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Economic Burden of Huntington's Disease in Europe and the USA: Results from the Huntington's Disease Burden of Illness Study (HDBOI)

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Running title: Economic Burden of Huntington's Disease (35/40 characters)

ABSTRACT

Background: The prevalence of Huntington's Disease (HD) has increased over time, however there is a lack of up-to-date evidence documenting the economic burden of HD by disease stage. This study provides an estimate of the annual direct medical, non-medical and indirect costs associated with HD from participants of the Huntington's Disease Burden of Illness Study (HDBOI) in five European countries and the USA.

Methods: The HDBOI is a retrospective, cross-sectional study. Data collection was conducted between September 2020 and May 2021. Participants were recruited by their HD-treating physicians and categorized as early (ES), mid (MS) or advanced stage (AS) HD. Data was collected via three questionnaires: a Case Report Form, completed by physicians that collected

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healthcare resource use associated with HD to compute direct medical cost, and optional patient and caregiver questionnaires which included information used to compute on non-direct medical and indirect costs. Country-specific unit cost sources were used.

Results: HDBOI cost estimates were: €12,663 (N= 2,094) for direct medical costs, €2,984 (N= 359) for non-direct medical and €47,576 (N= 436) for indirect cost. Costs are higher in patients who are at later stages of disease e.g., direct medical costs estimates were €9,220 (N=846), €11,885 (N= 701) and €18,985 (N=547) for ES, MS, and AS, respectively. Similar trends were observed for non-direct and indirect costs. Costs show large variations between patients and countries

Conclusion: Cost estimates from the HDBOI study show that people with HD and their caregivers bear a large economic burden, that increases as disease progresses.

KEY WORDS: Huntington's Disease, Economic burden, Cost of illness; Europe; United States

INTRODUCTION

Huntington's Disease (HD) is a rare inherited neurodegenerative disease that has a comprehensive negative impact on physical and mental well-being,[1] leading to long-term disability and ultimately death.[2] The prevalence of HD has increased over recent decades,[3] with estimates in Europe and North America ranging from 8.2 - 9 per 100,000 people[4]. HD is characterized by progressive motor and cognitive deficits,[5] and people with HD (PwHD) have an estimated life expectancy of 15–20 years following diagnosis of motor symptoms.[6] Early signs and symptoms of HD include personality changes, cognitive decline, mood swings, chorea and irritability.[7] Progressive decline in involuntary movements, voluntary motor control, cognitive behavior and functioning invariably require PwHD to be dependent on caregivers for assistance with regular daily care.[2] HD is a progressive disease that is often divided into stages (early, middle and late) based on the severity of patient's symptoms and loss of functionality.[8]

To date, no treatments have been effective in stopping or impeding the progression of HD. Medical management strategies attempt to reduce symptoms and maximize functionality.[9] In the absence of effective disease-modifying therapy, the burden of HD on patients' and their families remains high, increasing as the disease progresses. With disease progression, there is an associated patient and societal economic burden with increasing needs for outpatient services, medications, hospital visits, personal care assistants, caregiver support and social support programs.[7 10]

Despite this burden,there is little recent quantitative evidence of the economic burden of HD by disease stage. In the UK, the mean annual cost of HD across all disease stages was reported to be £21,605 in 2013, derived from primary and hospital care services, diagnostics, medications, informal care, and adaptive aids.[7] In the US, the mean total annualized cost per person with early-to late-stage HD ranged from $6,113 to $27,904 among commercially-insured (i.e., care provided by non-governmental (for-profit) agencies) PwHD.[10] These were direct medical costs only, based on inpatient, outpatient and emergency department visits, radiology, pharmacy, long-term care, and ancillary services.[10] In 2017, the annual all-cause healthcare costs in the US were estimated to be $41,631 for inpatient, outpatient, and pharmacy costs only.[11] These estimates are relatively dated and employed different approaches to deriving total costs from different cost categories, and are not comparable between countries. In the absence of recent and internationally comparable cost estimates, the Huntington's Disease Burden of Illness Study (HDBOI) study aimed to provide an up-to-date estimate the annual direct medical costs, direct

non-medical costs, and indirect costs of HD overall and by disease stage using comprehensive data for five European countries and the United States.

METHODS

The HDBOI Study

The HDBOI Study is a non-interventional, retrospective, cross-sectional, international burden of illness study of people with diagnosed HD in France, Germany, Italy, Spain, the United Kingdom, and the United States. An Expert Reference Group of clinicians (neurologists, psychiatrists, allied health professionals), patient advocates, and health economists constituted the steering committee. The HDBOI Study collected information related to the clinical, humanistic, and economic burden of HD on participants and caregivers; this analysis focused on economic outcomes including direct medical costs, direct non-medical costs, and indirect costs. HDBOI data was collected between September 2020 and May 2021. Ethical approval was granted to the HDBOI study by the Research Ethics Subcommittee at the University of Chester (RESC0420-1038). Electronic informed consent was obtained from all participants (or proxies for participants) in the study.

The HDBOI study is of descriptive nature and target sample size was informed by assessing similar burden of illness studies for rare diseases and based on the information provided by the fieldwork partners about distribution of HD patients and physicians across the studied countries. HD-treating physicians were invited via a fieldwork agency to recruit eligible PwHD during routine clinical consultations. Participating physicians could be neurologists, psychiatrists, general practitioners, internists, geriatricians or geneticists, who reported to be the primary provider of clinical care for PwHD and had access into the patient's medical records.

Eligible PwHD were adults (≥ 18 years) clinically diagnosed with manifest HD ≥ 12 months prior to the date of clinical consultation that was used for study recruitment (defined as the index date). PwHD who participated in a clinical trial for an HD treatment in the 12 months prior to the index date were not eligible.

PwHD were categorized as early (ES), mid (MS) or advanced (AS), as per Wild and Tabrizi 2014[8], manifest HD disease stage at the consultation date (index date) based on the opinion of the treating physician.

Study outcomes and data collection

HDBOI study data was collected via three questionnaires. 1) Case Record Form (eCRF): Physicians retrospectively extracted sociodemographic and clinical information related to HD diagnosis, disease history and symptomatology, health resource use associated with HD from the patients' medical records. 2) Patient Public Involvement Engagement-Patient (PPIE-P) Questionnaire: PwHD completed a questionnaire providing sociodemographic, health resource use, non-medical resource use associated with HD, as well as work productivity impairment associated with HD. For those PwHD with severe cognitive deficit the main caregiver completed the PPIE-P on behalf of the PwHD (proxy-respondents). 3) Caregiver questionnaire (PPIE-C): Caregivers completed a questionnaire providing information related to their own work productivity impairment associated with caregiving duties as well as information on informal care (total number of care-hours provided by all caregivers (including main caregiver)). All questionnaires were administered via an online platform. Whilst the eCRF is available for all the participants, the completion of the patient (PPIE-P) and caregiver (PPIE-C) questionnaires was optional and are available for a subsample of participants only.

This work evaluated different sources of costs, including annual direct medical costs, direct non-medical costs, and indirect costs associated with HD were analyzed (Appendix Table A1). Direct medical costs included those related to hospitalizations, medications, consultation visits, tests and examinations, over-the-counter and self-medication (OTC), physical aids and equipment, residential care, and professional caregiving services. Direct medical costs were calculated based on country-specific unit costs collated from public tariff information and general public data sources (-Supplementary materials Table S1). Direct non-medical costs included travel costs, transfer payments (state support), and alternative therapies.

Indirect costs assessed the impact of HD on patient and caregiver work productivity based on hours worked per week, absenteeism, informal care costs and early retirement. For actively employed PwHD and caregivers, productivity loss was quantified as the number of days missed from work due to HD in the past three months multiplied by the country average salary per day. This was multiplied by four to extrapolate 12-month work productivity impairment. For those unable to work due to HD, an opportunity cost was assigned based on one year of average salary per country. Indirect costs for informal care were calculated as the total number of hours per week of informal care multiplied by the number of weeks per year. Total hours per year was multiplied by the country average salary per hour. Specific variables contributing to each cost component are provided in Table A1.

A dataset of unit costs was created for each of resource use items captured in study questionnaires (see Appendix Table A1 and A2 for more information about cost components and sources). For other elements, e.g., transfer payments, information was provided by the PwHD/caregiver. All costs were computed for the 12-month period prior to the index date and analysed overall, by disease stage and country. Costs are reported in EUR 2020 for all outcomes; EUR estimates from previous years were inflated to 2020 using the Harmonised Indices of Consumer Prices (HICP; http://ec.europa.eu). In order to minimize underestimation of costs due to potentially reduced care interactions during the coronavirus disease 2019 (COVID-19) pandemic, healthcare resource use (used to compute direct medical costs) was extracted for a set time period before the pandemic (March 2019 through March 2020).

Statistical analysis

Descriptive statistics summarized demographic and clinical characteristics overall and by HD stage. Economic outcomes were analyzed descriptively, and by disease stage and country. Differences between economic outcomes by disease stage were explored and the statistical significance of these differences were assessed by analysis of variance (ANOVA) tests. No imputation of missing data was performed. All data were analyzed using STATA® 16 (StataCorp LLC, College Station, Texas; www.stata.com) and R (www.r-project.com).

RESULTS

HDBOI Study participants

A total of 2,094 PwHD were enrolled in the HDBOI Study, 40% of whom (n=846) were classified as ES, 34% as MS (n=701), and 26% as AS (n=547; Table 1). Distribution of study participants and HD severity were generally balanced across participating countries, with the most PwHD from Italy and the US (24% each). All participants had completed the eCRF, participant characteristics are provided in Table 1. Mean age of the overall sample was 47.3 years (SD, 13.7), and slightly more than half were men (60%) with the proportion of male participants increasing with disease severity. A total of 482 PPIE-P questionnaires were completed (23% of PwHD enrolled in the study), 42 of which (9%) were completed by proxy-respondents (caregiver on behalf of the PwHD). Completion rates of the PPIE-P and PPIE-C questionnaires by HD stage and country are provided in Supplementary Materials Table S2.Table 1. Demographic and clinical characteristics of PwHD by stage (eCRF source data)

Participants, n (%)	**Total**	**Early (ES)**	**Middle (MS)**	**Advanced (AS)**
Total	2094 (100)	846 (40)	701 (34)	547 (26)
Country				
Italy	492 (24)	190 (22)	182 (26)	120 (22)
United States	492 (24)	213 (25)	154 (22)	125 (23)
Spain	354 (17)	152 (18)	107 (15)	95 (17)
United Kingdom	272 (13)	91 (11)	111 (16)	70 (13)
Germany	264 (13)	96 (11)	85 (12)	83 (15)
France	220 (11)	104 (12)	62 (9)	54 (10)
Sex, male	1253 (60)	492 (58)	397 (57)	365 (67)
Age, mean (SD), years	47.3 (13.7)	43.2 (12.9)	48.2 (13.6)	52.3 (13.3)
BMI, mean (SD), kg/m^2	23.9 (3.5)	23.7 (3.5)	24.1 (3.4)	23.8 (3.7)

BMI, body mass index; HD, Huntington's disease; SD, standard deviation.

Direct and indirect costs of HD

Information regarding HD related healthcare resource use used to compute direct medical costs was available for all 2,094 PwHD. Information on direct non-medical costs was available for 359 PwHD and indirect costs for 436 PwHD. Mean annual direct medical costs for all PwHD were €12,663 (SD, €34,012), direct non-medical costs were €2,984 (€3,627), and indirect costs were €47,576 (€47,985). All costs increased with increasing level of HD severity (Figure 1 and Table 2).

Inpatient hospitalizations and residential care were the primary drivers of direct medical costs, with mean annual costs of €35,803 and €41,879 among those with ES HD, respectively, €30,698, and €56,673 for MS HD, and €12,658 and €45,977 for AS HD (Appendix Table A2). Caregiver state support accounted for 58% to 75% of all direct non-medical costs. Indirect costs were driven by lost productivity for PwHD (34% to 42%) and costs of informal care requirements (40% to 42%; Appendix Table A2). Total costs (sum of direct medical, non-medical and indirect costs), available for a subsample of 307 PwHD (patients with a completed CRF and PPIE-P and PPIE-C), were driven primarily by indirect costs, which accounted for 84%, 80% and 66% of ES, MS and AS total costs, respectively (Appendix Table A2).

When costs were analyzed by country, mean annual direct medical costs of HD were highest in the US (€27,743; [$33,707 in 2020 US dollars]), followed by the UK and Germany (Figure 2A). Direct non-medical costs were highest in Italy (€3,977) and the UK, and indirect costs were highest in the US (€74,228; [$90,187]), UK, and Italy (Figure 2B & C respectively).

Figure 1. Mean annual costs of HD by stage

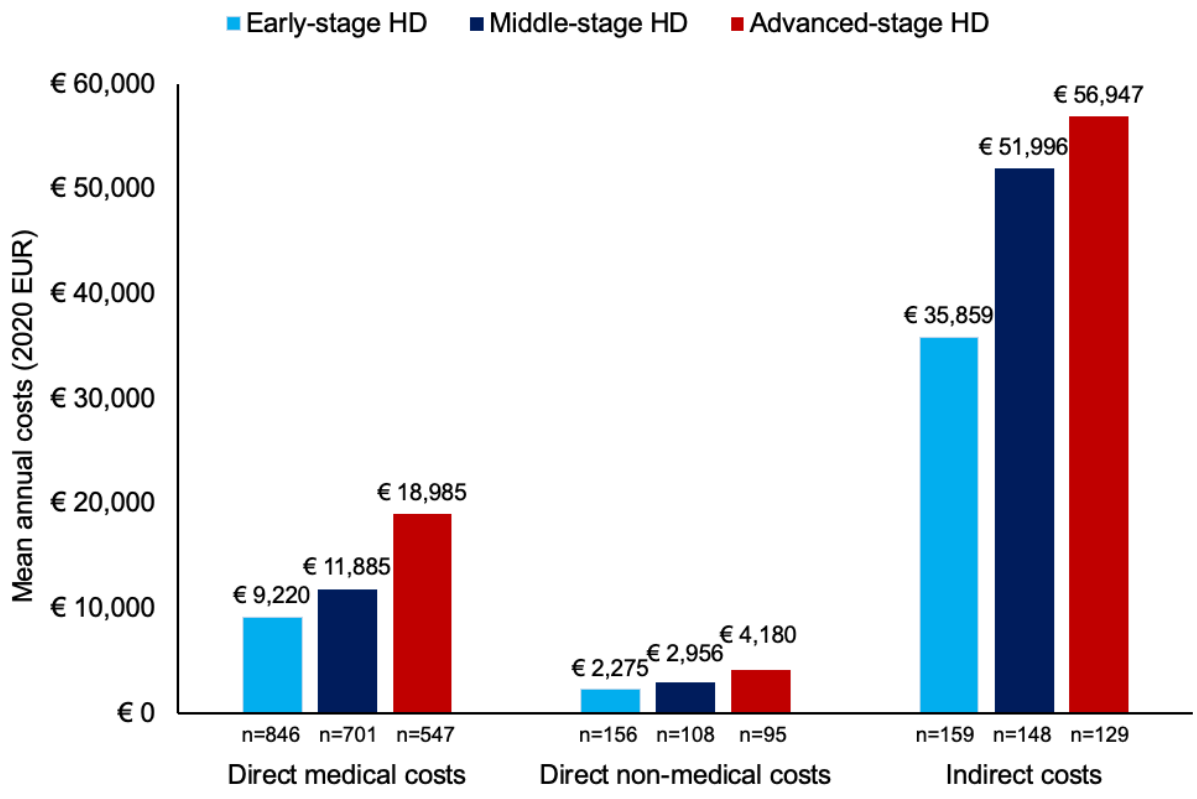


Table 2. Medical and Non-medical direct and indirect costs by severity

Mean (SD)	**Total**	**Early-stage HD**	**Middle-stage HD**	**Advanced-stage HD**
Direct medical costs*	€12,663 (€34,012)	€9,220 (€31,855)	€11,885 (€31,827)	€18,985 (€38,811)
Direct non-medical costs*	€2,984 (€3,627)	€2,275 (€3,530)	€2,956 (€3,632)	€4,180 (€3,500)
Indirect costs*	€47,576 (€47,985)	€35,859 (€44,874)	€51,996 (€45,549)	€56,947 (€51,723)
Total costs	€62,372 (€51,197) n=436	€42,477 (€45,651) n=159	€64,688 (€53,698) n=148	€86,177 (€44,966) n=129

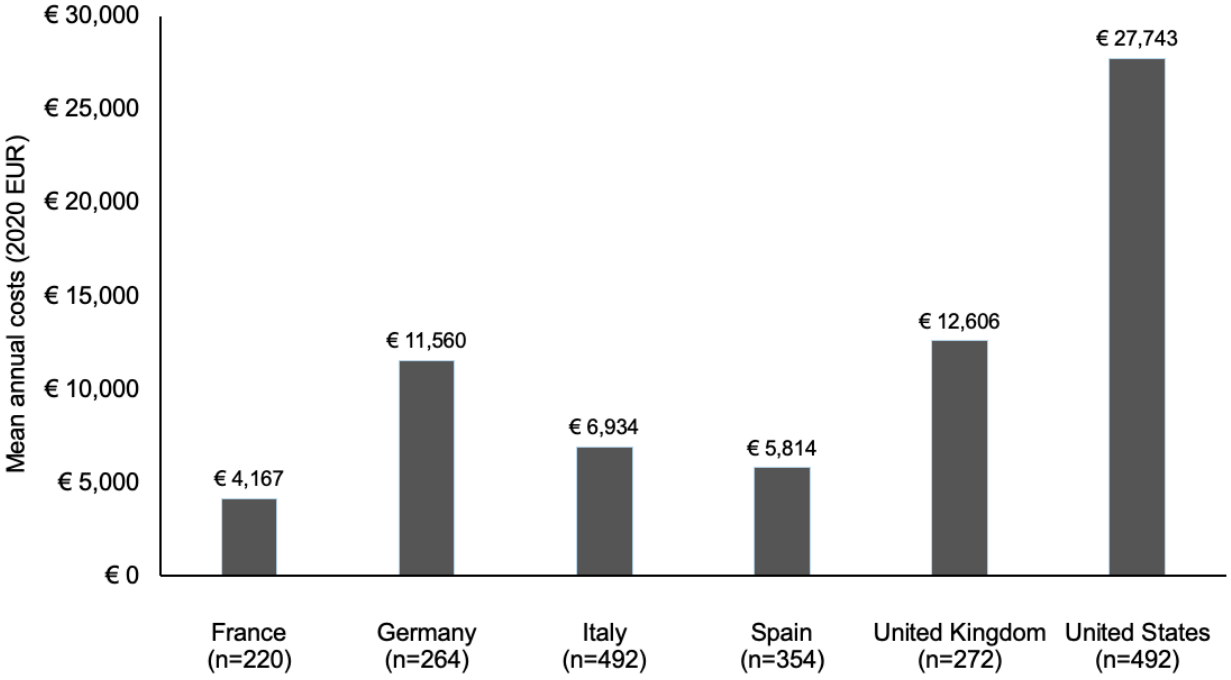
Total costs were comprised of medical and non-medical direct costs plus indirect costs. See Table A1 and A4 for detailed breakdown of cost categories.

HD, Huntington's Disease; SD, standard deviation.

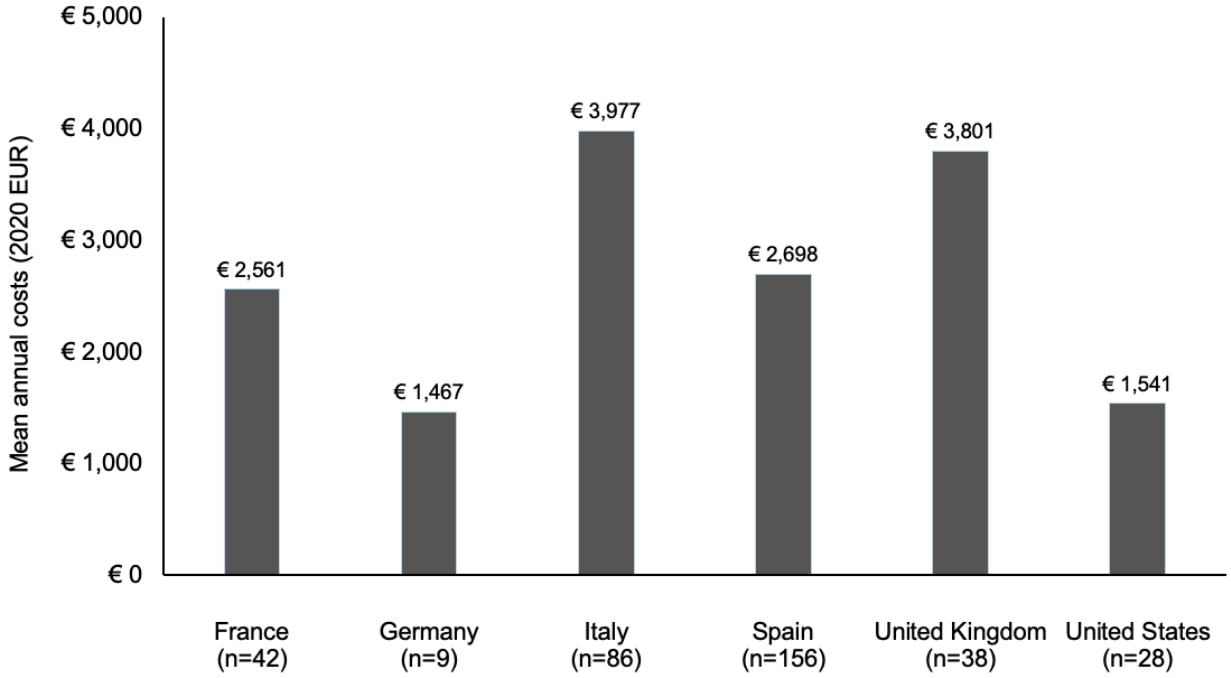
To assess the significance of differences between disease stages, one-way ANOVA tests were conducted for direct medical costs, direct non-medical costs, and indirect costs: * $p<0.001$

Figure 2. HD costs by country in the HDBOI Study (All costs presented in EUR 2020)

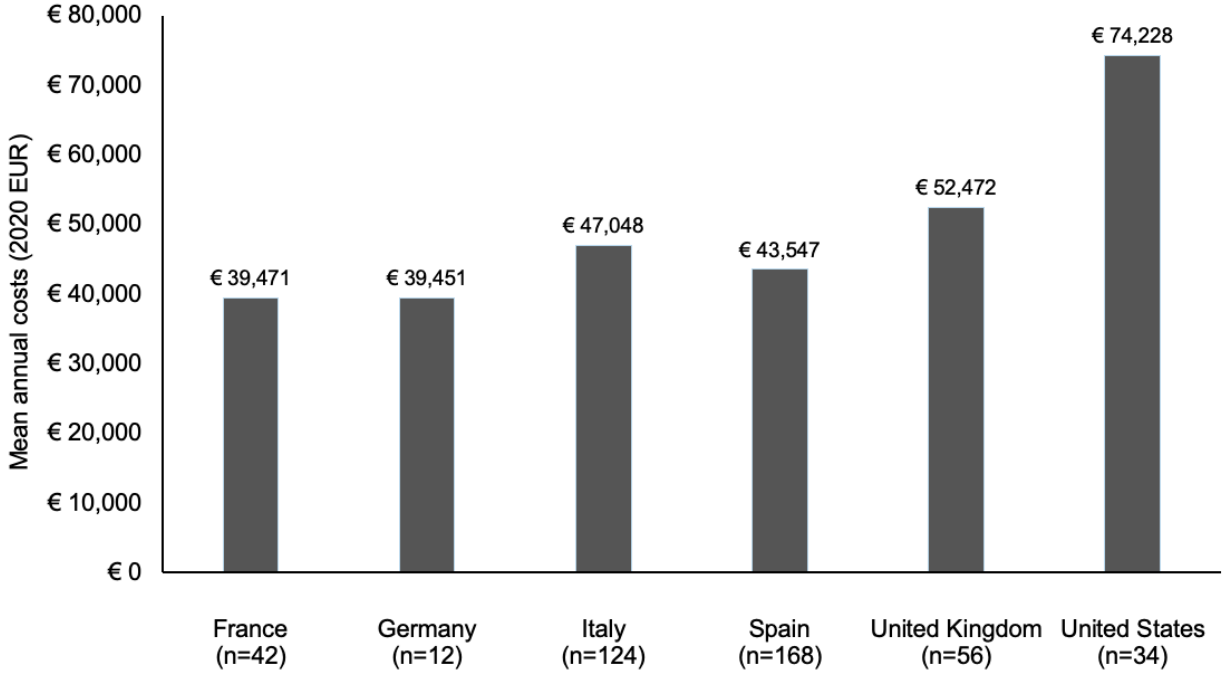
A) Direct medical costs



B) Direct non-medical costs



C) Indirect costs



DISCUSSION

The HDBOI study provides new insights into the patient characteristics and economic burden of PwHD across all stages of disease and from a multinational perspective. To our knowledge, the HDBOI is one of largest studies capturing a comprehensive estimate of the economic burden of HD. Results show that PwHD and caregivers bear a substantial economic burden that increases as disease progresses. Mean annual direct medical costs were high in this cohort and expectedly increased with the severity of HD, driven largely by hospitalizations and residential care costs. Direct non-medical costs accounted for the smallest proportion of costs overall, and were driven primarily by government support of caregivers, which also increased with the severity of disease. Indirect costs imposed the greatest economic burden to PwHD and caregivers, ranging from 66% to 84% of total costs across severities, driven primarily by PwHD lost work productivity and, in turn, costs of informal care needs. Costs varied across participating countries in the Europe and US, which may be expected based on differences in health system and social benefit structures, where direct medical costs and indirect costs were highest in the US, and direct non-medical costs were highest in Italy and the UK. This study provides updated information on the economic burden of progressive HD from a societal perspective, including the impact of HD on time missed from work and downstream care needs on both patients and their caregivers.

Our findings are generally consistent with previously reported HD cost estimates, though those estimates are not directly comparable to our estimates as they do not consider the same costs categories when computing total costs. Jones and colleagues (2016) reported mean annual costs of HD to be £21,605 in the UK (€30,160 in 2020 EUR also adjusted to HICP index) as derived from primary care visits, hospital care, diagnostics/testing, medications, informal care, and assistive devices.[7] Notably, patients with advanced HD (Stage V) were not included. The HDBOI study reported mean total costs in the UK of €75,992 in the overall population (n=36), and indirect costs alone of €52,472 (n=56). Indirect costs among those with advanced-stage HD were €60,534 (n=27) in the UK. The most recent study in the US was by Exuzides and colleagues (2021) who reported mean annual all-cause total healthcare costs of $41,631 (€40,328 in 2020 EUR) consisting of inpatient, outpatient, and pharmacy costs.[11] Divino and colleagues (2013) also reported estimates from the US that showed the mean total annualized cost per patient ranged from $3,257 to $37,495 (€3,473 - €39,974 in 2020 EUR). [10] The HDBOI Study reported direct medical costs of €27,743 in the US and a substantial indirect cost burden of €74,228 from lost work productivity). HDBOI estimates for total costs were substantially

higher than those previously reported for other neurodegenerative disease such us Parkinson's disease[12–14] or dementia.[15] In the absence of a robust body of literature on the economic burden of HD, this study provides important contributions to our understanding of the comprehensive burden of HD on patients, their caregivers, and society at large for several European countries and the US. These findings also support future applications for new technologies and medicines for HD to help improve patient access and quality of life. Additional studies are required to further disseminate quantitative information in this underserved research area, particularly for those with advanced HD.

Findings of this study should be interpreted in the context of certain strengths and limitations. Whilst the aim of the study was to minimize bias and to provide representative estimates of the burden of HD, due to the descriptive nature of the study, the sample of the HDBOI might not be fully representative of the HD population. Since recruitment was driven through the clinician office visits, advanced stage patients may have been underrepresented if they were admitted to long-term residential or nursing care homes. In addition, the assessment of participants' disease stage was based on the opinion of the treating physicians. As such, we cannot be certain that our disease stage classification fully corresponds with standardized measures. Cost estimates for advanced-stage PwHD may have been underestimated due to the small sample of patients with advanced disease and subsequent subgroup analyses. It should also be noted that available treatments and unit costs varied across countries. For Germany, direct medical costs may have been underestimated as only co-payments were publicly available, which do not reflect the true cost of the service delivered. Physician-reported outcomes related to the healthcare resource use behind medical costs may also have provided conservative estimates; due to the multidisciplinary nature of treating HD, some physicians may not have been aware of all medical encounters across providers and facilities. Healthcare resource use was extracted for a pre-COVID-19 time period. Capturing pre-pandemic healthcare resource use was expected to be representative of the true direct medical costs as HD progression is relatively slow, and changes in healthcare resource use and direct medical costs would be similarly slow. Items contributing to non-direct medical and indirect costs were collected for the 12 months prior to the index date, and might have been affected by the COVID-19 restrictions. Finally, there may have been a selection bias in participants' willingness to participate in the study, and potential recall bias for self- and proxy-respondents completing the PPIE-P and PPIE-C, though the recall periods were short (a maximum of 12 months).

Conclusions

This HDBOI study contributes to an underserved research area by providing an up-to-date picture of the economic burden of HD across disease stages. Results show that all three cost categories (direct medical, direct non-medical and indirect costs) increase as diseases progresses, with significant indirect costs associated to informal care and large productivity losses for both the PwHD and their caregivers. Moreover, the HDBOI study increases the evidence base for the international HD community by enabling stakeholders to make fully informed decisions and facilitate accurate economic evaluation of the burden of HD. Such work will be essential to understanding the potential economic benefits of disease-modifying treatment options and medical technology advances to support patient outcomes and quality of life. These findings clearly illustrate the substantial and increasing costs associated with HD, emphasizing the importance of early, effective interventions to slow or stop disease progression.

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Availability of data

The data that support the findings of this study may be available from HCD Economics, Ltd but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may be available from the authors upon reasonable request and with permission of HCD Economics Ltd.

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Disclosure of conflict of interest

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APPENDIX

Table A1. Variables contributing to component costs

Table A2. Breakdown of mean annual costs by stage

SUPPLENTARY MATERIALS (ONLINE ONLY)

Table S1. Costing data sources

Table S2. Completion of PPIE-P and PPIE-C questionnaires overall and by stage

Table A1. Variables contributing to component costs

Category	Data source	Variable
Direct Medical Costs		
Hospitalizations, surgical procedures	eCRF	Day case, outpatient; inpatient and length of stay
Medications	eCRF	For motor symptoms, psychotic/behavioural symptoms, others
Consultation visits	eCRF	Number of visits with HD physicians, nurse specialist, other physicians
Tests and examinations	eCRF	Blood, imaging, respiratory, genetic, reproductive treatment, physiotherapy, other
Self-medication (OTC)	PPIE-P	Over-the-counter (OTC) medications
Assistive equipment/aids	PPIE-P	Medical devices (e.g., crutches)
Residential care	eCRF	Type of residential care (e.g., specialised, non-specialised)
Professional caregiving services	PPIE-P	Hourly cost, hours per week
Direct Non-Medical Costs		
Travel costs	PPIE-P	Car, public transportation
Transfer payments	PPIE-P	State/government support
Alternative therapies	PPIE-P	Exercise, physiotherapy, holistic therapy
Indirect Costs		
Work productivity, patient	PPIE-P	Absenteeism, hours missed per week, early retirement
Work productivity, caregiver	PPIE-C	Absenteeism, hours missed per week, early retirement
Informal care	PPIE-P	Hours per week

Note: eCRF (Electronic Case Record Form), PPIE-P (Patient public involvement engagement questionnaire;), PPIE-C (Caregiver public involvement engagement questionnaire)

Table A2. Breakdown of mean annual costs by stage

Costs, mean (SD)	Early-stage HD	Middle-stage HD	Advanced-stage HD
Direct medical costs			
Consultations	€727 (€1,216) n=829	€767 (€975) n=693	€1,051 (€1,335) n=545
Tests/examinations	€515 (€1,434) n=837	€383 (€680) n=697	€452 (€1,134) n=541
Hospital outpatient	€911 (€1,243) n=42	€888 (€809) n=43	€916 (€1,192) n=92
Hospital inpatient	€35,803 (€102,653) n=28	€30,698 (€39,581) n=23	€12,658 (€42,550) n=60
Treatment	€6,333 (€25,525) n=667	€6,539 (€28,257) n=571	€7,922 (€26,248) n=454
Other medications	€7,612 (€17,781) n=64	€22,416 (€25,718) n=50	€10,383 (€22,827) n=23
OTC self-medication	€208 (€499) n=204	€221 (€454) n=164	€182 (€376) n=114
Medical devices	€192 (€400) n=204	€277 (€502) n=164	€592 (€1,778) n=114
Residential care	€41,879 (€46,946) n=16	€56,673 (€40,806) n=26	€45,977 (€31,915) n=98
Professional caregiver	€1,286 (€4,355) n=204	€2,308 (€9,831) n=164	€2,582 (€8,632) n=114
Direct non-medical costs			
Transportation	€737 (€2,425) n=204	€571 (€1,894) n=164	€599 (€1,072) n=114
State support, patient	€841 (€2,123) n=204	€1,199 (€2,497) n=164	€2,677 (€3,437) n=114
State support, caregiver	€5,134 (€5,834) n=22	€5,897 (€5,098) n=36	€4,778 (€3,359) n=43
Alternative treatments	€162 (€373) n=204	€177 (€446) n=164	€207 (€595) n=114
Indirect costs			
Lost productivity, PwHD	€23,216 (€16,848) n=75	€31,824 (€13,934) n=109	€34,343 (€10,295) n=98
Lost productivity, caregiver	€18,225 (€19,864) n=33	€12,988 (€15,621) n=46	€17,280 (€19,266) n=49
Informal care	€27,760 (€37,790) n=121	€30,243 (€37,046) n=120	€37,758 (€45,515) n=83

HD, Huntington's Disease; SD, standard deviation.