Survival, Mortality, Causes and Places of Death in a European Huntington's Disease Prospective Cohort

Filipe Brogueira Rodrigues, MD,[1,2] (iD) Daisy Abreu, MSc,[1,2] Joana Damásio, MD,[3] Nilza Goncalves, MSc,[1,2] Leonor Correia-Guedes, MD,[1,2,4] Miguel Coelho, MD, PhD,[1,2,4] Joaquim J. Ferreira, MD, PhD,[1,2,5,*] REGISTRY Investigators of the European Huntington's Disease Network

Abstract: **Background:** Huntington's disease (HD) is a rare and fatal inherited genetic disorder characterized by progressive motor, cognitive, and behavioral impairment. It leads to premature death, but data regarding advanced-stage disease are scarce. We sought to determine HD-associated survival, mortality, and causes and places of death.

Methods: Data from the European HD Network prospective study (REGISTRY) collected from 2001 through 2013 were used, including the Unified Huntington's Disease Rating Scale and death report forms. Group comparisons were performed using the *t* test or the χ^2 test. Survival analyses were computed through Kaplan-Meier estimates of median survival. All tests were 2-sided with a significance level of $P = 0.05$.

Results: In total, 5164 participants were analyzed. The mean age at diagnosis was 49 years, and the mean age at death was 58 years. At the end of the study period, there were 533 deaths (10.3% of patients). Median survival was 24 years from diagnosis and 35 years from symptom onset. The most frequent causes of death were pneumonia (19.5%), other infections (6.9%), and suicide (6.6%). The most frequent places of death were the hospital (29.8%), the home (23.9%), and nursing houses (19.8%).

Conclusions: Patients with HD tend to die from the same conditions as patients with other neurodegenerative diseases. However, compared with nonhereditary Parkinson's disease and Alzheimer's disease, the median time from onset to death is longer, and the places of death are distinctive.

Huntington's disease (HD) is a rare and fatal inherited genetic disorder caused by a CAG repeat expansion at the IT15 gene on chromosome 4.[1,2] It is characterized by progressive motor, cognitive, and behavioral impairment, invariably leading to premature disability, with no disease-modifying treatments currently available.[3] Despite this, the advanced stage of this condition has not been extensively studied, and knowledge about this phase of the disease would be essential to plan care and supportive services for individuals with HD and their families[4] and to define patient outcomes in clinical studies.

Prognostication,[5] advance-directive decision making, anticipating end-stage care needs[6] and life-prolonging procedures, and comfort-maximizing and quality-of-life–maximizing approaches are all essential matters for patients with HD and their carers. Because the current literature on this topic is limited and dated, we sought to determine the survival, mortality,

[1]Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal; [2]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; [3]Neurology Department, Hospital de Santo António-Centro Hospitalar do Porto, Porto, Portugal; [4]Department of Neurosciences, Neurology, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal; [5]Campus Neurológico Senior, Torres Vedras, Portugal

Correspondence to: Dr. Joaquim J. Ferreira, Laboratorio de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal; jferreira@medicina.ulisboa.pt

and causes and places of death of in patients with HD from the European Huntington's Disease Network's (EHDN) prospective cohort (the REGISTRY study[7]) and to help contribute to the improvement of care and clinical management and lessen the burden of the disease and improve the quality of life of patients and their families at this late stage in the disease.[8]

Materials and Methods

Ethical Approval

This study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committees for each study site contributing to the REGISTRY study. All participants gave informed written consent. Participants who lacked the capacity to consent and minors had consent given on their behalf as requested by country-specific ethical standards.

Participants

All participants were part of the EHDN multicenter, European, prospective observational study–REGISTRY.[7] Participants were recruited from 20 countries, although only 17 countries contributed data to our database (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, and the United Kingdom). Although REGISTRY recruited healthy controls, individuals at risk of HD, those with premanifest HD, and those with manifest HD, only the latter were included in our study. Participants were recruited from local HD clinics, and data collection followed a standard protocol, including the Unified Huntington's Disease Rating Scale (UHDRS),[9] using electronic-based report forms. After consent, participants were evaluated according to baseline and annual follow-up visits until study termination or death. EHDN monitors checked data regularly for completeness and plausibility. For the purpose of this analysis, patients with manifest HD were defined as those with a CAG-expanded allele of the HD gene and with a diagnostic confidence level (DCL) of 4.[10] In addition, although included participants had been recruited at the beginning of the study, mortality data were truncated from 2001 through 2013.

Clinical Information

Age at the onset of motor, cognitive, and behavioral symptoms; sex; and ethnicity from all manifest REGISTRY participants were extracted from study forms. For individuals who died, data were also extracted from the REGISTRY death report form, including age, place, and cause of death. These forms were completed by trained raters, and data were often gathered from patients' families. Although it was optional to include autopsy information, most participants who died did not undergo this procedure.

Statistical Analysis

Statistical analysis was performed with SPSS software, version 18 (SPSS, Inc., Chicago, IL) and R software (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics are presented as mean (±standard deviation [SD], minimum–maximum) for continuous variables and proportions for categorical variables. Group comparisons were performed using the t test or the χ^2 test, respectively. Survival analyses were computed through Kaplan-Meier estimates of median survival and 95% confidence intervals (CIs). Sex, the number of CAG repeats, age of onset, first manifestation, and country were planned to be tested as covariates. Unfortunately, this was not possible due to lack of statistical power. All tests were 2-sided with a significance level of $P = 0.05$.

Results

Participants

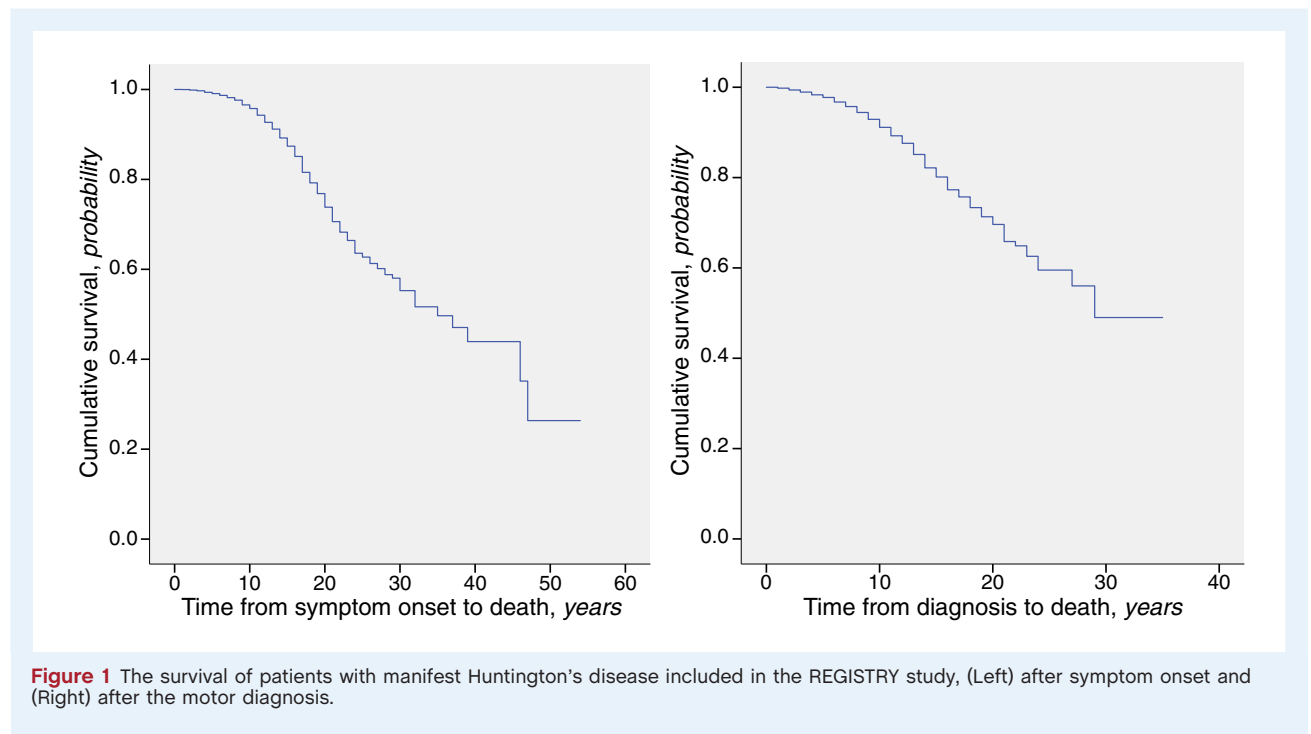In total, 5164 participants with manifest HD were analyzed (men, 49.0%, Caucasians, 98.0%; mean ± SD age at diagnosis, 47 ± 12 years [range, 5–86 years]). For detailed descriptions of the REGISTRY protocol and participants, please refer to publications by the EHDN[7] and Orth et al.,[11] respectively. At the end of the study period, from 2001 to 2013, there were 533 deaths (10.3% of patients). When considering only those who had died (men, 57.4%; Caucasians, 98.0%), the mean ± SD age at diagnosis was 49 ± 14 years (range, 9–85 years), and the mean ± SD age at death was 58 ± 13 years (range, 16–93 years). Differences between sex ($P < 0.001$) and the mean age at diagnosis ($P = 0.03$) were observed between those who had died and those who remained alive at the end of the study period. Most patients were from the United Kingdom (23.3%), followed by Germany (17%), Spain (16.3%), Italy (9.4%), and France (8.7%).

Survival

Median survival was defined as the time after which only 50% of the participants were still alive. The median survival from symptom onset to death was 35 years (95% CI, 29.2–40.8 years) (Fig. 1, left). Survival estimates for sex or other covariables could not be computed due to lack of statistical power. The median survival from motor diagnosis to death was 24 years (95% CI, 20.8–27.2 years) (Fig. 1, right). Again, survival estimates for sex or other covariables could not be computed.

Causes of Death

The most frequent cause of death was pneumonia (19.5%), followed by other infections (6.9%), suicide (6.6%), cancer (3.4%), stroke (2.6%), and trauma (0.9%). Other causes were identified in 36.4% of participants, and the cause of death was undetermined in 23.6% of deaths (Table 1). No significant difference

Figure 1 The survival of patients with manifest Huntington's disease included in the REGISTRY study, (Left) after symptom onset and (Right) after the motor diagnosis.

TABLE 1 Causes and places of death among patients with manifest Huntington's disease included in the REGISTRY study

Variable	No. of patients (%)	Age at death: Mean ± SD, y	Sex, % women	Disease duration: Mean ± SD, y	Symptom duration: Mean ± SD, y
Causes of death					
Pneumonia	104 (19.5)	57.27 ± 1.46	34.6	10.33 ± 0.52	15.96 ± 0.71
Other infection	37 (6.9)	54.32 ± 2.53	51.4	9.11 ± 0.88	14.24 ± 0.96
Suicide	35 (6.6)	49.05 ± 1.76	28.6	5.12 ± 0.76	8.68 ± 0.93
Cancer	18 (3.4)	65.06 ± 2.13	27.8	7.53 ± 1.14	14.18 ± 1.44
Stroke	14 (2.6)	62.73 ± 3.55	35.7	7.50 ± 1.32	14.29 ± 1.72
Trauma	5 (0.9)	54.00 ± 5.39	20.0	5.00 ± 1.84	10.20 ± 3.15
Other	194 (36.4)	58.60 ± 0.93	43.8	9.02 ± 0.33	13.11 ± 0.44
Unknown	126 (23.6)	57.83 ± 1.16	52.4	9.48 ± 0.39	13.42 ± 0.50
Places of death					
Hospital	152 (29.8)	57.83 ± 1.19	32.2	8.48 ± 0.37	13.08 ± 0.52
Home	122 (23.9)	56.32 ± 1.21	49.2	8.23 ± 0.48	12.72 ± 0.58
Nursing home	101 (19.8)	59.70 ± 1.52	47.5	11.01 ± 0.63	15.95 ± 0.86
Hospice care	17 (3.3)	50.88 ± 3.97	35.3	9.13 ± 1.18	13.06 ± 1.38
Unknown	118 (23.1)	57.42 ± 1.84	44.9	8.08 ± 0.66	13.75 ± 0.91

SD, standard deviation.

was observed in the distribution of causes of death between countries ($P = 0.372$) (Table S1).

Places of Death

The most frequent place of death was the hospital (29.8%), followed by home (23.9%), nursing houses (19.8%), and hospice care facilities (3.3%). The place of death was undetermined in 23.1% of deaths (Table 1). No significant difference was observed in the distribution of places of death between countries ($P = 0.419$) (Table S2).

Discussion

To the best of our knowledge, this is the first report of survival, mortality, causes and places of death in patients with manifest HD from an international, multicenter prospective study. In Europe, individuals with HD die a median of 35 years after symptoms onset, and 24 years after formal diagnosis, at a mean age of 58 years (see Fig. 1). In addition, death occurs most frequently from pneumonia and other infections, and the most frequent places of death are the hospital and home (see Table 1).

Apart from the biological characteristics of HD, such as the low kinetics of brain degeneration,[12] other independent factors could contribute to our results and justify their variability. Ideally, individual characteristics, such as the number of CAG repeats, age of onset, sex, and severity of motor, cognitive, and behavioral phenotype, should have been included in our analysis. Unfortunately, we did not have enough statistical power to study these characteristics, but we expect this to be possible with Enroll-HD,[13] a prospective, observational, multinational platform that will include North American, Australian, Latin American, Asian, and European centers.

When considering REGISTRY, as far as age of onset and survival are concerned, our results indicate that HD has a distinctive natural history among neurodegeneration: in contrast to patients with nonmonogenetic Alzheimer's disease and Parkinson's disease, patients with HD tend to be diagnosed sooner in life–between the fourth and fifth decades of life–and to live longer after motor diagnosis[14–17] and after symptoms onset, although reports on other conditions indicate a large variation possibly explained by age of onset. A similar analogy may be applicable to other forms of dementia, such as vascular dementia and mixed dementia.[14,15] These results were unexpectedly higher than the median survival times previously reported.[18–20] We believe this difference could be explained at least in part by a hypothetical better standard of care of patients who are followed at centers belonging to the EHDN. Some evidence suggests that collaboration with clinical and research networks may positively influence outcomes.[21] For the same reason, a drawback from our results is that they may not be extrapolated to patients who are followed outside these networks.

It is noteworthy that the mean ages of diagnosis (49 years) and death (58 years) were calculated assuming a normal distribution and that the median survival times (35 and 24 years after symptom onset and the formal diagnosis, respectively) were calculated using a nonparametric distribution. As such, these results cannot be directly compared.

The patients in this study died most frequently from the same conditions described in previous studies of HD[22–24] and other neurodegenerative diseases, such as Alzheimer's disease, vascular dementia,[14,25] and Parkinson's disease.[26] Those studies demonstrated that pneumonia leads to death 4.7 times more often in patients who have HD compared with the general population,[27] representing the primary cause of death.[22–24,28,29] According to the same studies, other frequent causes of death were other infectious processes,[22,23] suicide,[22,29,30] cardiovascular diseases,[22–24,28,29] and nutritional unbalances, such as cachexia.[22,23,29] Strikingly, these 4 conditions seemed to be as prevalent in patients with HD as they were in the general population.[27]

Two seminal studies from the 1980s based on death certificates in the United States reported on 2 major discrepancies compared with our results. Haines et al. described a higher frequency of cardiovascular diseases and of HD as a cause of death,[24] and Lanska and colleagues supported the former results on cardiovascular diseases.[22,27] There are reasons to believe that the overall improvement in cardiovascular primary and

secondary prevention strategies may justify these differences. We are also convinced that the diagnosis of HD as a cause of death is an issue of the past, which vanished with the introduction of more modern death certificate registries.

A great deal of research has been undertaken on suicide and associated behaviors in HD. Overall, in the general population, less than 1% of all deaths are caused by suicide[31]; however, in the REGISTRY data set, almost 7% of patients with HD committed suicide, a figure significantly higher than that in previous reports.[22,23] A previous analysis of this database reported that a high proportion (9.9%) of gene carriers present suicidal ideation[32]; whereas, in other data sets, the rate was even higher after isolating patients who had manifest HD, affecting one-fifth of the population with early HD.[33,34] As in the general population[35] and in patients with other neurodegenerative diseases like Parkinson's disease,[36] the frequency of completed suicide in patients with manifest HD may be less than one-half of the frequency of suicidal ideation, which is in line with these results.

Surprisingly, the place of death differed greatly from that of other patients with dementia (i.e., nursing homes)[37,38] and was comparable to the place of death of cancer patients (at hospital and at home).[37,38] We believe this may reflect the burden of the disease and the lack of competence and training in nursing homes to deal with the serious behavioral problems associated with HD. The possible willingness of HD families to care for their relatives also cannot be excluded. On the other hand, the high percentage of hospital deaths should ease tissue contributions to biobanks—a much-needed offer for advancing research into better understanding the disease.

Several aspects make REGISTRY an ideal database for answering our current questions. Because HD is a rare disease, its phenotype must be studied in large, multicenter, and multinational studies to achieve robust results. The 9221 participants, the 165 study sites, and the 20 countries signed up (although not all contributed data to our results) to the REGISTRY study qualify this data set as methodologically satisfactory. The annual follow-up and the HD-specific scales applied to patients enrolled in REGISTRY may help mitigate 2 of the major problems identified when studying advanced-stage HD: the irregular patient follow-up and the difficulty in quantifying disease status.[39] In addition, the REGISTRY protocol assures that generated data are of high quality by means of frequent monitoring carried out both locally at each site and centrally by trained monitors.[11]

Unfortunately, even after taking into account its advantages, our analysis included large numbers of patients without a specified cause or place of death. This potentially may lead to an under-representation of specific causes or places of death. This is likely to have happened, because the follow-up of patients with advanced-stage HD rarely takes place in hospitals, where EHDN sites are usually located, but occur in smaller and more personalized, continuous, and palliative care units, making it difficult to ascertain socially complex details about this period of life in patients with HD. Also, it was outside our power and ethical permits to gather this information from

families of patients who had died. Nevertheless, local EHDN sites should increase their compliance with this practice in the future. In addition, very few causes of death were confirmed by autopsy, which may further decrease the strength of our conclusions in this regard. Some of these issues would be solved at least in part by the introduction of a codification system for causes of death and with the use of electronic death certificates, a tool currently available in some countries. Importantly, generating uniform results is complex when using multinational studies.

In conclusion, our inferences give robustness to the results derived from previous smaller studies, establishing the overall survival of 24 years after motor diagnosis and 35 years after symptom onset, the most frequent cause of death (pneumonia), and the most important places of death (the hospital and the patient's home).

Finally, it would interesting to attempt to validate our findings with data from the COHORT study,[40] which included American and Australian patients, and with the Enroll-HD data set,[13] in which, because of the expected increased statistical power, more analyses should be feasible.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

F.B.R.: 1A, 1B, 2C, 3A
D.A.: 2A, 2B, 3B
J.D.: 3B
N.G.: 2A, 2B, 3B
L.C.G.: 2C, 3B
M.C.: 2C, 3B
J.J.F.: 1A, 2C, 3B

Acknowledgments

Disclosures

References

1. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306:234–238.

2. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971–983.

3. Mestre T, Ferreira J, Coelho MM, Rosa M, Sampaio C. Therapeutic interventions for disease progression in Huntington's disease. *Cochrane Database Syst Rev* 2009;3:CD006455.

4. Travers E, Jones K, Nichol J. Palliative care provision in Huntington's disease. *Int J Palliat Nurs* 2007;13:125–130.

5. Dawson S, Kristjanson LJ, Toye CM, Flett P. Living with Huntington's disease: need for supportive care. *Nurs Health Sci* 2004;6:123–130.

6. Klager J, Duckett A, Sandler S, Moskowitz C. Huntington's disease: a caring approach to the end of life. *Care Manag J* 2008;9:75–81.

7. European Huntington's Disease Network (EHDN). REGISTRY—an observational study of the European Huntington's Disease Network (EHDN). Available at: https://ClinicalTrials.gov/show/NCT01590589. Accessed on the 20 March 2017.

8. Kristjanson LJ, Aoun SM, Oldham L. Palliative care and support for people with neurodegenerative conditions and their carers. *Int J Palliat Nurs* 2006;12:368–377.

9. Huntington's Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency Huntington Study Group. *Mov Disord* 1996;11:136–142.

10. Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. *Mov Disord* 2014;29:1335–1341.

11. Orth M, Handley OJ, Schwenke C, et al. Observing Huntington's Disease: the European Huntington's Disease Network's REGISTRY. *PLoS Curr* 2010;2:RRN1184.

12. Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013;12:637–649.

13. CHDI Foundation Inc. Enroll-HD: A Prospective Registry Study in a Global Huntington's Disease Cohort. Available at: https://ClinicalTrials.gov/show/NCT01574053. Accessed on the 20 March 2017.

14. Molsa PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* 1986;74:103–107.

15. Barclay LL, Zemcov A, Blass JP, Sansone J. Survival in Alzheimer's disease and vascular dementias. *Neurology* 1985;35:834–840.

16. Willis AW, Schootman M, Evanoff BA, Perlmutter JS, Racette BA. Neurologist care in Parkinson disease: a utilization, outcomes, and survival study. *Neurology* 2011;77:851–857.

17. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease?. A prospective population-based long-term study *Neurology* 2010;75:1270–1276.

18. Roos RA, Hermans J. Vegter-van der Vlis M, van Ommen GJ, Bruyn GW. Duration of illness in Huntington's disease is not related to age at onset. *J Neurol Neurosurg Psychiatry* 1993;56:98–100.

19. Rinaldi C, Salvatore E, Giordano I, et al. Predictors of survival in a Huntington's disease population from southern Italy. *Can J Neurol Sci* 2012;39:48–51.

20. Foroud T, Gray J, Ivashina J, Conneally PM. Differences in duration of Huntington's disease based on age at onset. *J Neurol Neurosurg Psychiatry* 1999;66:52–56.

21. Tolson D, McIntosh J, Loftus L, Cormie P. Developing a managed clinical network in palliative care: a realistic evaluation. *Int J Nurs Stud* 2007;44:183–195.

22. Lanska DJ, Lavine L, Lanska MJ, Schoenberg BS. Huntington's disease mortality in the United States. *Neurology* 1988;38:769–772.

23. Heemskerk AW, Roos RA. Aspiration pneumonia and death in Huntington's disease. *PLoS Curr* 2012;4:RRN1293.

24. Haines JL, Conneally PM. Causes of death in Huntington disease as reported on death certificates. *Genet Epidemiol* 1986;3:417–423.

25. Beard CM, Kokmen E, Sigler C, Smith GE, Petterson T, O'Brien PC. Cause of death in Alzheimer's disease. *Ann Epidemiol* 1996;6:195–200.

26. Beyer MK, Herlofson K, Arsland D, Larsen JP. Causes of death in a community-based study of Parkinson's disease. *Acta Neurol Scand* 2001;103:7–11.

27. Lanska DJ, Lanska MJ, Lavine L, Schoenberg BS. Conditions associated with Huntington's disease at death. A case-control study. *Arch Neurol* 1988;45:878–880.

28. Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. *Am J Med Genet* 1986;24:305–311.

29. Sorensen SA, Fenger K, Olsen JH. Significantly lower incidence of cancer among patients with Huntington disease: an apoptotic effect of an expanded polyglutamine tract? *Cancer* 1999;86:1342–1346.

30. Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Suicide risk in Huntington's disease. *J Med Genet* 1993;30:293–295.

31. Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet* 2016;387:1227–1239.

32. Hubers AA, van Duijn E, Roos RA, et al. Suicidal ideation in a European Huntington's disease population. *J Affect Disord* 2013;151:248–258.

33. Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. *Am J Psychiatry* 2005;162:725–731.

34. Wetzel HH, Gehl CR, Dellefave-Castillo L, Schiffman JF, Shannon KM. Paulsen JS; Huntington Study Group. Suicidal ideation in Huntington disease: the role of comorbidity. *Psychiatry Res* 2011;188:372–376.

35. Borges G, Nock MK, Haro Abad JM, et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J Clin Psychiatry* 2010;71:1617–1628.

36. Kummer A, Cardoso F, Teixeira AL. Suicidal ideation in Parkinson's disease. *CNS Spectr* 2009;14:431–436.

37. Mitchell SL, Teno JM, Miller SC, Mor V. A national study of the location of death for older persons with dementia. *J Am Geriatr Soc* 2005;53:299–305.

38. Houttekier D, Cohen J, Bilsen J, Addington-Hall J, Onwuteaka-Philipsen BD, Deliens L. Place of death of older persons with dementia. A study in five European countries. *J Am Geriatr Soc* 2010;58:751–756.

39. Harezlak J, Gao S, Hui SL. An illness-death stochastic model in the analysis of longitudinal dementia data. *Stat Med* 2003;22:1465–1475.

40. Huntington Study Group COHORT Investigators;Dorsey E. Characterization of a large group of individuals with Huntington disease and their relatives enrolled in the COHORT study. *PLoS ONE* 2012;7: e29522.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1: Investigators of the European Huntington's Disease Network

Table S1. Causes of death per country

Table S2. Places of death per country