# The Relationship Between Age-of-Onset and the Behavioral Phenotypic Manifestations in Huntington's Disease

Thesis

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By

Megha Ranganathan

Graduate Program in Genetic Counseling

The Ohio State University

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Thesis Committee

Dawn C. Allain, MS, LGC, Advisor

Allison Daley, MS, MPH, LGC

Sandra Kostyk, MD, PhD

Abstract

**Objective:** The purpose of this study is to characterize behavioral manifestations of the Huntington's disease (HD) phenotype as associated with age-of-onset (AOO) of clinical presentation.

**Background**: Behavioral, cognitive, and motor symptoms are cardinal features of HD. The relationship between behavioral symptoms and AOO of clinical symptoms in HD has not been fully explored.

**Methods**: Participants were subjects with manifest HD registered in the Enroll-HD database (as of 2016). The major initial symptom at disease onset, motor, cognitive, or behavioral, and severity of behavioral symptoms at disease presentation in individuals with early onset HD (AOO <30 yrs), early-adult onset HD (AOO 30-59 yrs), and late-adult onset HD (AOO ≥60 yrs) was compared. Information on the Clinical Characteristics form and short version of the Problem Behaviors Assessment (PBA-s) was used to assess symptom presence and severity at disease onset. Descriptive statistics, chi-square tests, and multinomial logistic regression models were utilized for analysis.

**Results**: A total of 4,469 individuals were eligible for the study. Of individuals in the early onset cohort, 126 (26%) had behavioral symptoms as the presenting symptom compared to 678 (19%) individuals in the early-adult onset cohort and 56 (11%) in the late-adult onset cohort ($p<.0001$). A one year increase in AOO was associated with a 5.6% decrease in the odds of behavioral symptoms being the presenting symptom at disease onset ($p<.0001$). A one year increase in AOO was associated with a 5.5% decrease in the odds of presentation with severe behavioral symptoms of any type, particularly disorientation, delusions, and obsessive-compulsive disorder. There was no statistically significant relationship between AOO and risk of severe depression, suicidal ideation or hallucinations.

**Conclusions**: Individuals with earlier onset HD may be more likely to present with behavioral symptoms at disease onset than later-onset individuals. A better understanding of the relationship between AOO and the behavioral phenotype of HD will be helpful in developing therapies that aim to treat symptom specific disease presentations. The findings from this study may also influence how risk assessments are made by genetic counselors and other clinicians for individuals at risk for HD. The observations in this study offer important insight into future avenues of research.

Dedication

This thesis is dedicated to my parents, whose guidance and support made it possible for me to achieve my dreams.

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## Vita

June 2012……Cupertino High School

May 2016……B.A. Molecular and Cellular Biology,
University of California, Berkeley

2016 to present……M.S. Genetic Counseling,
The Ohio State University

## Fields of Study

Major Field: Genetic Counseling

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# Chapter 1. Background and Aims

## Background

Huntington's disease (HD) is a progressive neurodegenerative disease with an estimated prevalence of about 10-14 per 100,000 in Western populations (McColgan & Tabrizi, 2018). Roughly 30,000 people are diagnosed with HD in the United States and Canada with another 150,000 individuals at risk (Frank, 2014). HD is characterized by a triad of phenotypic manifestations: motor dysfunction, cognitive impairment, and neuropsychiatric symptoms (Martin & Gusella, 1986). American physician, George Huntington, is credited with the first explicit description of the clinical symptoms of this condition and its hereditary component in 1872 in his article titled "On Chorea" (Huntington, 1872). He named the disease "hereditary chorea" based on the characteristic symptom of the disease and its clear pattern of inheritance. However, it was not long before the syndrome was commonly referred to as Huntington's chorea. By the 1980s, the nomenclature changed to Huntington's disease with increasing recognition that chorea is only one of the many presenting symptoms of HD.

HD is caused by an expansion of the trinucleotide repeat sequence cytosine-adenine-guanine (CAG) in the *huntingtin* (*HTT*) gene, formerly known as IT15 for "interesting transcript" (The Huntington's Disease Collaborative Research Group, 1993). The *HTT*

gene is located on the short arm of chromosome 4 at 4p16.3 and consists of 67 exons (Gusella et al., 1983). Exon 1 contains the unstable CAG repeat region (Duyao et al., 1993; The Huntington's Disease Collaborative Research Group, 1993). The CAG expansion results in an abnormally long polyglutamine amino acid sequence. The resulting elongated protein is toxic to neuronal cells and thus, individuals with a repeat expansion exhibit the clinical symptoms of Huntington's disease (Gusella & MacDonald, 1995). Individuals typically have less than 27 CAG repeats on both alleles of the gene, which translates to functional huntingtin protein. Affected individuals have one expanded allele with ≥ 36 CAG repeats. Individuals with CAG repeats in the 36-39 range display reduced penetrance (Rubinsztein et al., 1996). Alleles consisting of 27-35 repeats are considered to be in the intermediate range or "gray zone." Intermediate allele carriers typically do not manifest symptoms of HD (Semaka & Hayden, 2014). However, they may be at increased risk for developing behavioral symptoms of HD (Killoran et al., 2013). The age-of-onset of symptoms is inversely correlated with CAG repeat size, meaning individuals with larger repeat sizes have earlier ages of onset while individuals with smaller repeat sizes have later ages of onset (Duyao et al., 1993). HD is an autosomal dominant condition that exhibits a tendency referred to as "anticipation." Due to anticipation, CAG repeat sizes can expand when transmitted to offspring, resulting in increasing severity and earlier onset of disease in subsequent generations (The Huntington's Disease Collaborative Research Group, 1993). For unknown reasons, this is particularly common when the abnormally expanded allele is transmitted through the paternal cell line (Ridley, Frith, Crow, & Conneally, 1988).

Individuals with HD exhibit abnormalities of both voluntary and involuntary movements. Problems with voluntary movements include clumsiness, impaired motor speed, loss of fine motor control and gait and balance disorders. As the disease progresses, other voluntary motor findings begin to emerge, including increased rigidity, bradykinesia, general lack of coordination, abnormal extraocular movements, brisk muscle stretch reflexes, and diminished rapid alternating movements (Liu et al., 2015; Ross et al., 2014). "The clinical diagnosis of adult-onset HD is typically made after the onset of involuntary motor abnormalities, primarily chorea" (Kirkwood, Su, Conneally, & Foroud, 2001). Chorea, the hallmark feature of HD, is an involuntary movement characterized by non-repetitive jerking or writhing movements of the limbs, face, or trunk. Chorea is often described as dance-like movements or involuntary movements that rapidly flit from region to region in an irregular pattern. It is present in over 90% of individuals with HD and generally increases during the first 10 years of disease progression (Pandey, 2013). Dystonia is seen in approximately 91% of individuals with HD and is defined as the loss of coordinated contraction of antagonistic muscle groups. This alters muscle tone and leads to abnormal movement and postures (van de Zande et al., 2017). HD patients may also present with dysarthria and in later stages, dysphagia. The motor symptoms continue to progress over time, and affected individuals become increasingly hypokinetic with prominent rigidity and dystonia. This eventually limits functional capabilities and renders affected individuals unable to perform daily activities (Kirkwood et al., 2001).

HD is also characterized by progressive cognitive decline. Cognitive decline begins early in disease progression and often precedes the manifestation of overt motor signs of HD (Baake et al., 2017). Cognitive impairments include diminished emotional facial pattern recognition, slowed thought processes, memory loss, impaired visuospatial and executive functional capabilities, and impaired ability to logically understand and interpret acquired knowledge (Papoutsi, Labuschagne, Tabrizi, & Stout, 2014; Peinemann et al., 2005). Early in the disease process, patients with HD may experience impairment of executive function, such as difficulty with mental organization, dual tasking, and planning. The cognitive symptoms eventually progress to lack of awareness of one's surroundings or of one's own disability. This is referred to as "anosognosia" and can make it difficult for people with HD to accept activity limitations or medications (Hoth et al., 2007). Additionally, memory deficits may occur early in the disease. However, unlike the case in Alzheimer's disease, verbal cues or priming can result in partial recall of information (Bourne, Clayton, Murch, & Grant, 2006). These difficulties with memory and visuospatial abilities typically occur in the later stages of HD (Bamford, Caine, Kido, Cox, & Shoulson, 1995).

Many individuals with HD present with neuropsychiatric or behavioral manifestations, such as depression, apathy, irritability, anxiety, bipolar disorder, psychosis, obsessive-compulsive disorder, and suicidal ideation. Studies have found that the prevalence of psychiatric symptoms in HD ranges from 15% to 98% (Leroi et al., 2002; Reedeker et al., 2012). Estimates of the prevalence of depression among individuals with HD also vary

widely, ranging from 9% up to 76% (van Duijn, Kingma, & van der Mast, 2007). A recent study from the REGISTRY cohort consisting of 1,993 HD mutation carriers from 15 European countries showed that apathy is the most common psychiatric symptom, occurring in about 47% of individuals with HD, with 28% being severe cases. Forty-two percent of individuals with HD had depression. Severe depression, obsessive-compulsive disorder, and irritability each occurred at a frequency of about 13%. Psychosis was relatively rare, occurring in about 4% of individuals, only about 1% being severe. In the REGISTRY cohort, about 7% of HD individuals died by suicide, a 7-fold increase compared to the approximately 1% rate of suicide in the general population (van Duijn et al., 2014). Other studies have found similar suicide rates in HD (Bird, 1999; Di Maio et al., 1993). The proportion of mutation positive individuals with suicidal ideation has been reported to be even higher – 9.9% (Hubers et al., 2013).

The mean age-of-onset (AOO) for HD is 35-45 years, but it can range from early childhood to the late 70s (Craufurd et al., 2015). The AOO in HD is described as the point in time when an expansion carrier develops clear motor signs of HD (Orth & Schwenke, 2011). The onset of motor disturbances is defined by the Unified Huntington's Disease Rating Scale (UHDRS) total motor score (TMS). Fifteen aspects of motor function are assessed in the motor section of the UHDRS. Each individual motor abnormality is rated on a scale from 0-4, with 0 being no motor abnormalities and 4 being clear motor abnormalities indicative of manifest HD. The TMS ranges from 0-134. A second assessment is used to determine the investigator's diagnostic confidence level

using a 0-4 scoring system (Huntington Study Group, 1996). Although onset of HD is defined by the onset of clear motor symptoms, subtle motor, cognitive and behavioral alterations may be present up to 20 years prior to disease onset.

Subtle psychiatric symptoms are often present decades prior to symptom onset, during the pre-manifest stage (Duff et al., 2007; Tabrizi et al., 2009). Some studies have shown that depression, apathy, and suicidal ideation may be some of the first behavioral symptoms to manifest in HD individuals, appearing several years before the onset of motor symptoms (Lenka et al., 2015). Because the earliest pathological changes in HD are in portions of the corpus striatum of the basal ganglia, cognitive and psychiatric behaviors may be affected before motor symptoms in HD (Aylward et al., 2011).

It is speculated that the behavioral phenotype may represent a prodromal stage of HD. In one prospective study using data from the Prospective Huntington At Risk Observational Study (PHAROS), participants who carried intermediate alleles for HD showed significantly increased behavioral abnormalities compared to non-expanded controls but similar motor, cognitive, and functional measures on the UHDRS. In particular, intermediate allele carriers showed significantly increased suicidal ideation and apathy scores (Killoran et al., 2013). These findings may suggest that certain behavioral symptoms could represent a spectrum of the early disease process, rather than a response to the debilitating nature of the disease. This also suggests the possibility that those with

lower repeat sizes, i.e. repeat sizes closer to intermediate range might be more prone to earlier onset of behavioral rather than motor symptoms.

However, the behavioral abnormalities in those with a clinical diagnosis of HD appear to be heterogeneous in their presentation and progression, manifesting at inconsistent points in the disease course in affected individuals (Kirkwood et al., 2001). Several studies have made attempts to characterize the behavioral symptoms of HD based on disease progression, stage of disease, or duration of illness. However, gaps in the literature suggest that there may be other factors contributing to the presence of behavioral symptoms in HD. Previous studies are also limited by relatively small sample sizes.

Interestingly, apathy is the only neuropsychiatric symptom that has been shown to directly correlate with the progression of motor and cognitive symptoms in HD (Baudic et al., 2006; Tabrizi et al., 2013; van Duijn et al., 2014). Apathy is defined as the primary absence of motivation, lack of drive or initiative, and emotional indifference (Gelderblom et al., 2017). A study conducted by Baudic et al. (2006) showed that the presence of apathy was associated with more severe cognitive disabilities, including attention deficits, impairment in executive functioning, and memory loss, particularly during earlier stages of HD. In a TRACK-HD study conducted by Tabrizi and colleagues (2013), participants with pre-manifest HD and early-stage HD were studied over 36 months to assess baseline predictors of disease progression. Amongst all the psychiatric indicators, apathy ratings specifically showed significant increases in the disease cohort compared to controls

(Tabrizi et al., 2013). Although these findings suggest that apathy may be a significant finding and indicator of disease progression in HD, the factors that impact whether apathy is present and its severity have not been clearly delineated.

Depression is another common finding during the early stages of HD, which has been found to manifest as early as 20 years prior to motor disease onset (Folstein, Abbott, Chase, Jensen, & Folstein, 1983; Kirkwood et al., 2001). Unlike apathy, depression has not been correlated with cognitive impairment, motor symptoms, or CAG repeat length in HD (Baudic et al., 2006; Weigell-Weber, Schmid, & Spiegel, 1996; Zappacosta et al., 1996). A study by Paulsen et al. (2005) that included 2,835 participants demonstrated that depressive symptoms increase during the earlier stages of HD and gradually decrease during the middle and later stages. The results from this study were attributed to two possible causes. First, the progressive increase in disability during the initial stages of HD is associated with loss of employment, loss of driving privileges, general loss of functioning, difficulty adjusting to a terminal illness, and increasing dependence on others, all of which may contribute to depressive symptoms. Second, dysfunction of the frontal-subcortical circuits may contribute to the biochemical etiology of depression in HD (Paulsen et al., 2005). Mayberg et al. (1990) demonstrated that individuals with HD or Parkinson's disease and depression are found to have hypometabolism in the orbitofrontal-inferior prefrontal cortex compared to individuals with HD or Parkinson's disease without depression, adding further evidence to the likelihood of a biological component to depression in HD.

There is conflicting evidence regarding an association between the presence of depression and the progression of other symptoms in HD. A study by Marder et al. (2000) that looked at 960 participants with HD showed that severe depression at baseline may be associated with a more rapid decline in functional ability. However, the REGISTRY study did not show any correlation between depressive symptoms and total functional capacity or disease duration (van Duijn et al., 2014). The conflicting evidence suggests that several factors may impact the presence of depressive symptoms as well as the progression of other clinical symptoms in HD.

One factor that may be associated with the presence of neuropsychiatric symptoms in HD is AOO. While associations between behavioral symptoms and disease stage have frequently been a topic of research, the relationship between behavioral symptoms and AOO has yet to be determined. A study looking at the clinical and genetic characteristics of late-onset HD (60 -79 years) showed that motor symptoms, such as chorea, impaired balance reflexes, or abnormal facial expressions are frequently the first symptoms of HD reported in late-onset cases (Lipe & Bird, 2009). In this retrospective observational study of 34 late-onset individuals, all cases had mild motor symptoms at onset, with a mean UHDRS motor score of 34. Motor symptoms included mild chorea, coordination difficulty, deterioration in hand writing, and voice changes. Of the 34 cases, 11 (33%) reported early psychiatric problems, of which apathy and depression were the most prevalent (Lipe & Bird, 2009). However, the severity of these psychiatric symptoms was

not determined. The results of this study suggest that motor symptoms may be more prevalent than psychiatric symptoms at disease onset amongst late-onset individuals. Based on this study, it appears that as yet undetermined biological features that contribute to determining AOO may play a role in the manifestation of specific behavioral, motor, and cognitive symptoms.

Another study conducted by Cornejo-Olivas et al. (2015) investigated the clinical and molecular features of late-onset HD in the Peruvian population. The study population consisted of 31 patients with late-onset HD, defined as onset ≥ 60 years of age. Researchers reviewed data for these cases, analyzing initial motor, cognitive, or psychiatric manifestations. They found that chorea was the most frequent initial symptom (92.3%) within the study population, while behavioral symptoms were much less frequent (7.7%). In terms of existing symptoms, or symptoms that existed at some point during the disease process, 89.8% of individuals with classic-onset HD, defined as onset <60 years of age, reported irritability while only 56.25% of the late-onset individuals reported irritability (Cornejo-Olivas et al., 2015). Since there was no data regarding the prevalence of depression amongst the classic phenotype group, a comparison could not be made between depression in the classic-onset and late-onset groups. A possible confounding factor in this study is the difference in population size between the two groups, classic-onset and late-onset. However, this study suggests that there may be a higher incidence of psychiatric symptoms amongst early-onset HD cases.

Lenka and colleagues (2015) conducted a retrospective chart review of 92 patients with HD in India with the goal of determining the demographic and genetic characteristics of patients who had behavioral symptoms at onset of HD versus those who had motor symptoms at onset. They found that there was no significant difference between the CAG repeat lengths of those with initial behavior symptoms and those with initial motor symptoms. However, in comparison to patients with initial motor symptom, the patients with initial behavioral symptoms had significantly earlier AOO ($p=0.03$) and longer disease duration ($p=0.04$). The average AOO for patients with initial behavioral symptoms was 33.7 years, while the average AOO for patients with initial motor symptoms was 39.2 (Lenka et al., 2015), supporting the hypothesis that patients with earlier AOO may present with more behavioral symptoms than those with later AOO.

While it has been well established that behavioral symptoms are a cardinal feature of Huntington's disease, studies have yet to clearly characterize these symptoms and their relation to AOO. An accurate determination of factors associated with AOO is critical in order to develop appropriate and personalized therapies for those with the expansion mutation. Further characterization of symptom presentation associated with AOO may ultimately change how the clinical diagnosis of HD (i.e. motor vs. behavioral symptoms) is defined. This may affect when and how interventions and neuroprotective therapies that aim to slow the progression of the disease are initiated. Furthermore, understanding the relationship between AOO and clinical symptoms of HD can influence how risk assessments for people at risk for HD are made by genetic counselors and other

healthcare providers. The goal of this study was to use information collected in the Enroll-HD database on individuals with manifest HD to better understand how AOO of HD relates to the presentation of behavioral symptoms.

## Aims

The overarching purpose of this study is to understand and characterize the behavioral manifestations of the Huntington's disease (HD) phenotype associated with age-of-onset (AOO) using data from the International Enroll-HD database. Specifically, we aimed to:

1) Compare difference in symptoms at disease presentation in individuals with early onset HD (<30 yrs), early-adult onset HD (≥30 yrs and ≤59 yrs), and late-adult onset HD (>59 yrs)
2) Compare behavior-specific Problem Behaviors Assessment (PBA) scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD
3) Compare overall PBA scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD

# Chapter 2. Methods

## Data Collection from Enroll-HD

This retrospective chart review utilized clinical data obtained from the Enroll-HD study. Enroll-HD is an observational, prospective, international registry study of a global Huntington's disease cohort conducted by the CHDI Foundation. The Enroll-HD study has three main objectives:

(1) To improve the understanding of the dynamic phenotypic spectrum and the disease mechanisms of HD

(2) To promote the development of evidence-based guidelines to inform clinical decision making and improve health outcomes for the participant/family unit

(3) To provide a platform to support the design and conduct of clinical trials

At its core, the Enroll-HD platform includes an ongoing, prospective, open-ended, globally standardized, longitudinal, observational study of HD. To date, this study has collected clinical and genetic information on over 8,714 participants enrolled in 125 clinical sites located in 13 countries across five continents – North America, South America, Europe, Asia and Australia. To achieve the previously mentioned objectives, de-identified and coded data and biological samples collected as part of the study are made available to investigators to conduct research (Landwehrmeyer et al., 2017).

One of the major advantages of using the Enroll-HD database is that it is rigorously collected and provides access to a large, well-characterized population of individuals with HD and controls. The study procedure includes baseline and annual assessments conducted by trained and certified clinical personnel. All efforts are taken to ensure that the highest level of internal consistency is maintained within the Enroll-HD study. Investigators are trained to perform standardized assessments through a variety of methods, including online training videos, practice videos, training sessions during investigator meetings, test assessments for certification, and didactic teaching methods. Study investigators also undergo a recertification process at periodic intervals. Each clinical site is encouraged to use the same rater to administer assessments to a particular participant for the duration of the study. Clinically validated assessment tools are utilized to measure various outcomes, such as The Motor and Diagnostic Confidence Index subscales of the UHDRS to assess motor symptoms of HD and the Problem Behaviors Assessment Short Version (PBA-s) for behavioral assessments. The HD genetic status of all participants is confirmed through genetic testing at a research lab. A blood sample is collected from all participants and genotyping of the DNA is performed using standard procedures for CAG repeat size analysis, with several routine quality control procedures in place to ensure quality and integrity of the DNA. All personal and clinical information and blood samples are de-identified to ensure participant confidentiality. Informed consent is obtained from study participants at study enrollment or from a legally acceptable representative for individuals with impaired cognitive and mental function.

The Enroll-HD dataset was requested by Sandra Kostyk, MD, PhD, Enroll-HD site investigator and thesis committee member, through an application procedure outlined on www.enroll-hd.org. A data use agreement was obtained from the CHDI Foundation. De-identified data was obtained in Microsoft Excel format from the CHDI.

## Study Participants

Participants eligible for this study were individuals registered in the Enroll-HD database with manifest HD. Individuals who tested positive for the HD expansion mutation but are pre-symptomatic, mutation-negative controls, individuals at risk for HD who have not undergone genetic testing, familial controls (family members who are not genetically related to the participant), and community controls were not eligible for this study.

## Clinical Information Obtained and Methodology

A review of the baseline data on eligible participants within the Enroll-HD database was performed. The following de-identified information was extracted from the Enroll-HD database record for eligible participants: sex, race, marital status, education status, employment status, drug and alcohol use information, HD Clinical Characteristics form results, Problem Behaviors Assessment (PBA) results collected at baseline, family history of HD, HD genetic testing results, and CAG repeat length.

## Data Analysis

The Division of Biostatistics within the College of Public Health at The Ohio State University provided statistical support and data analysis for this project. The statistical software, R, was used for data analysis. Descriptive statistics (means and proportions) were used to characterize demographics of participants.

*AIM 1: Compare difference in symptoms at disease presentation in individuals with early onset HD (<30 yrs), early-adult onset HD (≥30 yrs and ≤59 yrs), and late-adult onset HD (>59 yrs):*

Data from the Enroll-HD Clinical Characteristics form was used to compare the difference in symptoms at disease presentation between the early onset, early-adult onset, and late-adult onset groups. The Clinical Characteristics form contains information about the presenting symptoms of HD in participants. Symptoms are divided into 6 categories and are assigned a number for statistical analysis as follows: 1 (motor), 2 (cognitive), 3 (psychiatric), 4 (oculomotor), 5 (other), and 6 (mixed). Due to small values for oculomotor and other symptoms, these two categories were combined with motor and mixed categories respectively. Information about initial presenting symptoms is obtained from the participant, the family members, and the examiner. The examiner's judgement of the initial major symptom at disease presentation and AOO of disease was utilized, since this assessment is most likely to assimilate information from the participant, caregiver or family member, and other sources. The number of individuals with initial

presenting symptoms in each of the major symptom categories was quantified and further categorized into three groups: early onset HD (AOO <30 yrs), early-adult onset HD (AOO ≥30 yrs and ≤59 yrs), and late-adult onset HD (AOO >59 yrs). Differences were compared using marginal empiric probabilities. A chi-square test of independence was used to demonstrate the significance of the relationship between AOO and type of symptoms at disease presentation.

Standard multinomial logistic regression modeling was used to perform a refined analysis of the relationship between AOO and symptom type at disease onset. The analysis models the odds of different symptom types (motor, cognitive, or behavioral) at disease onset as a function of the AOO of disease while controlling for potential confounding factors.

*AIM 2: Compare behavior-specific Problem Behaviors Assessment (PBA) scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD:*

The Problem Behaviors Assessment (PBA) is a semi-structured interview intended to allow for a more reliable evaluation and better understanding of the behavioral symptoms in HD (Kingma, van Duijn, Timman, van der Mast, & Roos, 2008). It is an instrument used for rating the presence, severity, and frequency of behavioral symptoms of HD. The PBA offers a reliable assessment of the behavioral symptoms of HD, with an estimated

interrater reliability of 0.82 (95% CI=0.65–1.00) for severity scores and 0.73 (95% CI=0.47– 1.00) for frequency scores (Kingma et al., 2008). This tool has not been used in previous studies that have characterized the behavioral symptoms of HD in relation to AOO, making this study a novel analysis of these symptoms.

For this study, data from the short form of the PBA (PBA-s) was used. The PBA-s consists of 11 items that cover the majority of the behavioral symptoms that can be observed in HD, specifically depressed mood, suicidal ideation, anxiety, irritability, anger or aggressive behavior, apathy, perseverative thinking, obsessive-compulsive behaviors, delusions/paranoid thinking, hallucination, and disoriented behaviors. It incorporates a 5-point rating scale, one subscale for severity and one for frequency. The scores for severity are assigned as follows: 0 (absent), 1 (slightly present, questionable), 2 (mild or present but not a problem), 3 (moderate, symptom causing problem), 4 (severe or almost intolerable for career).

Results from the PBA-s assessment for all participants were provided in the Enroll-HD dataset. The number of individuals with each severity score rating was quantified and categorized by the AOO that was determined in the first part of this study. Based on these numbers, the empiric probability for individuals in each age group to have each of the 11 behavioral symptoms at various levels of severity were calculated.

Multinomial logistic regression modeling was used to perform a refined analysis of the relationship between AOO and severity of specific behavioral symptoms. The analysis models the odds of severe behavioral symptoms as a function of the AOO of disease while controlling for potential confounding factors.

*AIM 3: Compare overall PBA scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD:*

Data from the PBA-s was used for the final part of this study. Each participant's highest severity score (0-4) was identified. The number of individuals having each severity score as their highest severity score was quantified and categorized by AOO, which was determined in the first part of this study. Based on these numbers, the empiric probability for individuals in each age group to have each of the severity scores as their "worst" score was calculated.

Multinomial logistic regression modeling was used to perform a refined analysis of the relationship between AOO and severe behavioral symptoms of any type. The analysis models the odds of severe behavioral symptoms as a function of the AOO of disease while controlling for potential confounding factors.

# Chapter 3. Results

## Study Participants

A total of 8,714 participants were registered in the complete Enroll-HD dataset. Registered participants include individuals with manifest HD, pre-manifest HD expansion mutation carriers, individuals at risk for HD who have not undergone genetic testing, mutation-negative controls, familial controls (family members who are not genetically related to the participant, such as a spouse), and community controls. Of the 8,714 individuals in the complete dataset, 4,469 met eligibility criteria. Four hundred seventy-nine of these individuals had AOO prior to 30 years of age, 3,478 had AOO between 30-59 years of age, and 512 individuals had AOO at 60 years or later. The breakdown of study participants is summarized in Figure 1.

## Study Participant Characteristics

The participant demographic characteristics are summarized in Table 1. The average AOO for participants was 24 years (SD 5.4) for the early onset group, 45 (SD 8.0) for the early-adult onset group, and 65 years (SD 4.8) for the late-adult onset group. The average CAG repeat length was 51 (SD 6.7) for the early onset group, 44 (SD 2.5) for the early-adult onset group, and 41 (SD 1.2) for the late-adult onset group. The majority of participants were Caucasian, with 92.9% (n=445) in the early onset group, 94.4%

(n=3281) in the early-adult onset group, and 95.7% (n=490) in the late-adult onset group identifying as Caucasian individuals. Most of the early onset individuals were single (62.2%; n=298) while most of the late-adult onset individuals were partnered or married (74%; n=379). Compared to both the early-adult onset (20.1%; n=698) and late-adult onset (21.7%; n=111) groups, the early onset group had a lower percentage of divorced, separated, and widowed individuals (10%; n=48). The majority of individuals in all three groups were unemployed (early onset: 79.7%; n=380, early-adult onset: 79.2%; n=2753, late-adult onset: 92.7%; n=473).

Substance use amongst participants by AOO is summarized in Table 2. Thirteen percent (n=62) of individuals in the early onset group reported a history of alcohol abuse compared to 10.1% (n=349) of individuals in the early-adult onset group and 4.5% (n=23) of individuals in the late-adult onset group. A greater proportion of individuals in the early onset group also reported a history of smoking, current smoking, history of drug abuse, and current drug abuse than in the other two age groups. In the early onset group, 55.4% (n=265) of individuals had a history of smoking compared to 50.1% (n=1737) in the early-adult onset group and 46.9% (n=240) in the late-adult onset group. In the early onset group, 22% (n=105) of individuals had a history of drug abuse compared to 9.1% (n=317) in the early-adult onset group and 2.3% (n=12) in the late-adult onset group.

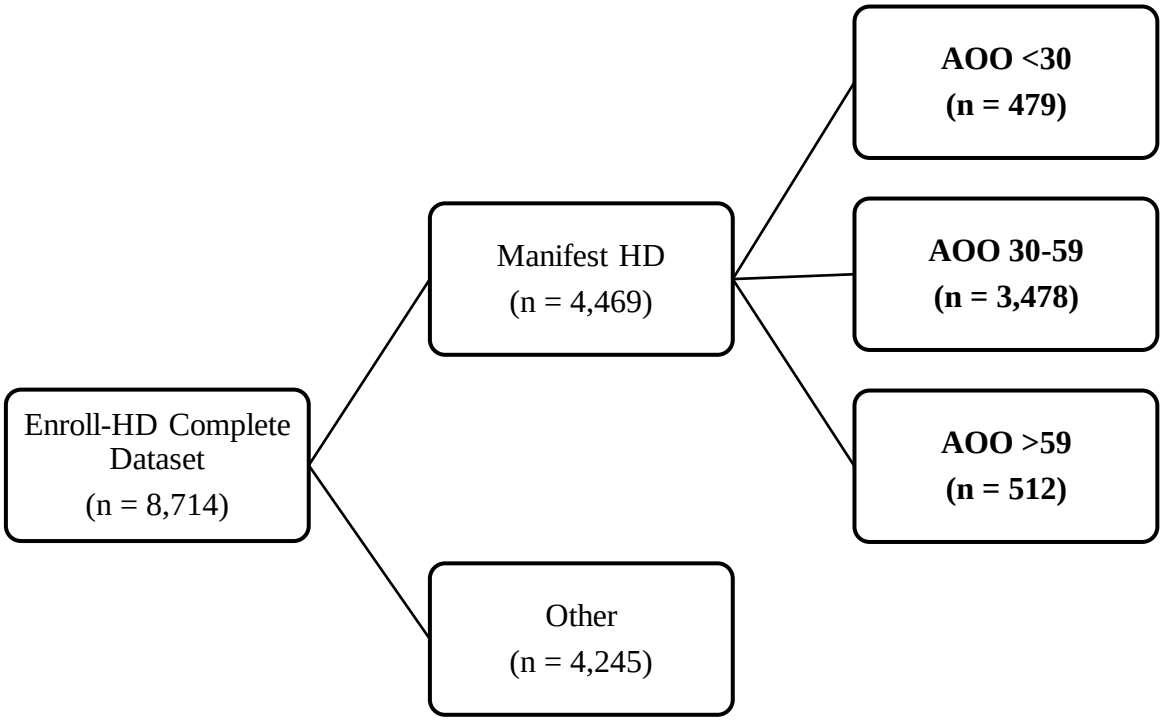


Figure 1. Study participants

| | AOO <30 (n=479) | AOO 30-59 (n=3478) | AOO >59 (n=512) |
|---|---|---|---|
| AOO mean ± SD (range) | 24 ± 5.4 (1-29) | 45 ± 8.0 (30-59) | 65 ± 4.8 (60-84) |
| CAG repeat length mean ± SD (range) | 51 ± 6.7 (40-98) | 44 ± 2.5 (36-58) | 41 ± 1.2 (36-46) |
| **Sex** | | | |
| Male | 225 (47%) | 1707 (49%) | 269 (52.5%) |
| Female | 254 (53%) | 1771 (51%) | 243 (47.5%) |
| **Race** | | | |
| Caucasian | 445 (92.9%) | 3281 (94.4%) | 490 (95.7%) |
| Hispanic/Latino | 11 (2.3%) | 55 (1.6%) | 3 (0.6%) |
| American – Black | 6 (1.3%) | 39 (1.1%) | 2 (0.4%) |
| Asian | 1 (0.2%) | 26 (0.7%) | 2 (0.4%) |
| American Indian/Native American | 1 (0.2%) | 14 (0.4%) | 0 (0%) |
| Mixed | 8 (1.7%) | 20 (0.6%) | 2 (0.4%) |
| Other | 7 (1.5%) | 42 (1.2%) | 13 (2.5%) |
| **Marital status** | | | |
| Single | 298 (62.2%) | 521 (15%) | 22 (4.3%) |
| Partnered/married | 133 (27.8%) | 2256 (64.9%) | 379 (74%) |
| Divorced/separated/widowed | 48 (10%) | 698 (20.1%) | 111 (21.7%) |
| **Education** | | | |
| Primary school (or less) | 16 (3.4%) | 145 (4.2%) | 56 (11%) |
| Secondary | 303 (63.7%) | 1803 (52.1%) | 244 (47.8%) |
| Post-secondary | 75 (15.8%) | 607 (17.5%) | 68 (13.3%) |
| Tertiary | 82 (17.2%) | 907 (26.2%) | 142 (27.8%) |
| **Job status** | | | |
| Full-time employed | 57 (11.9%) | 451 (13%) | 20 (3.9%) |
| Part-time employed | 38 (8%) | 206 (5.9%) | 11 (2.2%) |
| Self-employed | 2 (0.4%) | 65 (1.9%) | 6 (1.2%) |
| Not employed | 380 (79.7%) | 2753 (79.2%) | 473 (92.7%) |

Table 1. Participant demographics characteristics

| | AOO <30 (n=479) | AOO 30-59 (n=3478) | AOO >59 (n=512) |
|---|---|---|---|
| **History of alcohol use** | 62 (13%) | 349 (10.1%) | 23 (4.5%) |
| **Current alcohol use** | 149 (31.1%) | 1317 (37.9%) | 205 (40%) |
| **History of smoking** | 265 (55.4%) | 1737 (50.1%) | 240 (46.9%) |
| Pack years ± SD | 5.97 ± 9.56 | 11.01 ± 17.73 | 11.92 ± 21.68 |
| **Current smoker** | 184 (38.4%) | 943 (27.1%) | 56 (10.9%) |
| Pack years ± SD | 4.3 ± 8.16 | 6.85 ± 22.32 | 3.39 ± 13.34 |
| **History of drug abuse** | 105 (22%) | 317 (9.1%) | 12 (2.3%) |
| **Current drug abuse** | 24 (5%) | 77 (2.2%) | 3 (0.6%) |
| **Current caffeine use** | 364 (76.2%) | 2801 (80.6%) | 407 (79.6%) |
| **3+ Cups of coffee/tea/soda per day** | 193 (53%) | 1405 (50.2%) | 178 (43.7%) |

Table 2. Substance use amongst participants by AOO

*AIM 1: Compare difference in symptoms at disease presentation in individuals with early onset HD (<30 yrs), early-adult onset HD (≥30 yrs and ≤59 yrs), and late-adult onset HD (>59 yrs)*

Of the individuals with AOO <30 years, 42% (n=200) were reported to have motor symptoms as the major presenting symptom of HD at disease onset, 26% (n=126) had behavioral symptoms as the major symptom at disease onset and 9% (n=41) had cognitive symptoms as the major symptom type at disease onset. In addition, 22% (n=107) of individuals with AOO <30 years were reported to have multiple symptoms or other symptoms as the initial major symptom type and the major symptom type at onset was not reported for 1% (n=5) of individuals with AOO <30.

Among the individuals with AOO between ages 30-59, about 50% (n=1755) of the participants were reported to have had motor symptoms as the major presenting symptom type at onset, 19% (n=678) had behavioral symptoms, and 10% (n=337) had cognitive symptoms. Another 20% (n=696) were reported to have multiple or other symptoms as the initial major symptoms at disease onset and less than 1% (n=12) of individuals did not report the initial major symptom.

Of the individuals with AOO >59 years, the majority had motor symptoms as the initial major symptom type at disease onset (67%; n=343), 11% (n=56) had behavioral symptoms, and 4% (n=23) had cognitive symptoms as the major initial symptom type.

An additional 17% (n=89) had multiple or other symptoms at disease onset and less than 1% (n=1) of individuals did not report the initial major symptom. This data is summarized in Table 3 and Figure 2.

| | Motor | cognitive | behavioral | multiple/ other | NA |
|---|---|---|---|---|---|
| **AOO <30 (n=479)** | 200 (42%) | 41 (9%) | 126 (26%) | 107 (22%) | 5 (1%) |
| **AOO 30-59 (n=3478)** | 1755 (50%) | 337 (10%) | 678 (19%) | 696 (20%) | 12 (0%) |
| **AOO >59 (n=512)** | 343 (67%) | 23 (4%) | 56 (11%) | 89 (17%) | 1 (0%) |

Table 3. Marginal comparison of AOO to symptom type at disease presentation with empiric probabilities

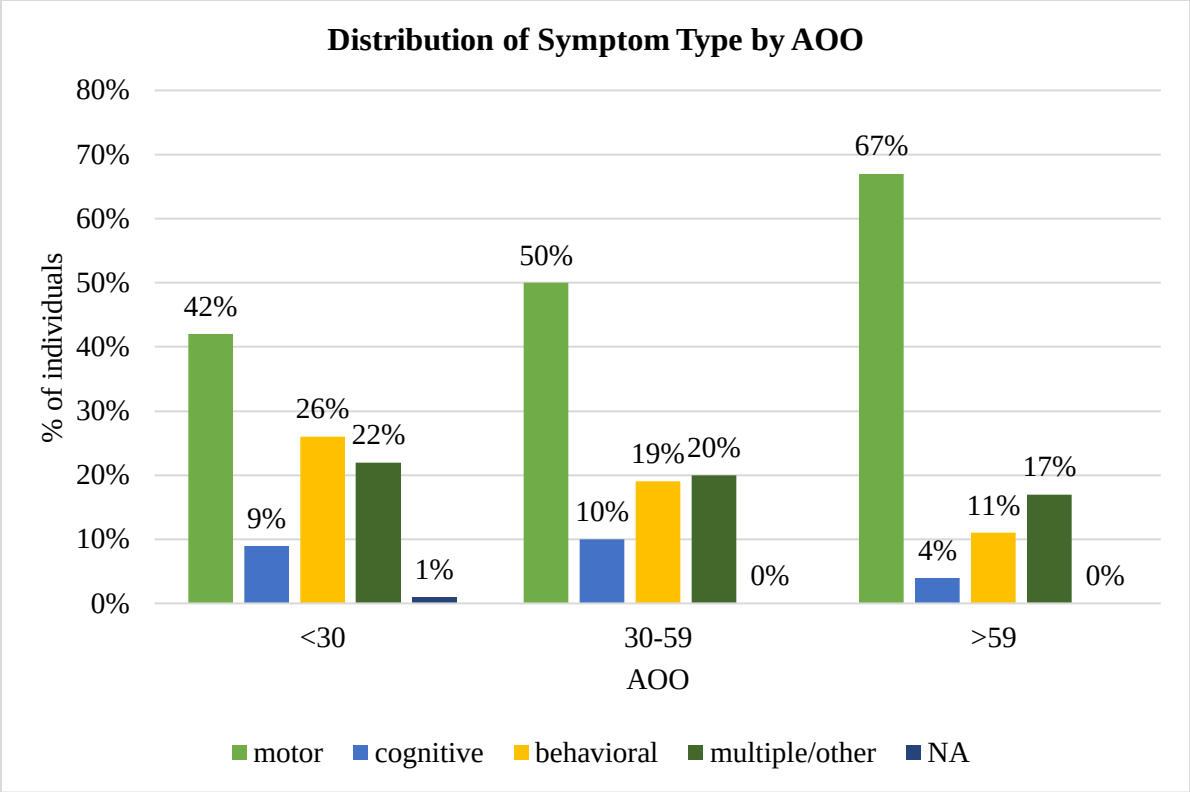


Figure 2. Distribution of symptom type by AOO

A chi-square test of independence showed a statistically significant relationship between AOO of HD and the type of symptoms at disease presentation ($p<.0001$).

A multinomial logistic regression model was used for a more refined analysis of symptom type based on AOO of disease. Potential confounding factors included high CAG repeat length, race, and sex, since these factors could independently affect the presence of behavioral symptoms. Therefore, these factors were included as covariates in the model to account for potential confounding. The logistic regression model allowed for the following three conclusions to be determined:

1) A one-year increase in the AOO of HD is associated with a 2.4% increase in the odds of motor symptoms being the main category of symptoms experienced at disease onset ($p<.0001$).
2) A one-year increase in the AOO of HD is associated with a 3.2% decrease in the odds of cognitive symptoms being the main category of symptoms experienced at disease onset ($p<.0003$).
3) A one-year increase in the AOO of HD is associated with a 5.6% decrease in the odds of behavioral symptoms being the main category of symptoms experienced at disease onset ($p<.0001$).

These conclusions are shown in Figures 3, 4, and 5.

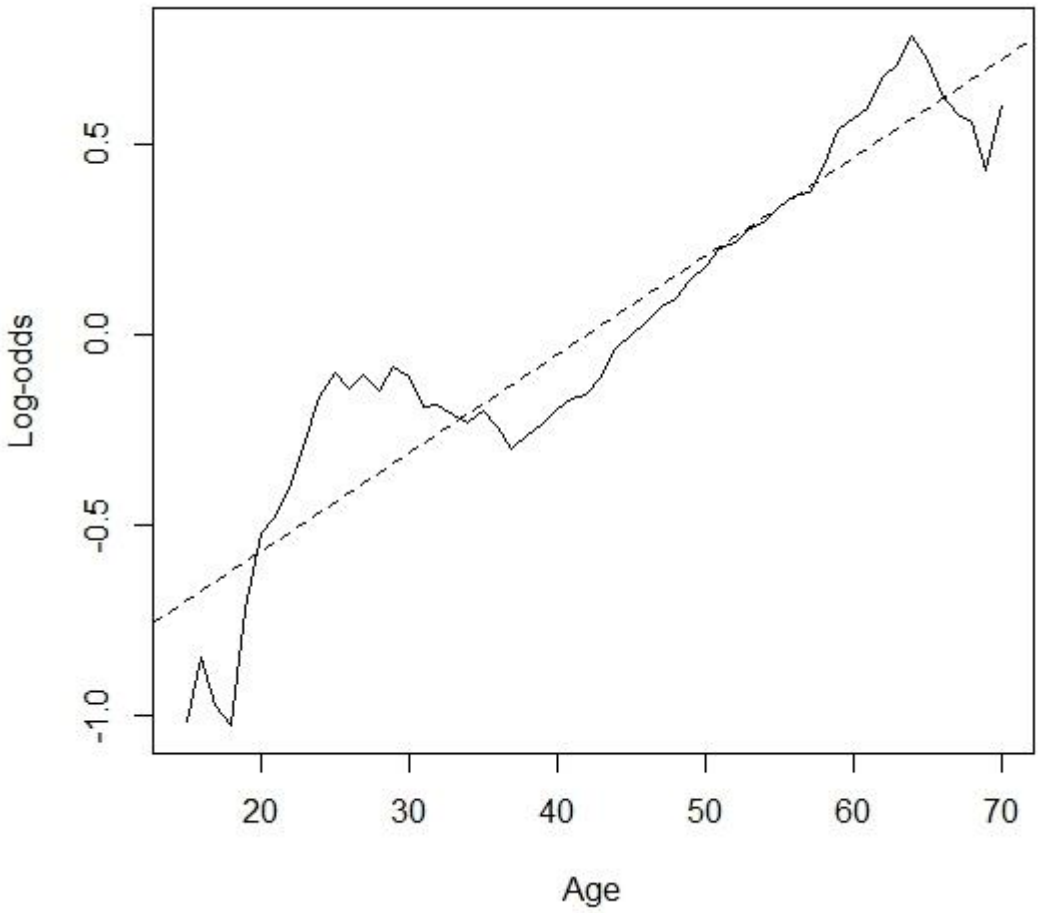


Figure 3. Rolling log-odds of motor symptoms by AOO

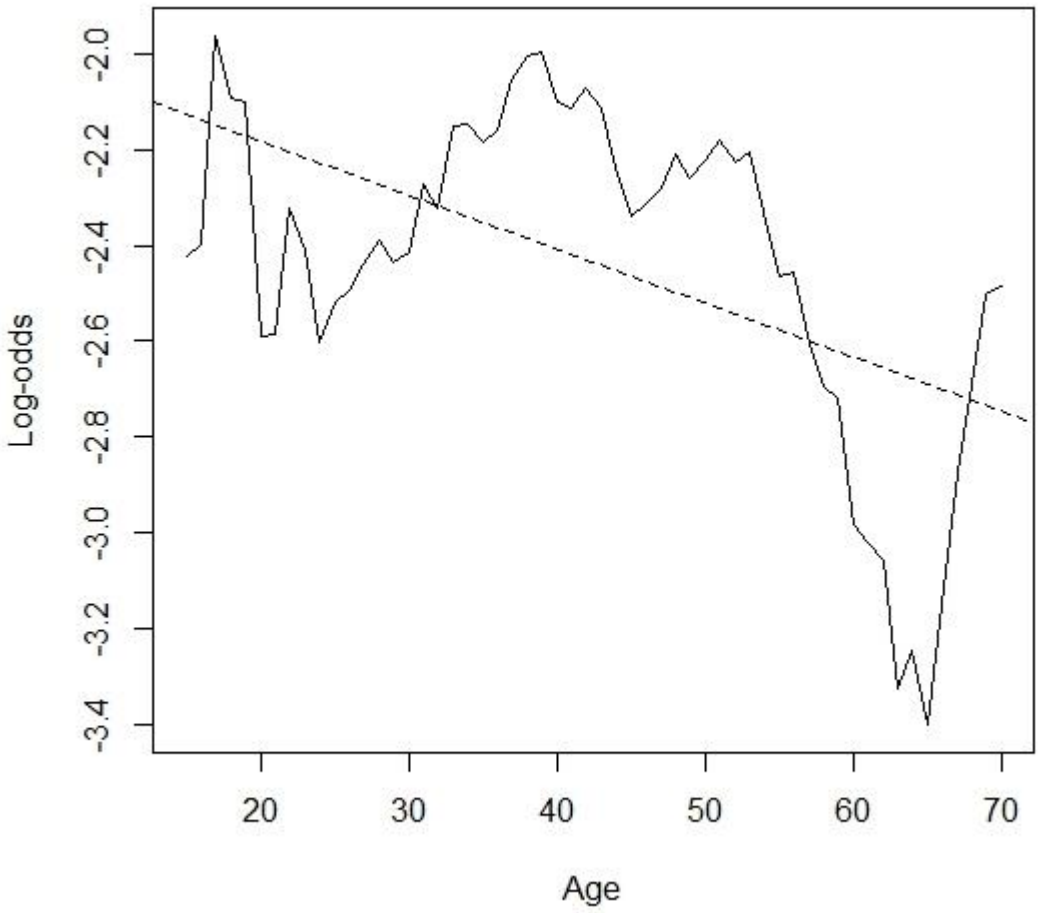


Figure 4. Rolling log-odds of cognitive symptoms by AOO

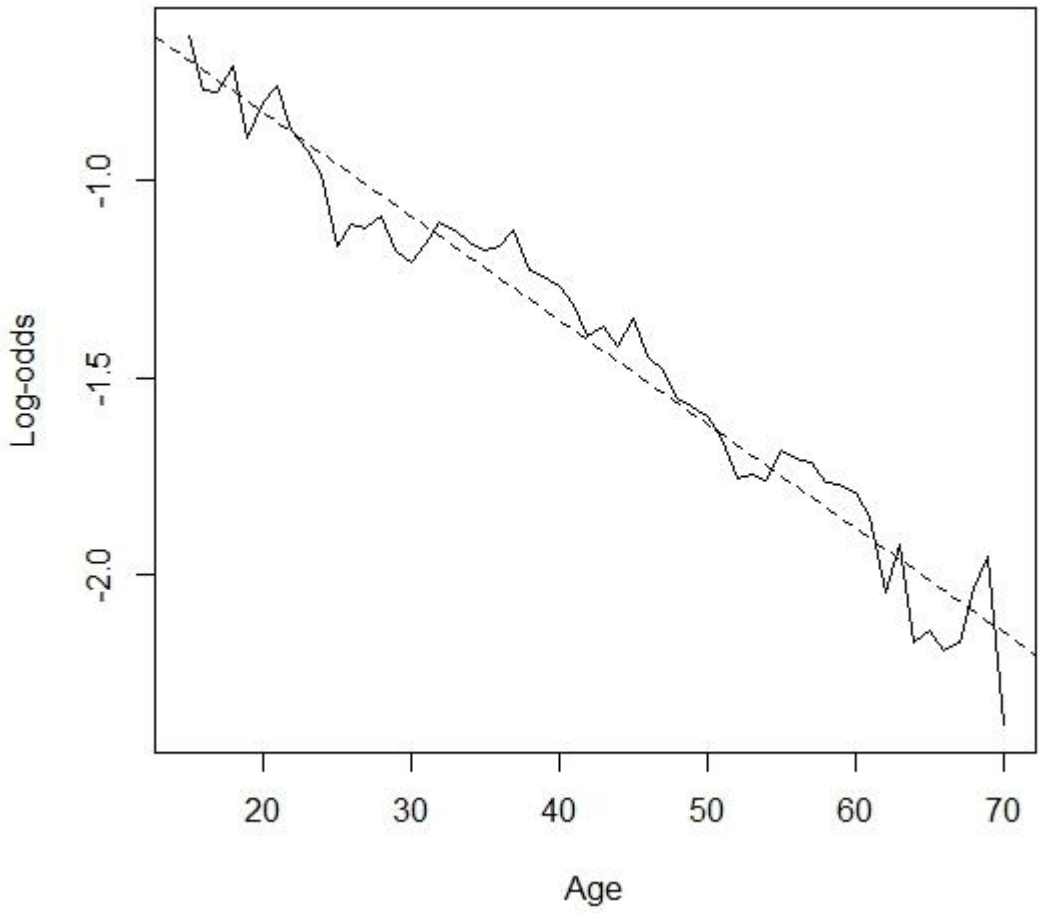


Figure 5. Rolling log-odds of behavioral symptoms by AOO

*AIM 2: Compare behavior-specific Problem Behaviors Assessment (PBA) scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD*

Table 4 summarizes the percentage of individuals in the early onset, early-adult onset, and late-adult onset age groups who experienced 11 behavioral symptoms at different levels of severity (0-4). Several trends can be observed in this data. About 11% of individuals in the early onset group and 11% of individuals in the early-adult onset group reported a severity score of 3 for depression compared to 5% of individuals in the late-adult onset group. Similarly, 12% of individuals in the early onset group and 11% in the early-adult onset group reported a severity score of 3 for anxiety compared to 7% of individuals in the late-adult onset group. Thirteen percent of individuals in the early onset and early-adult onset groups reported a severity score of 3 for irritability compared to 7% of individuals in the late-adult onset group. Nine percent of individuals in the early onset group and 8% in the early-adult onset group reported a severity score of 3 for anger/aggression compared to 6% of individuals in the late-adult onset group. Finally, 8% of individuals in the early onset group reported a severity score of 3 for obsessive-compulsive disorder compared to 4% in the late-adult onset group. Empiric probability distributions of symptom severity at baseline offer a noteworthy initial exploration. However, it is not apparent whether these trends are statistically significant based on the empiric values alone.

Additionally, by taking the percentage of individuals who had a severity score of 0 for each behavioral symptom and subtracting it from 1, we can determine the frequency at which these symptoms were experienced. This demonstrates that apathy, anxiety, irritability, depression, and perseverative thinking are the most frequently experienced behavioral symptoms in all three age groups.

| | Severity Score | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| **Depression** | | | | | |
| All | 49% | 12% | 27% | 11% | 1% |
| AOO <30 | 49% | 12% | 28% | 11% | 1% |
| AOO 30-59 | 48% | 12% | 28% | 11% | 1% |
| AOO >59 | 57% | 12% | 25% | 5% | 1% |
| **Suicidal ideation** | | | | | |
| All | 91% | 4% | 4% | 1% | 0% |
| AOO <30 | 89% | 5% | 4% | 1% | 1% |
| AOO 30-59 | 91% | 4% | 4% | 1% | 0% |
| AOO >59 | 93% | 3% | 4% | 1% | 0% |
| **Anxiety** | | | | | |
| All | 45% | 15% | 27% | 11% | 2% |
| AOO <30 | 45% | 14% | 26% | 12% | 3% |
| AOO 30-59 | 45% | 16% | 27% | 11% | 2% |
| AOO >59 | 50% | 14% | 27% | 7% | 1% |
| **Irritability** | | | | | |
| All | 46% | 16% | 23% | 12% | 2% |
| AOO <30 | 42% | 17% | 25% | 13% | 3% |
| AOO 30-59 | 46% | 16% | 23% | 13% | 2% |
| AOO >59 | 50% | 18% | 24% | 7% | 1% |
| **Anger/aggression** | | | | | |
| All | 71% | 8% | 12% | 8% | 2% |
| AOO <30 | 66% | 9% | 14% | 9% | 3% |
| AOO 30-59 | 70% | 8% | 12% | 8% | 2% |
| AOO >59 | 78% | 8% | 9% | 6% | 0% |
| **Apathy** | | | | | |
| All | 44% | 12% | 23% | 17% | 5% |
| AOO <30 | 42% | 12% | 24% | 17% | 5% |
| AOO 30-59 | 43% | 12% | 23% | 17% | 5% |
| AOO >59 | 49% | 10% | 19% | 17% | 5% |

Table 4. Empiric probability distributions of symptom severity (0-4) across different age groups for 11 behavioral symptoms

| | | | | | |
|---|---|---|---|---|---|
| **Perseverative thinking** | | | | | |
| All | 56% | 10% | 21% | 11% | 2% |
| AOO <30 | 57% | 10% | 18% | 12% | 3% |
| AOO 30-59 | 55% | 10% | 22% | 11% | 2% |
| AOO >59 | 59% | 10% | 19% | 10% | 2% |
| **Obsessive-compulsive disorder** | | | | | |
| All | 76% | 7% | 10% | 6% | 1% |
| AOO <30 | 69% | 7% | 13% | 8% | 3% |
| AOO 30-59 | 76% | 7% | 9% | 6% | 1% |
| AOO >59 | 81% | 6% | 9% | 4% | 1% |
| **Delusions/paranoia** | | | | | |
| All | 94% | 3% | 2% | 1% | 1% |
| AOO <30 | 91% | 4% | 3% | 1% | 1% |
| AOO 30-59 | 94% | 3% | 2% | 1% | 0% |
| AOO >59 | 97% | 2% | 1% | 0% | 0% |
| **Hallucinations** | | | | | |
| All | 98% | 1% | 1% | 0% | 0% |
| AOO <30 | 97% | 1% | 2% | 0% | 0% |
| AOO 30-59 | 98% | 1% | 1% | 0% | 0% |
| AOO >59 | 99% | 0% | 0% | 0% | 0% |
| **Disoriented behavior** | | | | | |
| All | 72% | 15% | 9% | 2% | 2% |
| AOO <30 | 71% | 16% | 9% | 3% | 1% |
| AOO 30-59 | 73% | 15% | 9% | 2% | 2% |
| AOO >59 | 70% | 16% | 8% | 3% | 2% |

Multinomial logistic regression modeling was used for the refined analysis of severity of behavioral symptoms at disease presentation by AOO. Potential confounding factors included high CAG repeat length, race, sex, as well as age at study enrollment, since these factors could independently affect the presence of behavioral symptoms. Therefore, these factors were included in the symptom severity model to control for any potential confounding. For the purpose of this analysis, severity scores of 1 or 2 were considered mild scores and scores of 3 or 4 were considered severe. Using logistic regression models, it was determined that a one year increase in AOO is associated with:

1) 3.7% decrease in the odds of severe irritability ($p=1x10^{-6}$)
2) 4.0% decrease in the odds of severe anger/aggression ($p=1x10^{-5}$)
3) 5.4% decrease in the odds of severe perseverative thinking ($p<3x10^{-12}$)
4) 5.8% decrease in the odds of severe apathy ($p<2x10^{-16}$)
5) 6.8% decrease in the odds of severe obsessive compulsive behavior ($p<3x10^{-10}$)
6) 8.8% decrease in the odds of severe delusions ($p=2x10^{-6}$)
7) 9.4% decrease in the odds of severe disorientation ($p<3x10^{-16}$)

Additionally, there is a discernable trend between an increase in AOO and decrease in the odds of severe anxiety (p=0.041), but it is not statistically significant when adjusting for multiple testing. There was no statistically significant relationship found between AOO and odds of severe depression (p=.60), suicidal ideation (p=.54), or hallucinations (p=.07). These findings are portrayed in Figures 6-16.

**Depression**

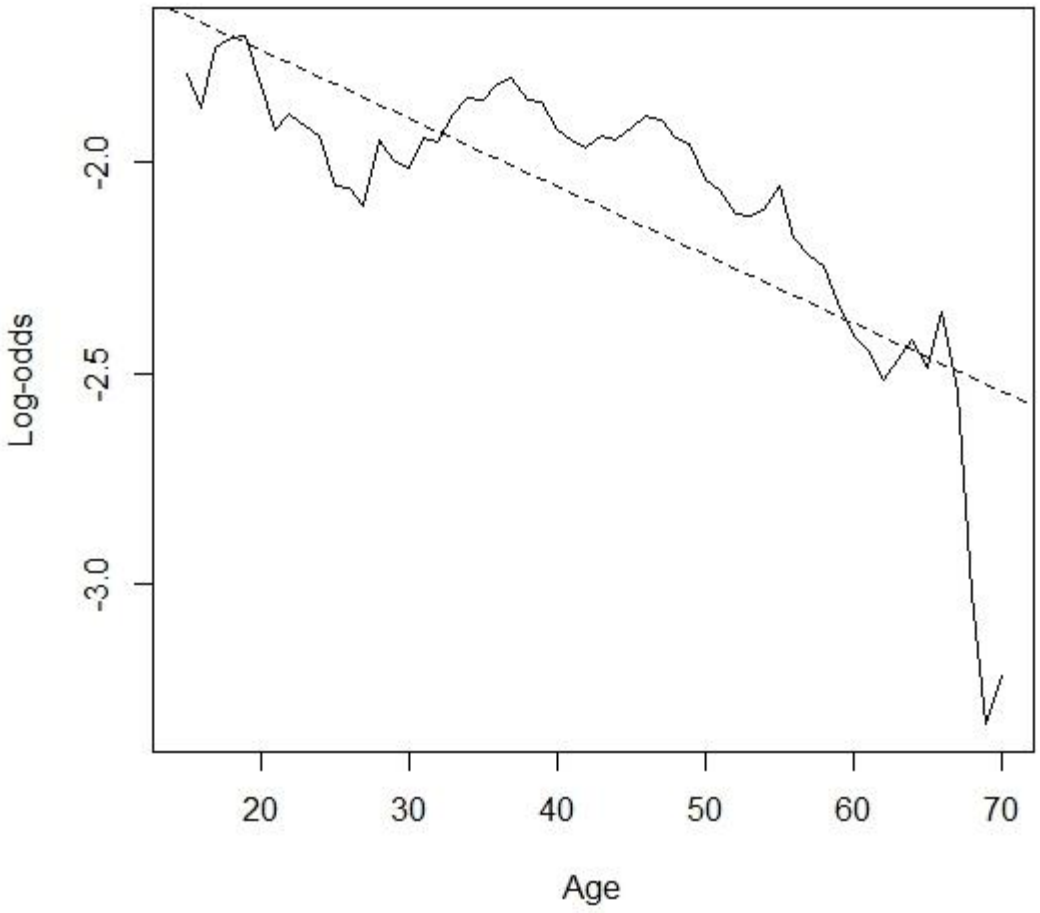


Figure 6. Pointwise estimates of the log-odds of depression by AOO

**Suicidal Ideation**

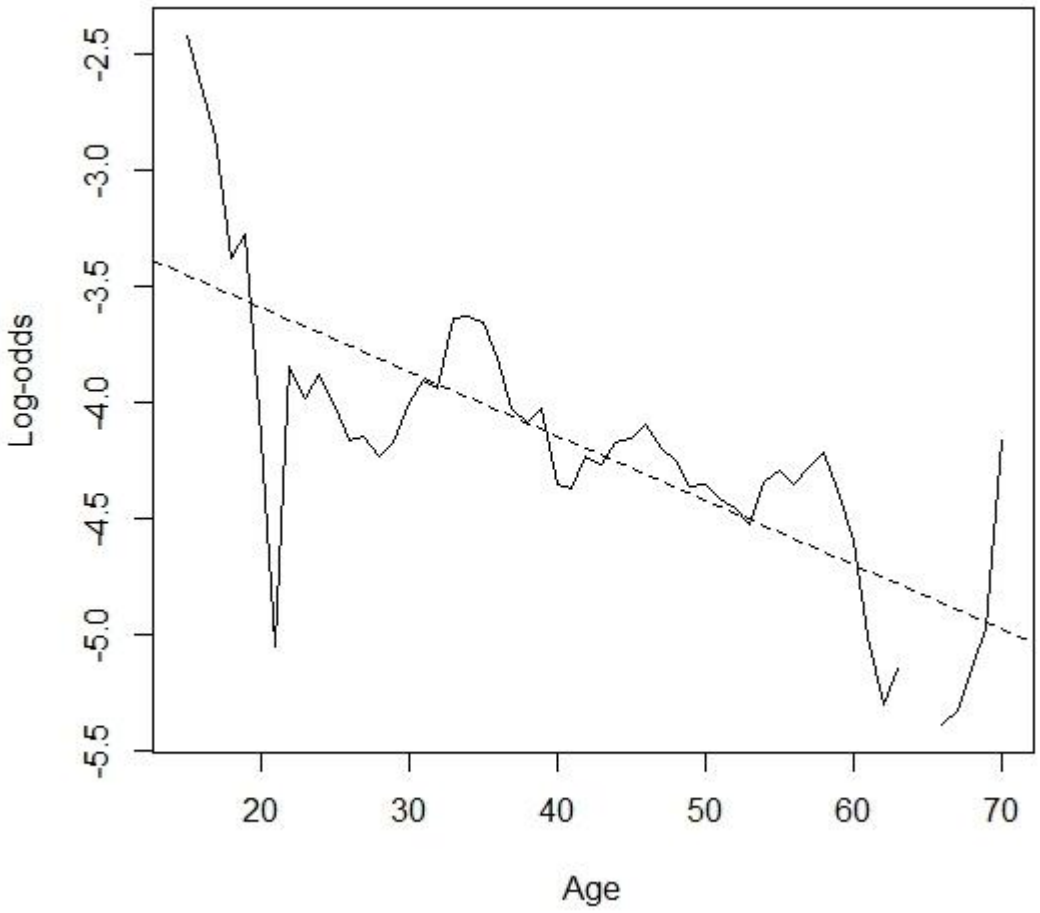


Figure 7. Pointwise estimates of the log-odds of suicidal ideation by AOO

**Anxiety**

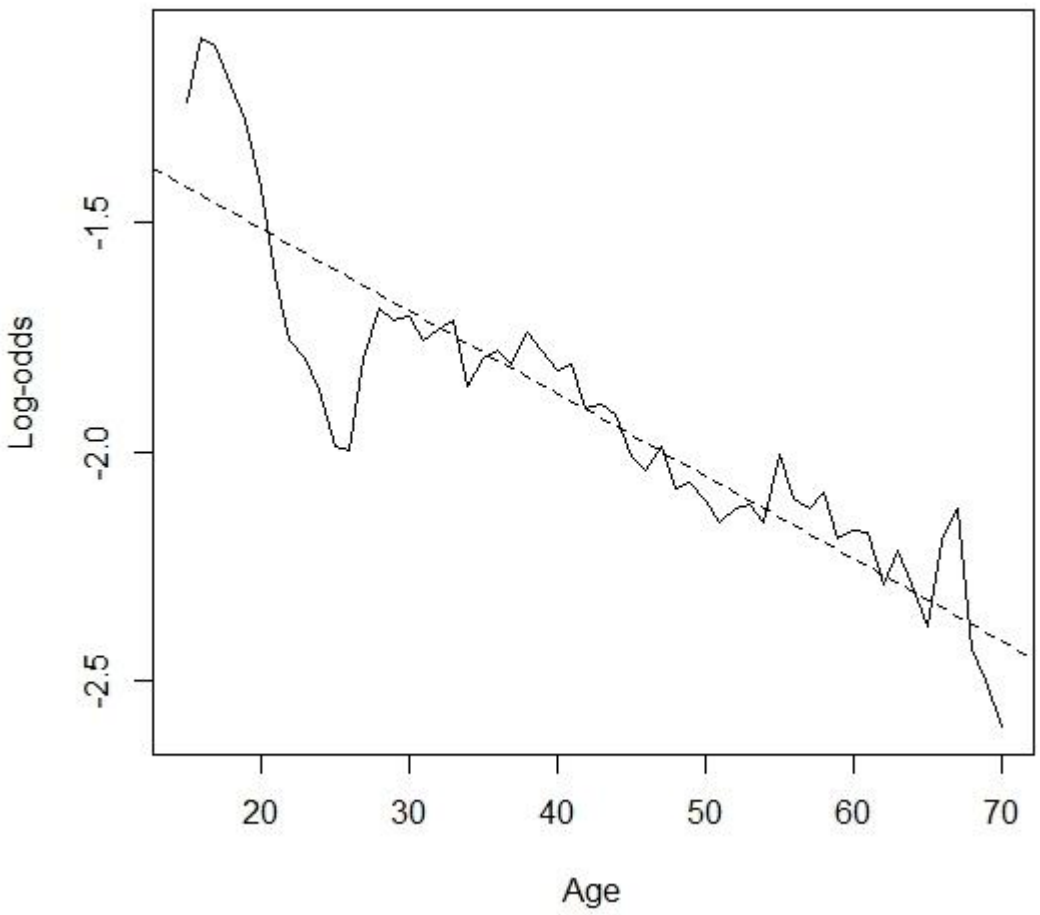


Figure 8. Pointwise estimates of the log-odds of anxiety by AOO

**Irritability**

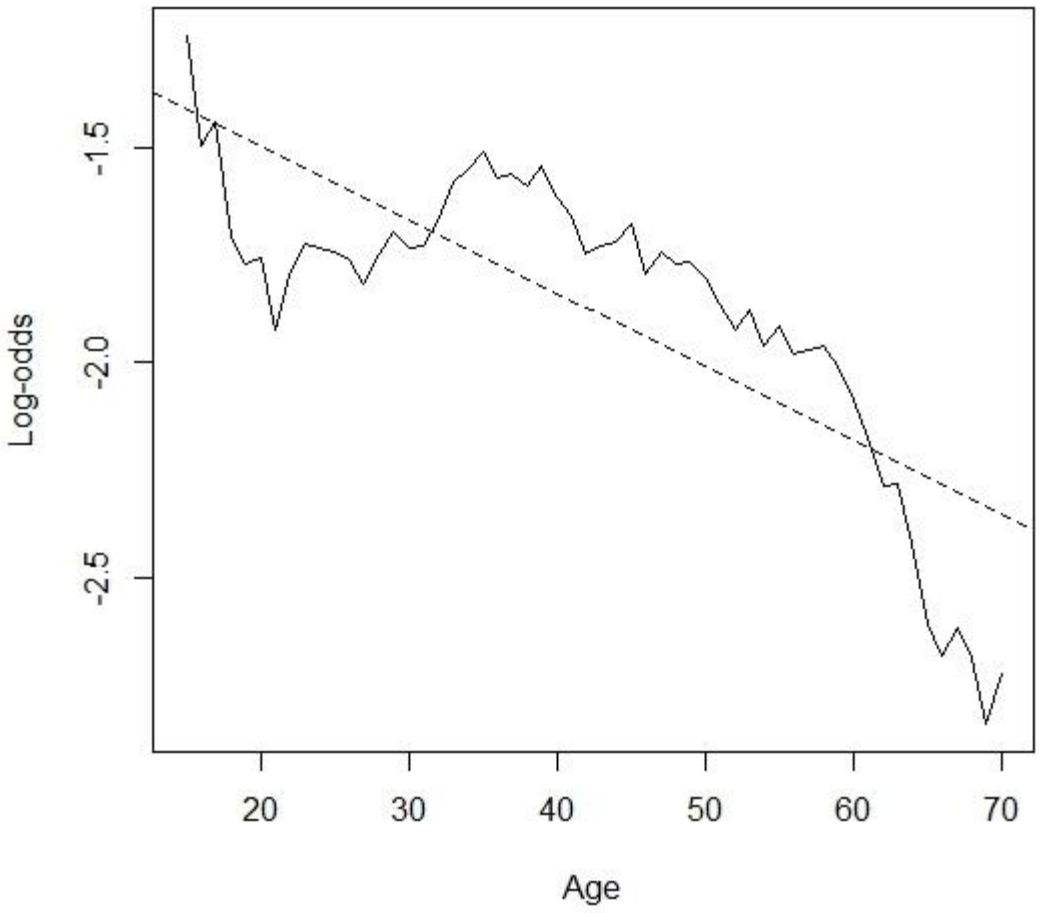


Figure 9. Pointwise estimates of the log-odds of irritability by AOO

**Anger/Aggression**

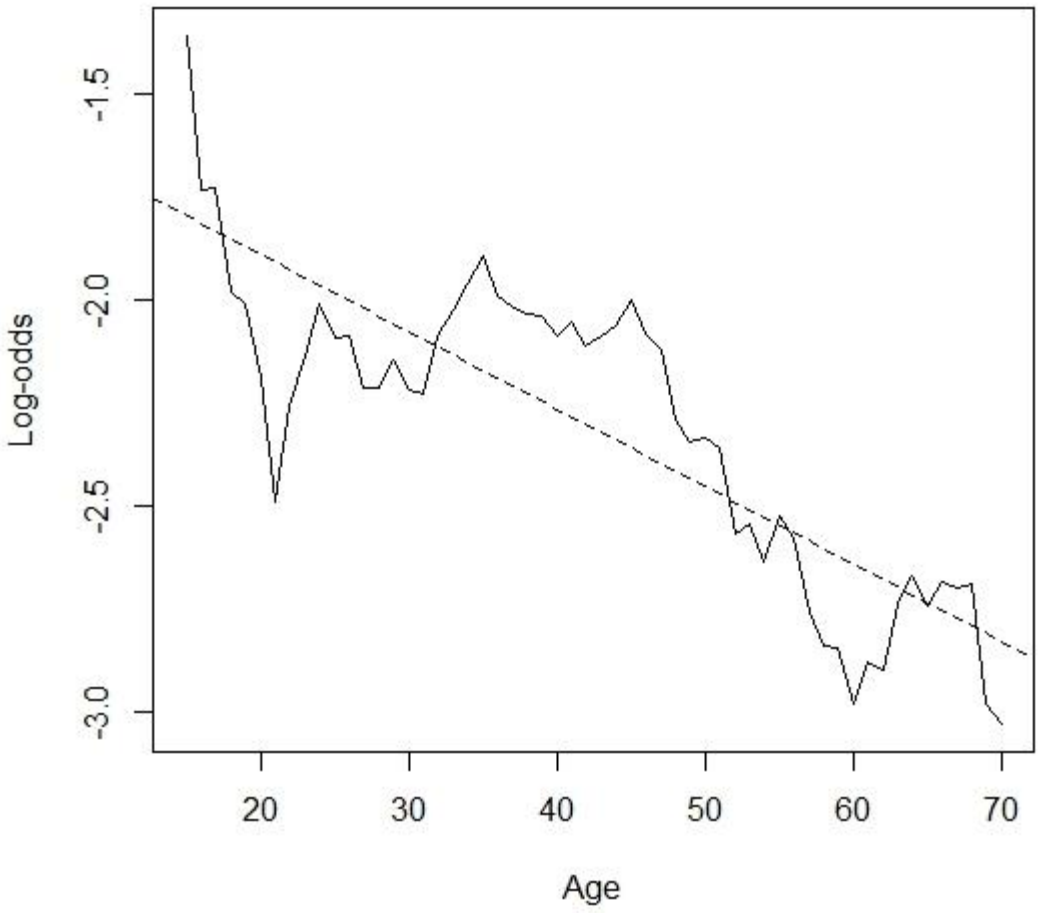


Figure 10. Pointwise estimates of the log-odds of anger/aggression by AOO

**Apathy**

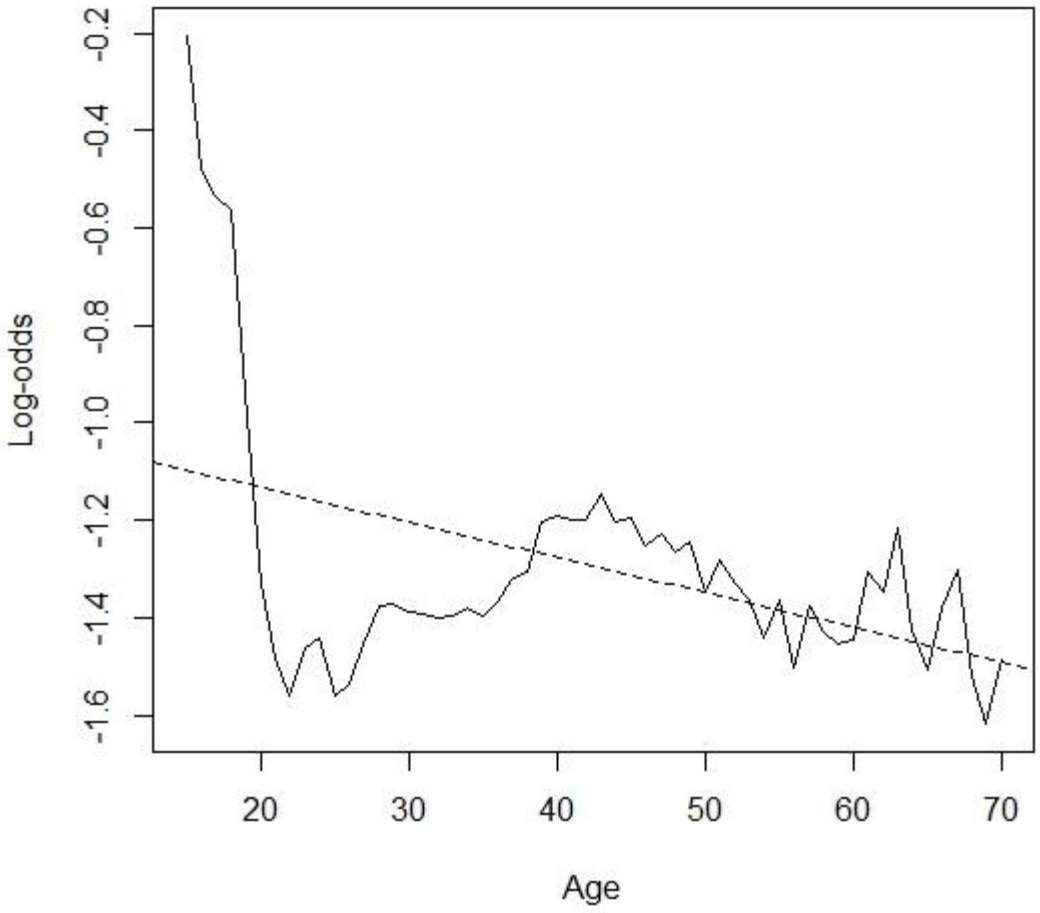


Figure 11. Pointwise estimates of the log-odds of apathy by AOO

**Perseverative Thinking**

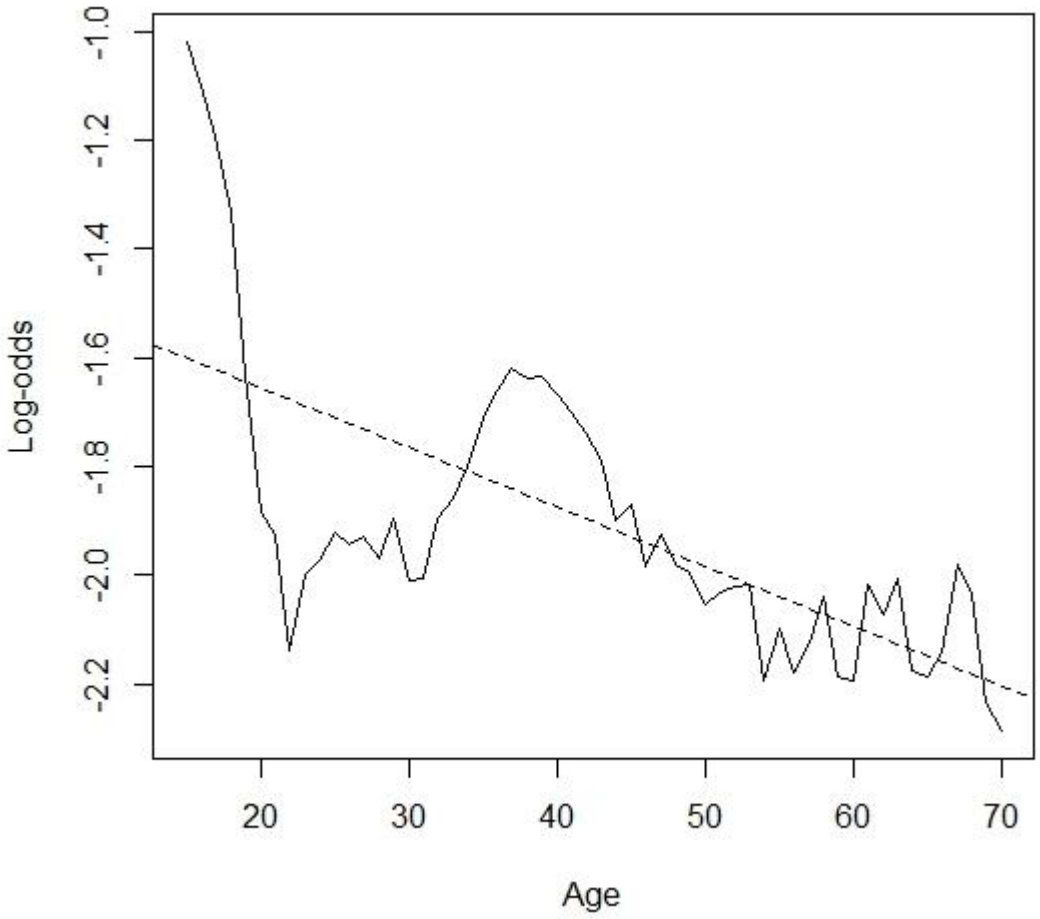


Figure 12. Pointwise estimates of the log-odds of perseverative thinking by AOO

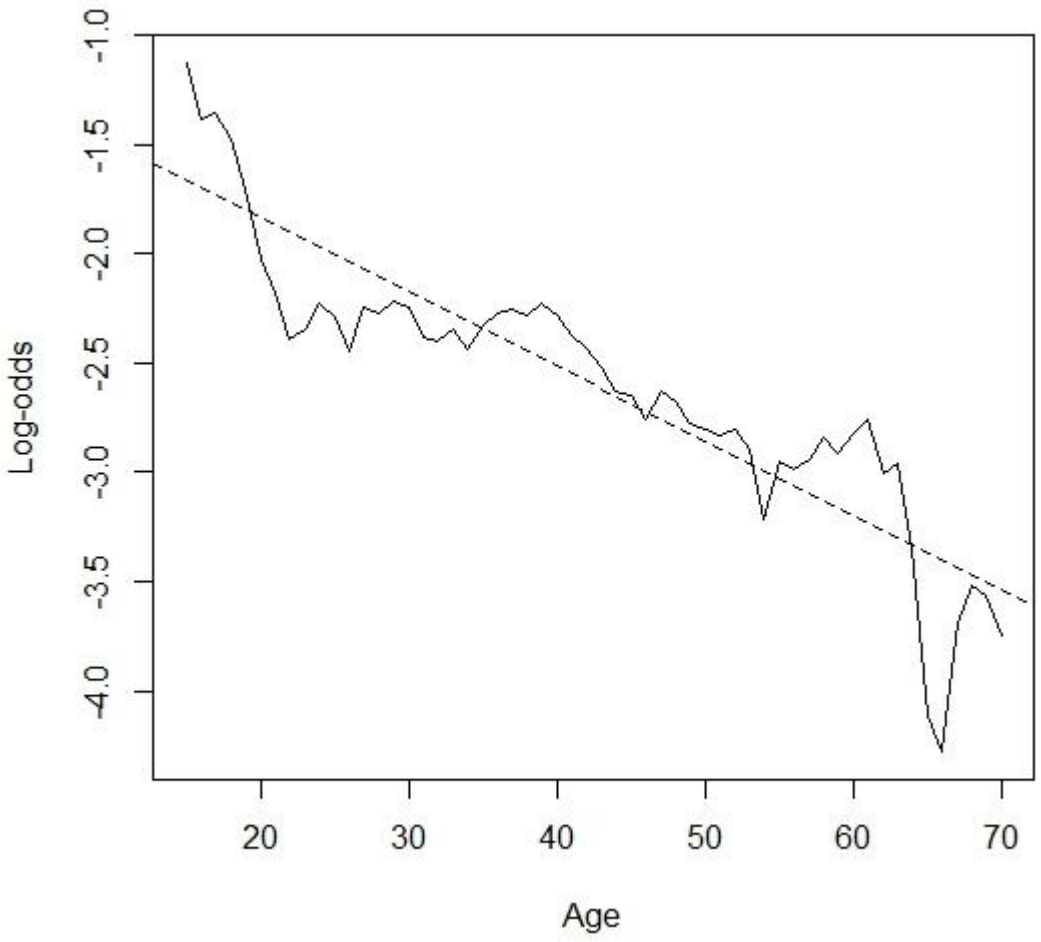


Figure 13. Pointwise estimates of the log-odds of obsessive-compulsive behavior by AOO

**Delusions/Paranoia**

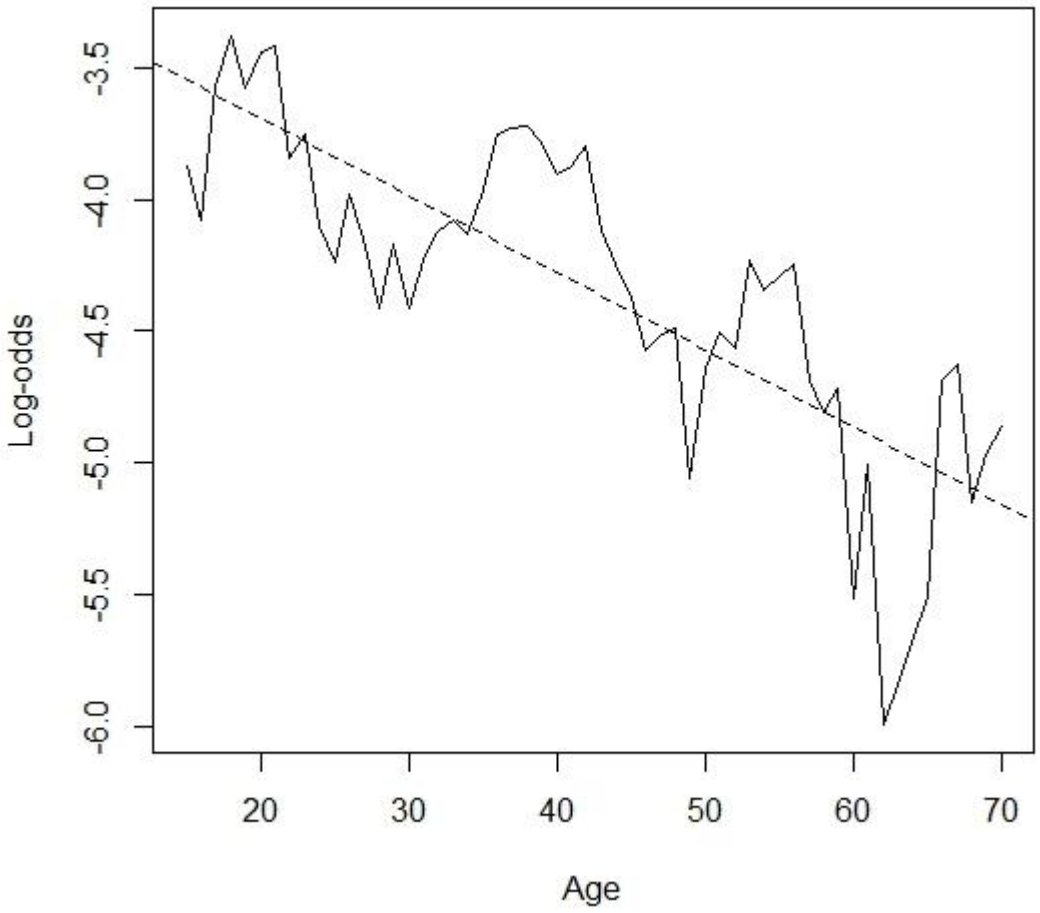


Figure 14. Pointwise estimates of the log-odds of delusions/paranoia by AOO

**Hallucinations**

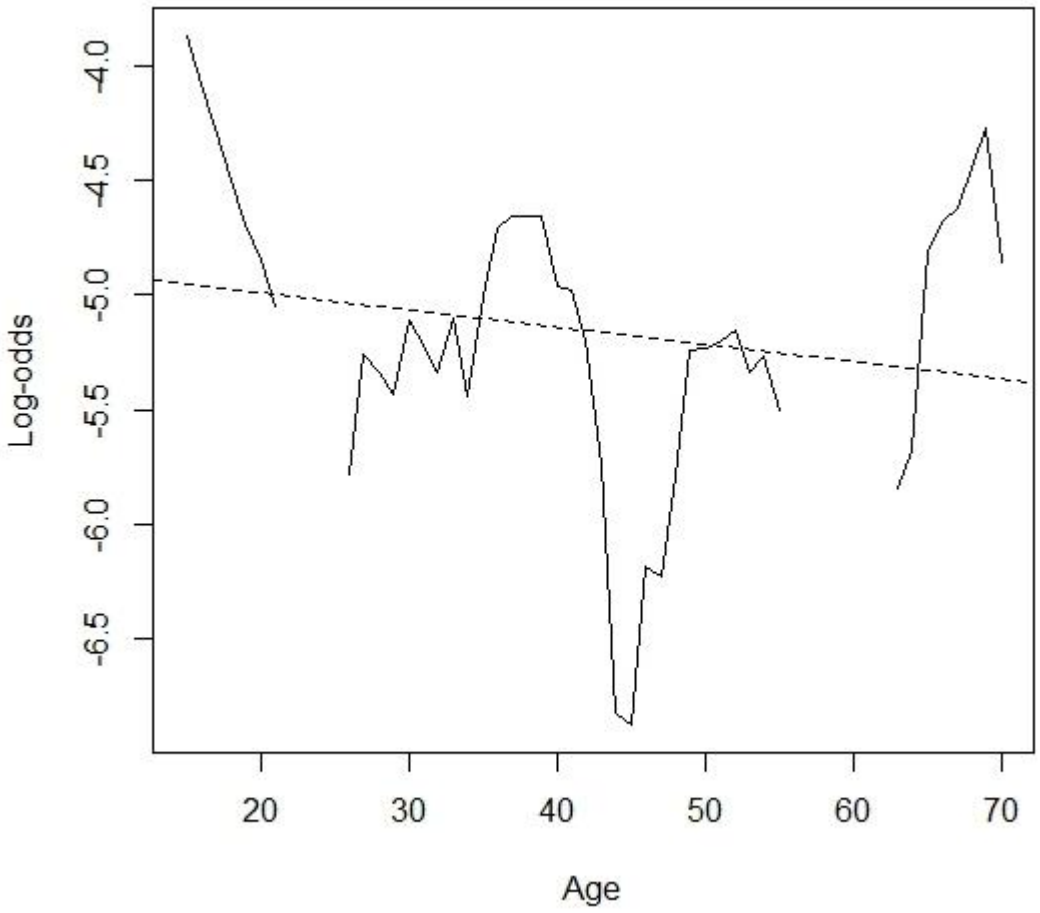


Figure 15. Pointwise estimates of the log-odds of hallucination by AOO

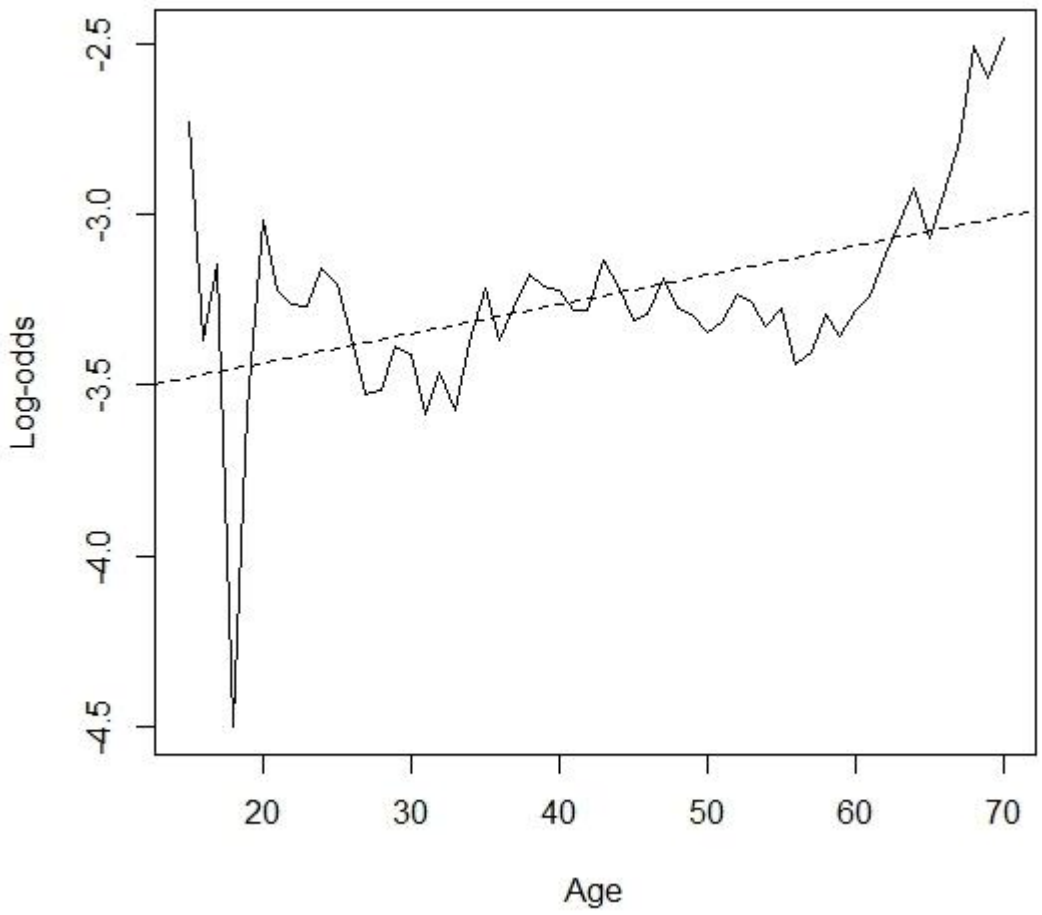


Figure 16. Pointwise estimates of the log-odds of disoriented behavior by AOO

*AIM 3: Compare overall PBA scores for severity in individuals with early onset HD, early-adult onset HD, and late-adult onset HD*

Table 5 summarizes the probability of individuals in the early onset, early-adult onset, and late-adult onset age groups to report each of the severity scores (0-4) as their "worst" severity score for any behavioral symptom. Notably, 33% of individuals in the early onset group and 34% in the early-adult onset group reported severity scores of 3 as their worst severity score compared to 29% in the late-adult onset group. About 13% of individuals in the early onset group reported a severity score of 4 as their worst severity score compared to 10% in the early-adult onset group and 9% in the late-adult onset group.

| | Severity Score | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| **All** | 10% | 10% | 36% | 33% | 10% |
| **AOO <30** | 10% | 9% | 35% | 33% | 13% |
| **AOO 30-59** | 10% | 11% | 35% | 34% | 10% |
| **AOO >59** | 14% | 10% | 38% | 29% | 9% |

Table 5. Empiric probability distribution of "worst" symptom severity (0-4) across different age groups

The empiric values alone do not demonstrate any statistically significant results. Therefore, multinomial logistic regression modeling was used to determine a trend in overall severity score for behavioral symptoms by AOO. Once again, CAG repeat length, race, sex, and age at study enrollment were included as covariates in the logistic regression model to control for any potential confounding. The results of this model showed that a one year increase in AOO is associated with a 5.5% decrease in the odds of severe behavioral symptom of any type ($p<1x10^{-10}$).

**Maximum Severity**

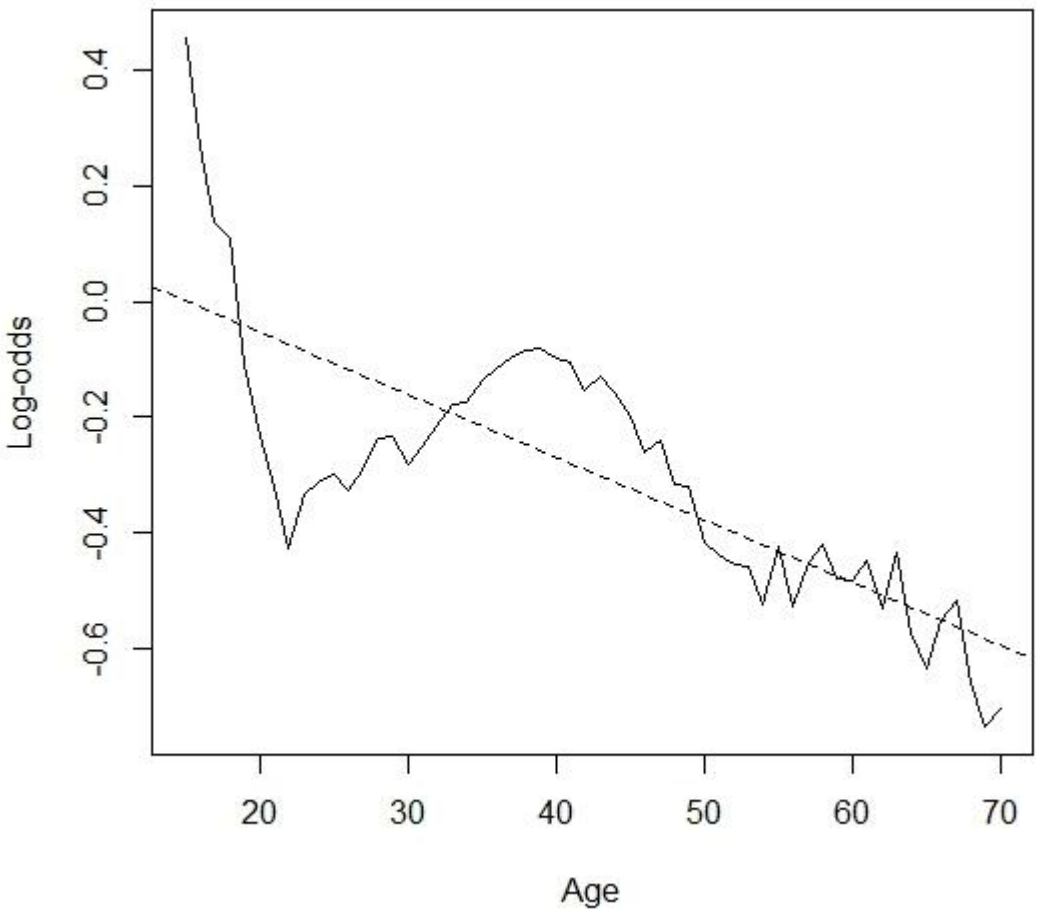


Figure 17. Pointwise estimates of the log-odds of "worst" severity score by AOO

# Chapter 4. Discussion, Limitations, and Conclusions

## Discussion

Very few research studies have explored the relationship between AOO of HD and the behavioral phenotypic manifestations of the disease. Some studies have aimed to characterize the behavioral symptoms of HD based on disease progression, stage of disease, duration of illness, or CAG repeat length. However, many of these studies have reported insignificant results, suggesting that there may be other factors contributing to the presence of behavioral symptoms in HD. In an attempt to resolve this gap in the literature, this study served the purpose of investigating one possible factor, AOO, and how it may potentially influence the presence of behavioral symptoms at disease onset and the severity of these behavioral symptoms.

The first part of this study aimed to determine whether there was a correlation between the AOO of HD and the presence of behavioral symptoms at disease onset. The results from a marginal univariate analysis revealed a clear correlation between AOO of HD and symptom type at disease onset. Specifically, the probability of behavioral symptoms being the major presenting symptom at disease onset seems to decrease with increasing AOO. Conversely, the probability of motor symptoms being the major presenting symptom at disease onset seems to increase with increasing AOO. This shows an inverse relationship between AOO and the probability of behavioral symptoms at onset and a

direct relationship between AOO and the probability of motor symptoms at onset. The findings from the marginal analysis were further supported by the results of the multinomial logistic regression analysis, which showed a statistically significant increase in the odds of motor symptoms being the major initial category of symptoms with every one-year increase in AOO and statistically significant decrease in the odds of behavioral symptoms being the major initial category of symptoms with every one-year increase in AOO. The results demonstrated a negative correlation between AOO and the presence of cognitive symptoms at disease onset as well.

These findings are in line with previous studies, which found that motor symptoms are commonly the first presenting symptoms of HD in late-onset cases (Cornejo-Olivas et al., 2015; Lenka et al., 2015; Lipe & Bird, 2009). However, previous studies have only speculated the presence of an inverse relationship between AOO and behavioral symptoms at disease onset. The study by Cornejo-Olivas et al. (2015), which consisted of a study population of 31 Peruvian individuals with late-onset HD from a total cohort size of 329 individuals with HD, showed that motor symptoms were the major presenting symptom in 92.3% of the late-onset cohort while behavioral symptoms were the major presenting symptom in only 7.7% of the late-onset cohort. However, the study by Cornejo-Olivas et al. did not find a significant difference in the probability of different symptom types based on varying AOO. This study further clarified the relationship between AOO and symptom type at onset by utilizing a much larger population size (n=4,469), by examining the relationship between symptom type and AOO in both late-

onset and early-onset individuals, and by determining the incremental changes in probability of different symptom types by AOO.

The results from this analysis are particularly concerning. If individuals affected with early-onset HD and their family members or caregivers are unaware of the increased risk for behavioral abnormalities, it is reasonable to speculate that they may not recognize the behavioral symptoms quickly or attribute them to a medical condition, deterring them from obtaining the appropriate treatment. Rather, they may attribute these behavioral changes to other aspects of the affected individual's life. For example, many individuals with early-onset HD may have parents or other family members who are also affected with HD. It is reasonable to assume that any behavioral changes experienced by younger individuals at risk for HD may be ascribed to the changes in their surrounding environment associated with a relative affected with HD or the individual's assimilation to the diagnosis in a close relative. More education for patients with HD, caregivers, genetic counselors, and healthcare providers is critical to promote early detection of behavioral symptoms associated with early-onset HD and to allow for appropriate intervention and treatment.

While it has been well established that behavioral symptoms can be some of the earliest symptoms to present in HD, these behavioral symptoms have commonly been attributed to a prodromal stage of HD (Killoran et al., 2013). The observed difference in this study in the probability of individuals in late and early onset groups to have behavioral

symptoms as the major presenting symptom of HD demonstrates that behavioral symptoms may not merely be a manifestation of the prodromal stage of HD, but rather, they may represent a spectrum of the disease presentation and progression.

One possible explanation behind the relationship between AOO and symptom type at disease onset discovered in this study could be the temporal sequence of pathological changes that occur in HD. Another explanation could be that many individuals with early-onset HD have affected parents and are more aware of their risk to develop the disease. Therefore, they may be more attuned to recognizing subtle symptoms of HD, such as behavioral symptoms that occur during the prodromal stage. Consequently, the age at which they report their initial symptoms of HD to have occurred may be much earlier than their actual age of motor disease onset. Controlling for family history in future studies as a confounding factor may resolve this alternative explanation.

The second part of this study explored the relationship between AOO and the presence and severity of specific behavioral symptoms at disease onset. The results showed that apathy, anxiety, irritability, depression, and perseverative thinking were the most commonly experienced behavioral symptoms in all three age groups. These findings add supporting evidence to previous studies that have found apathy to be the most frequently experienced behavioral symptom in HD, with depression and irritability also being common findings in affected individuals (van Duijn et al., 2014). Disorientation, delusions, and obsessive-compulsive behaviors were most frequently experienced at

higher levels of severity by individuals with earlier AOO, followed by perseverative thinking, apathy, anger/aggression, and irritability. It is interesting to note that there seemed to be a greater decrease in the odds of severe disorientation with increasing AOO compared to other behavioral symptoms of HD. One explanation as to why individuals with earlier AOO may experience more severe disorientation could be that there is a starker difference between their mental clarity before and after symptom onset compared to individuals with later AOO, who may attribute some of their symptoms of disorientation to aging.

Previous studies have failed to identify an association between depression and other factors of HD, including cognitive impairment, motor symptoms, or CAG repeat length (Baudic et al., 2006; Weigell-Weber et al., 1996; Zappacosta et al., 1996). Therefore, it is unsurprising that this study did not find any statistically significant correlation between depression and AOO of HD ($p=0.60$). As mentioned earlier, a study by Mayberg et al. (1990) found that individuals with HD and depression have hypometabolism in the orbitofrontal-inferior prefrontal cortex compared to individuals with HD without depression, suggesting the prospect of a biological component to depression in HD. However, the lack of evidence suggesting a correlation between depression and other clinical and genetic factors in HD leads to speculation that depression in HD may in fact be a response to the debilitating nature of the disease. This would provide one explanation for the similar frequency of depression across individuals with HD and different clinical and genetic characteristics. However, one could also make a case that

the opposite hypothesis is reasonable. Perhaps the biological etiology behind depression in HD differs from the biological cause behind other symptoms observed in HD. This study also did not identify a statistically significant correlation between AOO and the presence of severe suicidal ideation or hallucinations, suggesting that individuals with HD may be at an equally severe risk for these behavioral symptoms regardless of AOO.

The final part of this study examined overall severity scores to determine whether there was a difference in the overall severity of behavioral symptoms experienced by individuals with different AOO. The study showed that marginally, a greater proportion of individuals in the early and early-adult onset groups had higher overall severity scores than the individuals in the late-adult onset group. Multinomial logistic regression modeling demonstrated that a one year increase in AOO is associated with a 5.5% decrease in the odds of severe behavioral symptoms of any type ($p<1x10^{-10}$). This finding is significant because it implies that not only do individuals with early-onset HD have a higher likelihood of having behavioral symptoms as the presenting symptom of disease, but they are also at higher risk for more severe behavioral abnormalities than individuals with later AOO. This further delineates the need for more awareness of the risks associated with earlier onset HD so that caregivers and clinicians can provide the appropriate care and treatment for these individuals.

This study poses many significant implications for genetic counseling of patients with HD. Genetic counselors should be aware of the effect that apathy can have on a patient.

While the role of a genetic counselor is to educate families about the disease and its medical, familial, and psychological implications, apathetic individuals may be less attentive during the session. Furthermore, apathetic individuals may have diminished motivation to fight the progressive symptoms of HD or to follow up on medical recommendations from healthcare providers. The consequences of apathy and other behavioral symptoms on the genetic counseling session provide support for the recommendation that an unaffected caregiver be present at the genetic counseling session along with the patient. Behavioral symptoms may also impact the way patients perceive information that genetic counselors provide. For example, an individual with depression may have a much more reactive response to finding out that he or she has HD than an individual without depression. An affected individual's anxiety may be further exacerbated when thinking about how the results of genetic testing would impact their actions, such as making accommodations to prepare for the future. Although behavioral symptoms have been shown to be a part of the disease phenotype, it is also important to recognize situations in which behavioral symptoms are in fact defense mechanisms or the result of an underlying psychological issue that needs to be addressed by the genetic counselor. Genetic counselors should pay close attention to these behavioral symptoms and counsel patients accordingly.

The presence of behavioral symptoms in the patient may also impact the psychological welfare of the caregiver. For example, the parents of an individual displaying apathy may be frustrated by their child's lack of will-power to fight the disease. Irritability in the

patient may make it difficult for family members to interact with the individual. Therefore, genetic counselors should be prepared to address psychosocial issues in not only the patient, but also the caregivers.

Finally, genetic counselors should be aware of how the behavioral manifestations of HD could affect the counselor and change the temperament of the counselor's interaction with the patient. A phenomenon known as countertransference occurs when the patient or the patient's experiences provoke certain associations, thoughts, and images in the counselor, altering the nature of the genetic counseling session (Kessler, 1992). For example, an apathetic patient may invoke impatience in the genetic counselor or remind the genetic counselor of her adolescent child, who has recently become increasingly lethargic and uninterested in conversing with her. A young patient experiencing suicidal ideation may trigger memories of a childhood friend who committed suicide in the past. As demonstrated by these examples, countertransference could negatively influence the nature of the genetic counseling session. Additionally, lack of knowledge of the behavioral symptoms of HD may impact how genetic counselors perceive the patient. For example, the genetic counselor may mistake apathy associated with the disease for a coping mechanism or the patient's transference of feelings towards the genetic counselor in the counseling session. However, knowledge of the behavioral manifestations of HD could prevent misattribution of the behavioral symptoms of HD and also enhance the genetic counselor's ability to empathize with patients, allowing for more appropriate use of primary and advanced empathy to help the client better cope with their symptoms.

## Limitations

One major limitation of this study is that clinical information regarding age and symptoms at onset was collected retrospectively on individuals already known to be affected with HD. Demographic and clinical history obtained during enrollment is subject to recall bias, and data analysis is based on the assumption that the information obtained is accurate. One example of recall bias resides in the assessment of the major initial symptom at disease onset. Participants and family members who provide information on the participant's clinical history may not recall all information accurately or may have different perceptions of their disease characteristics. This study utilized the investigator's assessment of age of symptom onset and major initial symptom type at onset because this assessment was most likely to account for information from the patient, family members, and any other available clinical information, thus reducing recall bias from the patient and family members alone. However, the investigator's assessment is also subject to biases of individual investigators at different clinical sites. For example, in a situation where the participant reported behavioral symptoms as the major initial symptom, some examiners may report behavioral symptoms as the major initial symptom type while others may attribute these symptoms to a prodromal stage of HD rather than true disease onset. Future studies that assesses prospective clinical data to determine the relationship between AOO and symptom type at onset may address this limitation.

The PBA-s tool used in this study is also limited. The PBA was administered to participants in Enroll-HD during their baseline visit for enrollment. Participants are

enrolled at different times in their disease course. Additionally, ratings are based on the patient's average behavior over the 4 weeks preceding the baseline visit, and not based on the patient's overall disease progression. Therefore, the information obtained through the PBA may not be indicative of severity and frequency of behavioral symptoms at disease onset. In an attempt to obtain more accurate results from this analysis, age at baseline enrollment was incorporated into the multivariate logistic regression model as a possible confounding factor. Additionally, while the PBA has an interrater reliability of 0.86, there is still the possibility of bias on the part of the examiner. Although the results from the PBA analysis are limited, they provide a strong starting point for future research on this topic.

Another limitation of this study is the possibility of other confounding factors that were not accounted for in the analysis. One major confounding factor could be family history of HD. A recent study that investigated 4,285 HD mutation positive individuals demonstrated that individuals with a positive family history are more likely to report behavioral manifestations as the major initial symptom of HD than motor manifestations (Kringlen, Kinsley, Aufox, Rouleau, & Bega, 2017). As mentioned earlier, individuals with earlier onset HD are more likely to have a parent or other family member affected with HD and may be more aware of their risk to develop HD. Therefore, they may be more attuned to recognizing the subtler symptoms of HD, including behavioral changes, at a much earlier stage than individuals with late-onset HD. Younger individuals are also more inclined towards developing behavioral abnormalities, such as depression, apathy,

and anxiety than older individuals, even in the general population. Therefore, the findings of this study may simply reflect the representation of behavioral symptoms in the general population. This study also did not compare our participants to mutation-negative controls. Perhaps utilizing individuals who tested negative for the HD expansion mutation but shared similar environmental exposures to the participants as controls may have accounted for some potential confounding factors.

Finally, this study is limited by the cutoffs used for different age groups. In this study, early onset HD was defined by disease onset at earlier than 30 years of age. Early-adult onset HD was defined by disease onset between ages 30 and 59. Late-adult onset HD was defined as disease onset at age 60 or later. One limitation of these age boundaries is that many individuals in the early-onset age category would be classified as having juvenile onset HD, which can have a distinctive clinical presentation from adult-onset HD (Nance & Myers, 2001; Gonzalez-Alegre & Afifi, 2006; Yoon et al., 2006). Another limitation of the age cutoffs in this study is the resulting imbalance in the number of participants in each category, with the early-adult onset age group being much larger than the other two age groups.

## Conclusions

This study provided further data to support findings from earlier studies that showed that individuals with late-onset HD tend to have more motor symptoms at disease onset than behavioral symptoms. Additionally, it provided a more thorough analysis of the

relationship between AOO and symptoms at disease presentation. The data suggests that increasing AOO in HD is associated with decreasing odds of behavioral and cognitive symptoms being the major symptom type at disease presentation and increasing odds of motor symptoms being the major symptom type at disease presentation. Specific behavioral symptoms, particularly disorientation, delusions, and obsessive-compulsive behaviors tend to manifest more severely in individuals with earlier onset of disease. Although not the most severely experienced behavioral symptom, apathy was experienced at the highest frequency across all AOO. Finally, earlier AOO is also associated with higher severity of behavioral symptoms overall.

The findings from this study highlight a possible distinction in the clinical manifestations of individuals with different ages of onset of HD. Clinicians and caregivers of individuals at risk for HD should be aware of the increased likelihood for behavioral symptoms to be an early manifestation of HD in individuals at risk. Recognizing these symptoms is the first step towards providing these individuals with personalized treatment and interventions and enrolling them in clinical trials and therapies. Early intervention can help to prevent consequences resulting from untreated behavioral symptoms that can pose a potential danger to the affected individuals and the people around them. The findings from this study may also influence genetic counseling and risk assessment. Understanding the relationship between age-of-onset and clinical symptoms of HD can influence how risk assessments for people at risk for HD are made by genetic counselors

and other healthcare providers. Genetic counselors should also be aware of the how these findings may affect the genetic counseling process.

It is important to recognize the many limitations in this study. Therefore, future research should focus on analyzing the relationship between AOO and different symptoms of HD at disease presentation while accounting for more confounding factors, by utilizing a tool similar to the PBA-s that better assesses symptoms at disease presentation, and by assessing prospective clinical data. Further characterization of the HD phenotype associated with AOO may ultimately change how the clinical diagnosis of HD is made and may affect when and how interventions and neuroprotective therapies that aim to slow the progression of the disease are initiated. It is also important to recognize that behavioral symptoms and mental health related issues can be a common finding in the general population. Therefore, not all behavioral symptoms experienced by individuals with HD are attributable to the disease alone. Overall, this study adds substantial data to the HD literature and greatly increases scientific understanding of the relationship between AOO and behavioral symptoms in HD, allowing for more awareness and better care for individuals with HD and providing an impetus for future research in this area.

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