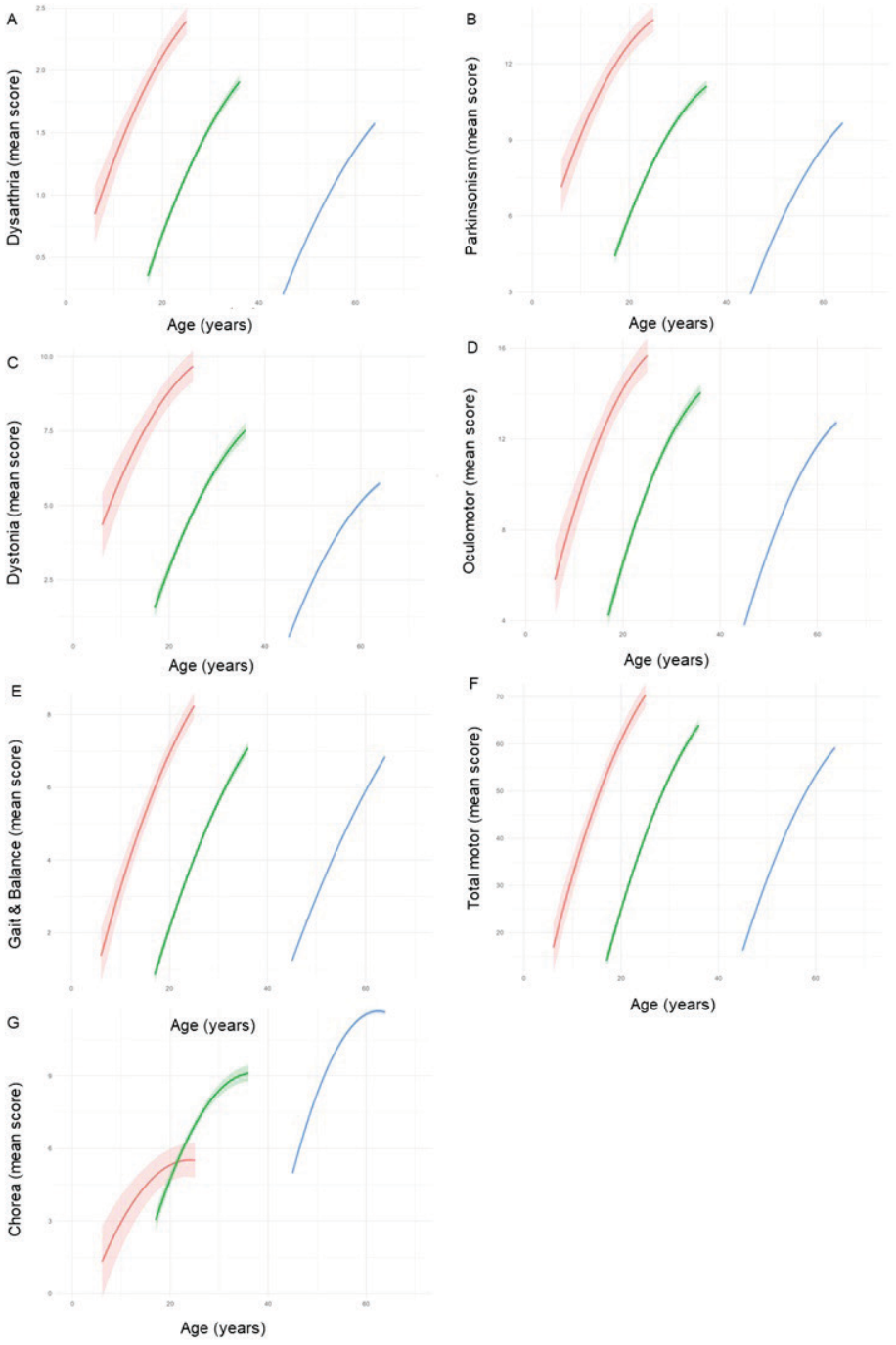

Figure 4. The associated severity of motor subdomain characteristics over time in AO-HD subtypes

Figure 4. Continued

UHDRS-TMS data from the ENROLL-HD dataset were used to assess severity across three AO-HD subtypes: cJHD (red line), aJHD (green line), and AHD (blue line). Scores are graphed as a function of age at measurement for TMS items, with a range of 0 (no abnormalities) to 4 (most severe abnormalities):

(A) 'dysarthria' (max score 4), (B) 'finger taps L + R, rigidity L + R, and body bradykinesia' (max score 20), (C) 'dystonia in: trunk, upper extremities L + R, lower extremities L + R' (max score 20), (D) 'ocular pursuit H + V, saccade initiation H + V, and saccade velocity H + V' (max score 24), (E) 'gait, tandem walking, and retropulsion' (max score 12), (F) UHDRS-TMS total score (max score 124), and (G) 'chorea in: face, buco-oro-laryngeal area, trunk, upper extremities L + R, lower extremities L + R' (max score 28).

Statistics and between-group comparisons of fitted mean scores related to these slopes are detailed in Table 3.

Abbreviations: AO-HD = Age at Onset-defined HD subtype; UHDRS-TMS = Unified Huntington Disease Rating Scale – Total Motor Score; cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease; AHD = Adult-onset Huntington Disease; L = left; R = right; H = horizontal; V = vertical

Table 3. Fitted severity and annual progression of specified motor and neurocognitive clusters in AO-HD subtypes

Outcome measure	AO-HD subtype	Mean score*	SE	Comparison	p-value	Mean annual change*	SE	Comparison	p-value
UHDRS-TMS 'dysarthria'	cJHD	1.38	0.16	aJHD	**<.001**	0.25	0.04	aJHD	**.030**
	aJHD	0.89	0.04	AHD	**<.001**	0.19	0.02	AHD	**.002**
	AHD	0.66	0.01	cJHD	**<.001**	0.10	0.00	cJHD	**.007**
UHDRS-TMS 'parkinsonism'	cJHD	9.85	0.73	aJHD	**<.001**	0.75	0.18	aJHD	.487
	aJHD	7.11	0.18	AHD	**<.001**	0.65	0.09	AHD	.409
	AHD	5.46	0.06	cJHD	**<.001**	0.52	0.03	cJHD	.437
UHDRS-TMS 'dystonia'	cJHD	6.47	0.76	aJHD	**<.001**	0.87	0.22	aJHD	.339
	aJHD	3.87	0.19	AHD	**<.001**	0.72	0.11	AHD	.058
	AHD	2.64	0.06	cJHD	**<.001**	0.44	0.04	cJHD	.142
UHDRS-TMS 'oculomotor'	cJHD	9.86	1.08	aJHD	.204	1.53	0.27	aJHD	.052
	aJHD	8.26	0.27	AHD	**.019**	1.21	0.14	AHD	**.013**
	AHD	7.48	0.09	cJHD	.065	0.77	0.05	cJHD	**.024**
UHDRS-TMS 'gait and balance'	cJHD	4.07	0.51	aJHD	.220	0.79	0.12	aJHD	**.023**
	aJHD	3.33	0.13	AHD	.932	0.63	0.06	AHD	**.005**
	AHD	3.38	0.04	cJHD	.356	0.41	0.02	cJHD	**.009**
UHDRS-TMS 'chorea'	cJHD	3.36	1.02	aJHD	**.020**	0.75	0.30	aJHD	.906
	aJHD	5.76	0.26	AHD	**<.001**	0.81	0.16	AHD	.676
	AHD	8.29	0.09	cJHD	**<.001**	0.67	0.05	cJHD	.966
UHDRS-TMS 'total score'	cJHD	37.03	3.73	aJHD	.448	5.65	0.72	aJHD	.053
	aJHD	33.10	0.94	AHD	.935	4.81	0.37	AHD	**<.001**
	AHD	32.75	0.33	cJHD	.475	3.33	0.13	cJHD	**.007**
UHDRS-SDMT	cJHD	23.13	2.47	aJHD	**.042**	-2,79	0.44	aJHD	.119
	aJHD	28.33	0.63	AHD	**.001**	-2,35	0.23	AHD	**.005**
	AHD	25.29	0.22	cJHD	.651	-1,55	0.08	cJHD	**.024**

Table 3. Continued

Outcome measure	AO-HD subtype	Mean score*	SE	Comparison	p-value	Mean annual change*	SE	Comparison	p-value
UHDRS-SIT	cJHD	27.36	3.03	aJHD	.735	-1,24	0.57	aJHD	.994
	aJHD	29.32	0.66	AHD	**<.001**	-1,21	0.30	AHD	.977
	AHD	25.08	0.20	cJHD	.726	-1,14	0.10	cJHD	.986

* 5-years after onset

Results are categorized by motor and neurocognitive outcome measures, as detailed in the text and Figure 3, according to AO-HD subtype. The left panel displays the predicted mean scores† and standard errors (SE), while the right panel shows the predicted mean annual changes† and SE, along with between-group comparisons for each outcome measure. Row 1 compares cJHD with aJHD, row 2 compares aJHD with AHD, and row 3 compares AHD with cJHD. Statistical significance was adjusted for multiple testing using the Tukey method (inflated p-values). P-values < 0.05, adjusted for the three comparisons (cJHD vs aJHD, cJHD vs AHD, and aJHD vs AHD), are considered statistically significant.

† Scores are based on model coefficients that show the predicted severity and annual change for a female patient 5-years after first symptom onset (cJHD: AO=6, AM=11; aJHD: AO=17, AM=22; AHD: AO=45, AM=50).

Abbreviations: cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease; AHD = Adult-onset Huntington Disease; AO-HD = Age at Onset-defined HD subtype; UHDRS-TMS = Unified Huntington Disease Rating Scale – Total Motor Score; UHDRS-SDMT = Unified Huntington Disease Rating Scale – Symbol-Digit-Modalities-Test; UHDRS-SIT = Unified Huntington Disease Rating Scale – Stroop-Interference-Test; SE = Standard Error; AO = Age at Onset; AM = Age at Measurement

DISCUSSION

This study identifies different disease characteristics at onset, as well as differences in the occurrence, severity and rate of progression of HD clinical characteristics over time in JHD subtypes compared with AHD.

The cJHD population represents the extreme end of the HD spectrum, in which disease progression is known to be accelerated.[7] By comparing a total of 46 patients with cJHD with those with aJHD and AHD, we confirm earlier reported findings such as: (1) a high prevalence of neurocognitive abnormalities at disease onset;[7,13] (2) more often motor changes related to speech, parkinsonism, and oral dyskinesia[6,7] (3) less often chorea;[6,7] (4) neurocognitive changes reminiscent of the AHD phenotype;[20,21] and (5) a higher occurrence of behavioral changes and lower depression complaints.[6,13] Replication of these former findings confirms their association with the cJHD phenotype in comparison with prototypical disease onset in adulthood. We extend this knowledge by showing that the cJHD population more often suffers from (1) secondary developmental regression in motor domains rather than a primary neurodevelopmental delay and (2) a spastic gait disorder. Furthermore, linear mixed regression models suggest faster worsening of dysarthria, gait, balance, oculomotor changes and psychomotor speed over time in association with an earlier onset and in contrast to other motor and neurocognitive subclusters.

The aJHD population is believed to be in closer resemblance with the AHD population compared with cJHD. By comparing 238 patients with aJHD with patients with cJHD and AHD, our study suggests alternative patterns in the aJHD population by (1) a higher prevalence of psychiatric abnormalities and a lower prevalence of motor changes at disease onset; (2) a higher occurrence of psychiatric changes related to psychosis and apathy during the disease course and (3) a higher occurrence of pain interference in daily life. Furthermore, linear mixed regression models suggest that the aJHD subtype has motor changes that are more severe and progress faster when compared to the AHD subtype and better performance on neurocognitive tasks with faster deterioration of psychomotor speed over time. These findings highlight that clinical characteristics in the aJHD population are not directly similar to those in the AHD population or its other counterpart, cJHD.

Multivariable linear mixed regression models were used to describe differences between AO-HD subtypes in the associated severity and progression of specified sub-motor and neurocognitive domains. Because of the unknown relationship of the

independent variables (AO and AM) on the outcome measures in the different AO-HD subtypes and to allow for a relatively flexible description of disease progression, a linear model with quadratic functions of AO and AM on the mean score was used to describe between group differences in associated severity. In addition, linear functions of AO and AM on the mean annual change rate were used to describe between group differences in the associated progression over time. Based on these 2 models, we tentatively conclude that divergent patterns of severity and progression for motor and neurocognitive subclusters are associated with the AO-HD subtypes. Whereas the occurrence and severity of parkinsonism and dystonia are positively associated with the JHD population, their rate of progression over time is comparable to the AHD phenotype. In contrast, faster worsening of symptoms in JHD as compared to AHD is associated with dysarthria, oculomotor and gait and balance changes. For neurocognitive clusters, a pattern of better neurocognitive performance in the aJHD population is paralleled by faster associated worsening of psychomotor speed over time in both JHD subtypes when compared to AHD. These different patterns in severity and progression rate demonstrate that AO and AM influence subclusters in different ways. Of note is the descriptive nature of these models, which should not be interpreted as prediction model or to infer causality. The distribution of datapoints across the age spectrum (X-axis) differs widely between the AO-HD subtypes, which can result in an inaccurate extrapolation over the entire age spectrum in small samples, as is the case in the cJHD subtype. Moreover, the association that we observe is likely to be influenced by covariates that have not been considered in our models.

Our study is the first to report a higher occurrence of apathy and psychosis specifically in the aJHD population. This finding shows that the occurrence of psychosis in HD does not follow a linear relationship with AO or CAG-repeat size. It is of interest that the predilection of this age group is also seen in the onset of idiopathic schizophrenia and might suggest similar risk factors in the onset of this phenotype.

Another interesting finding of our study is the higher occurrence of pain interference in daily life in patients with aJHD, when compared with patients with cJHD and AHD. A higher occurrence of pain has been linked to the JHD population before, but until now a trend toward higher CAGs and therefore earlier onset of disease was observed.[22] Furthermore, no comparison was made with AHD. Although a selection bias could influence our results (SF12 questionnaire in Enroll-HD is an optional

part that is easily left out in case of a to high patient burden during annual visits) assessment of pain by using observational pain scales in addition to more extended self-reported pain scales in both patients with JHD and AHD could help clarifying the prevalence and origin of pain in different AO-HD subtypes.

We cannot exclude the possibility of bias influencing our study results. Information bias might have contributed to the lower estimates for depression in the cJHD population because depressive complaints are easily misrecognized in any childhood population.[23,24] The fact that the HD-JUNIOR dataset uses unspecified medical data, however, does help minimize this risk. A selection bias may influence the cJHD population of Enroll-HD, because more severe cases are less likely to participate in prospective studies. Furthermore, we chose to omit missing cases from analyses. These patients might be different in certain respect from the patients who were included in our analyses, which would lead to some degree of selection bias. Another risk is a recall bias in the retrospectively collected data. Finally, using CAG-repeat length, as used in previous studies, or using age at motor onset for the definition of JHD populations can be more accurate depending on the research question. In this study we choose to define our groups by AO of any HD-related sign, rather than CAG-repeat or age at motor onset. In our opinion this definition relates better to patients presenting in clinical practice, prevents a selection bias of patients with neurocognitive/psychiatric onset yet without a motor phenotype and relates to a certain neurodevelopmental state that potentially influences disease characteristics.

The JHD population is a small heterogeneous group of patients that requires a tailored approach to what is known in HD research, as they represent the extreme end of the HD spectrum. We believe that future studies should include the structural comparison of AO-HD subtypes or different CAG-repeat lengths in all types of (pre)clinical HD research. Furthermore, better identification of clinical characteristics such as developmental changes, gait abnormalities and pain would help to understand their origin and therefore how to treat them. Finally, ongoing (international) collaborations are the only way forward in this very rare form of the disease. Pooling data from several JHD registries worldwide is an important next step in our understanding of JHD. To support these efforts, data from the Dutch HD-JUNIOR registry are available on request.

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SUPPLEMENTARY TABLES

Supplementary Table 1. PDS5 outlier exclusion criteria

Subject ID	Original AO-HD subtype	Reason for exclusion
R439327326	cJHD	Age at enrolment ≥30 years (high risk recall bias), disease duration ≥25 years (>2 SD from mean disease duration with cJHD group)
R707469384	cJHD	Age at enrolment ≥25 years (high risk recall bias), disease duration ≥20 years (>2 SD from mean disease duration with cJHD group)
R35157828X	cJHD	Age at enrolment ≥25 years (high risk recall bias), disease duration ≥20 years within 2 SD from mean, but clinically still very unlikely in case of cJHD phenotype)
R985739546	aJHD	Age at enrolment ≥55 years (high risk recall bias), disease duration ≥35 years (>2 SD from mean disease duration with aJHD group)
R976576146	aJHD	Age at enrolment ≥45 years (high risk recall bias), disease duration ≥25 years (>2 SD from mean disease duration with aJHD group)
R044544548	aJHD	Age at enrolment ≥35 years (high risk recall bias), disease duration ≥25 years (>2 SD from mean disease duration with aJHD group)
R036972168	aJHD	Age at enrolment ≥35 years (high risk recall bias), disease duration ≥20 years (>2 SD from mean disease duration with aJHD group)
R870934436	aJHD	Age at enrolment ≥40 years (high risk recall bias), disease duration ≥20 years (>2 SD from mean disease duration with aJHD group)
R176379066	aJHD	Age at enrolment ≥40 years (high risk recall bias), disease duration ≥20 years (>2 SD from mean disease duration with aJHD group)
R478714630	aJHD	Age at enrolment ≥35 years (high risk recall bias), disease duration ≥20 years (>2 SD from mean disease duration with aJHD group)

Abbreviations: cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease; SD = standard deviations

Supplementary Table 2. Frequencies and proportions of HD disease characteristics at onset in AO-HD subtypes and stratified by dataset

	childhood-onset JHD		adolescent-onset JHD		adult-onset HD
	ENROLL-HD	HD-JUNIOR	ENROLL-HD	HD-JUNIOR	ENROLL-HD
Motor onset	19/33 (57.6%)	6/9 (66.7%)	92/201 (45.8%)	5/11 (45.5%)	6040/8630 (70.0%)
Neurocognitive onset	14/31 (45.2%)	5/9 (55.6%)	47/198 (23.7%)	5/11 (45.5%)	1228/8177 (15.0%)
Psychiatric onset	9/32 (28.1%)	3/9 (33.3%)	92/197 46.7%)	6/11 (54.5%)	2630/8472 (31.0%)
Mixed onset	11/37 (29.7%)	4/9 (44.4%)	44/225 (19.6%)	3/11 (27.3%)	1815/9490 (19.1%)
Other onset	2/37 (5.4%)	0/9 (0%)	3/225 (1.3%)	0/11 (0%)	31/9490 (0.3%)

Data represent number of patients reporting symptom/number of patients within group (within group percentage)

Supplementary Table 3. Frequencies and proportions of specified disease characteristics at onset in JHD subtypes of the HD-JUNIOR dataset

		cJHD	aJHD	Fisher's exact p-value
Motor	Walking abnormalities	3/9 (33%)	3/16 (19%)	.630
	Balance complaints	0/9 (0%)	2/16 (13%)	.520
	Excessive movements	0/9 (0%)	1/16 (6%)	1.000
	Fine motor skill loss	3/8 (38%)	2/17 (12%)	.283
	Speech problems	0/9 (0%)	2/16 (13%)	.520
	Tics (vocal or motor)	1/9 (11%)	1/16 (6%)	1.000
	Learning difficulties	3/9 (33%)	2/16 (13%)	.312
Neurocognitive	Memory complaints	0/9 (0%)	1/17 (6%)	1.000
	Attention deficit	2/9 (22%)	1/16 (6%)	.530
	Irritable aggressive behavior	0/9 (0%)	7/16 (39%)	**<.027**
	Depressive complaints	0/9 (0%)	3/16 (19%)	.280
	Social withdrawal	1/9 (11%)	0/16 (0%)	.360
Psychiatry	Obsessive compulsive behavior	1/9 (11%)	0/16 (0%)	.360
	Substance abuse	0/9 (0%)	1/17 (6%)	1.000
	Anxiety complaints	1/9 (11%)	0/16 (0%)	.360
	Suicidal behavior	0/9 (0%)	1/17 (6%)	1.000
	Apathy	1/9 (11%)	0/17 (0%)	.346
	Fatigue	1/9 (11%)	0/17 (0%)	.346
	Crying or screaming	1/9 (11%)	0/17 (0%)	.346
'Other'	Pain	1/9 (11%)	2/16 (13%)	1.000
	Developmental delay	1/9 (11%)	0/16 (0%)	.360
	Develepmental regression	5/9 (56%)	0/16 (0%)	**<.002**

Results are catagorized by symptom or sign domain. Shown are the number of participants having specified sign, symptom or complaint / total number of participants (within group proportion having symptom). Fisher's exact test (two-tailed) was used to determine if there was a significant association between JHD subtype and the occurence of a specified disease characteric at onset. p-values <.05 were considered statistically significant and are presented in bold.

Abbreviations: cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease

Supplementary Table 4. Frequencies and proportions of psychiatric disease characteristics during the disease course in AO-HD subtypes and stratified by dataset

	childhood-onset JHD		adolescent-onset JHD		adult-onset HD
	ENROLL-HD	**HD-JUNIOR**	**ENROLL-HD**	**HD-JUNIOR**	**ENROLL-HD**
Depression	18/37 (48.6%)	3/9 (33.3%)	171/225 (76%)	6/13 (46.2%)	7039/9503 (74.1%)
Irritability	34/37 (91.9%)	8/9 (88.9%)	157/225 (69.8%)	13/13 (100%)	6741/9501 (71%)
Aggression and Violence	26/37 (70.3%)	8/9 (88.9%)	120/225 (53.3%)	13/13 (100%)	3863/9502 (40.7%)
Apathy	22/37 (59.5%)	2/9 (22.2%)	169/225 (75.1%)	9/13 (69.2%)	6212/9502 (65.4%)
Psychosis	5/37 (13.5%)	3/9 (33.3%)	51/225 (22.7%)	5/13 (38.5%)	1213/9502 (12.8%)
Perseveration and Obsession	25/37 (67.6%)	7/9 (77.8%)	147/225 (65.3%)	8/13 (61.5%)	5419/9502 (57%)

Data represent number of patients reporting symptom/number of patients within group (within group percentage)

Supplementary Table 5. Cognitive measures in JHD subtypes of the HD-JUNIOR dataset

	cJHD (n=7)	**aJHD (n=9)**
Years after onset	3.7±3.1 (0-10)	5.4±4.0 (1-14)
Full IQ	80.8±19.4 (60-113)	75.8±5.0 (72-84)
Verbal IQ (VIQ)	80.0±12.4 (62-92)	88.5±8.5 (80-100)
Performance IQ (PIQ)	71.0±11.1 (63-87)	70.0±6.7 (66-80)
VIQ/PIQ Δ	4.8±14.3 (-5-26)	15.2±12.2 (2-34)

Abbreviations: cJHD = childhood-onset (Juvenile) Huntington Disease; aJHD = adolescent-onset (Juvenile) Huntington Disease; n = number of participant's; IQ = Intelligence Quotient; SD = Standard Deviation