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Natural History and Burden of Huntington's Disease in the UK: A Population-Based Cohort Study

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Abstract (word count: 226/250)

Background

Huntington's disease (HD) is a rare neurodegenerative disease that presents with progressive psychological, cognitive and motor impairment. These diverse symptoms place a high burden on the patient, families and the healthcare systems they rely on. This study aimed to describe the epidemiology and clinical burden in individuals with HD compared with controls from the general population.

Methods

This cohort study utilised data from general practitioner (GP) medical records to estimate the prevalence and incidence of HD between Jan 2000 and Dec 2018. A cohort of incident HD cases were matched 1:3 to controls from the general population, in whom common clinical diagnoses, medications and healthcare interventions were compared at the time of first recorded diagnosis and at a time close to death. Incidence rates of common diagnoses and mortality were compared with matched controls in the time following HD diagnosis.

Results

Prevalence of HD increased between 2000 and 2018, whilst incidence remained stable. Prevalence of psychiatric diagnoses and symptomatic treatments were higher in HD cases than controls. A higher relative risk of psychotic disorders, depression, insomnia, dementia, weight loss, pneumonia and falls was observed in HD cases. Risk of death was >4 times higher in HD, with a median survival of ~12 years from first recorded diagnosis.

Conclusions

This study demonstrates the significant and progressive clinical burden in individuals up to 18 years after first recorded diagnosis.

INTRODUCTION

Huntington's disease (HD) is a rare, genetic, neurodegenerative disease that typically affects people in mid-life and is ultimately fatal (1, 2). HD is characterised by cognitive, behavioural and motor symptoms that contribute to functional decline, including the ability to walk, talk and self-feed (3, 4). Cognitive and behavioural manifestations such as depression, apathy and irritability can occur years before diagnosis of motor onset and deteriorate steadily as the disease progresses (5-7). Motor symptoms are initially subtle and gradually worsen over time, typically including chorea, dystonia, abnormal gait and balance, difficulty with speech and swallowing, and bradykinesia (4).

The estimated prevalence of HD varies globally and appears to have increased in the years since predictive testing became available. In a study of HD epidemiology in the UK, Evans et al, 2013, reported that the prevalence of HD doubled between 1990 and 2010 (8), although incidence seemingly appears constant at 7.2 new cases (95% confidence interval [CI] 6.5–7.9) per million person years (PY) (9). Whilst the reason for increasing prevalence is unclear, the heavy burden that the disease places on individuals with HD and their families warrants efforts to better understand the epidemiology of the disease and the associated clinical burden it places on individuals and public health systems.

In this population-based study, we describe the epidemiology and clinical disease burden associated with HD over an 18-year study period using linked UK electronic medical records (EMRs). This study reports the incidence, prevalence and mortality of HD in the UK, describes the clinical profile of patients at two time points (at first recorded diagnosis and close to death) and provides incidence rates of relevant clinical diagnoses, medications, healthcare interventions compared with a matched cohort from the general population.

METHODS

Study population

HD cases were defined as those with ≥1 Read code indicative of a diagnosis of HD (F134.00 Huntington's chorea; Eu02200 Dementia in HD) as defined previously (Evans et al, 2013; Wexler et al, 2016). Individuals were aged ≥18 years at the time of first recorded HD diagnosis (HD index) and had ≥1 day of eligible data during the study period. Free text associated with the HD diagnosis code was reviewed to ensure that diagnosis codes with reference to a patient without HD or with a family history of HD were not included.

An overall UK-wide HD cohort was used for estimating prevalence and incidence of HD. Prevalent individuals were those with a diagnosis of HD any time prior to, or during, the study period (2000–2018), whilst incident individuals were those who had their first recorded diagnosis of HD during the study period, without a prior record of HD. A minimum 1 year of continuous enrolment, free from HD diagnosis was required to limit the likelihood of a prevalent individual being defined as part of the incident cohort.

For the comparative analysis, a restricted cohort of incident individuals with HD was defined, who were also eligible for linkage to the Office for National Statistics (ONS) death registry and 2015 small area-level English Index of Multiple Deprivation (IMD) (a deprivation score assigned to each GP according to multiple domains such as income, employment, education and crime within the GP postcode) (10). HD cases were matched to a control group from the general Clinical Practice Research Datalink (CPRD) population who did not have any recorded codes indicative of HD, but who had eligible data for research at the time of HD index of the equivalent case individuals. Controls

were matched 3:1 (sex, year of birth, socio-economic status [IMD] and practice location) to HD cases. Since the English IMD was used, the comparative analysis was restricted to individuals registered at GP practices in England.

Study design

This was a cohort study that took place between 1 January 2000 and 31 December 2018. Annual prevalence and incidence of HD were first described in the overall HD cohort. Prevalence of clinical diagnoses, medications and healthcare interventions of interest were described in the restricted cohort of incident HD cases and matched controls at two equivalent time points: 1) at the time of HD index (i.e. the date of first recorded diagnosis), and 2) 3 months prior to death (i.e. a proxy for more advanced disease). Incidence rate ratios (IRRs) were calculated to explore relative rates of clinical diagnosis in HD cases and controls in the years after index. Survival time and risk of death were compared in HD cases and controls and underlying cause of death described.

Data sources

The CPRD-GOLD captures primary care data from anonymised GPs across the UK. With coverage of ~7% of the UK population, it is thought to be broadly representative of the UK general population in terms of age, sex and ethnicity (11).

For the comparative analysis, data were linked to the ONS death register which captures complete death recordings of all individuals in England and Wales, including occurrence, date and cause of death. Data were also linked to small area-level English IMD as a composite measure of socio-demographic deprivation. More information on linkage of CPRD data can be found here: https://cprd.com/linked-data.

Statistical methods

Prevalence of HD

Overall prevalence of adult HD (≥18 years) was reported as the number of cases of HD per 100,000 people (± 95% CI) across the entire study period. Annual prevalence was calculated (cases of HD per 100,000 people and 95% CI for each calendar year between 2000 and 2018). Results were stratified by age group, sex and geographical location (across the UK). A linear regression model was fit to examine whether the trend was statistically significant over time.

Annual incidence of HD

Annual incidence (newly diagnosed cases of HD per 100,000 PY and 95% CI for each calendar year between 2000 and 2018) was calculated as the total number of adults in the UK whose first HD record occurred during eligible data in each given calendar year, divided by the total person time of individuals in the at-risk population (i.e. no previous diagnosis of HD) and eligible for ≥1 day during that year. Trends were assessed via linear regression analysis.

Disease burden in incident HD cases versus matched controls

Demographics

Demographics including age, sex, IMD, Charlson comorbidity index (CCI), CCI comorbidities, marital status, body mass index (BMI), smoking status, alcohol consumption status, weight and geographical region were described for the overall (UK) and restricted (England only) matched cohorts.

Characteristics were assessed by looking back up to 1 year before HD index. Demographics in the matched controls were described at an equivalent time point to the respective matched case or using the closest available data. Group comparisons were conducted with t-test/Mann–Whitney U test for continuous variables and Chi-squared/Fisher's exact test for categorical variables, as appropriate.

Prevalence of clinical diagnoses, medications and interventions of HD in England

Code lists were compiled for specified clinical diagnoses, medications and interventions of relevance to individuals with HD defined *a priori* following literature assessment and clinical input (see Code list in supplementary materials). A look-back period of 1 year was used to capture diagnosis codes on or before each time point of interest. Percentage of individuals who experienced a clinical event during this look-back window was reported. To compare HD cases with controls, crude and adjusted odds ratios (ORs) were obtained via inverse probability of treatment-weighted generalised linear models, adjusting for age, gender, region, BMI, smoking status, alcohol status, socio-economic status (IMD), and CCI. *P*-values and CIs were calculated via non-parametric bootstrapping and corrected with the Benjamini–Hochberg method for multiple comparisons.

Incidence of clinical diagnoses of HD in England

Incidence of clinical diagnoses following index was calculated per 1,000 PY (95% CI). The number of individuals who experienced their first record of an event during the study period was divided by the total number of years in which individuals were at risk of experiencing the event. Person time was calculated up until the first event, death, end of eligible data or end of the study period, whichever came first. Crude IRRs and *p*-values were reported to compare incidence in HD cases with controls, with Benjamini–Hochberg correction for multiple comparisons.

Mortality

The Kaplan–Meier (KM) method was used to estimate the unadjusted survival times for incident HD and matched controls, from HD index date (or equivalent in controls) until death or end of the study period, whichever came first. Median survival time (95% CI) was calculated. Date of death was defined as the earliest date recorded in CPRD or ONS, to avoid overestimation of survival rates. Those that were lost to follow-up in CPRD were assumed to be alive for the duration of the study period unless a death date was seen in the ONS death registry. Hazard ratio (HR), reflective of risk of death in HD versus controls, was calculated via Cox proportional hazards regression method with adjustment for *a priori* baseline covariates including age, sex, IMD, CCI, smoking, alcohol consumption, BMI and geographical region at index. Primary underlying and mentioned cause of death (ICD-10 codes) were described for cases and controls independently.

RESULTS

Prevalence and incidence of HD in the UK

Overall, 881 prevalent cases of HD were ascertained during the study period, from a total population of 10,757,951 persons (Table 1). Prevalence of HD per 100,000 people (95% CI) was 8.2 cases (7.7–8.8) and was highest in those aged 55–64 years (*N* = 1,211, 10.3 cases [9.7–10.9]) (Table S1). Highest prevalence was reported in Scotland (*N* = 173, 11.2 cases [9.7–13.0]) and lowest in London (*N* = 38,

3.1 cases [2.2–4.2]) (Table S2). Prevalence was similar in males (N = 414, 8.0 cases [7.3–8.8]) and females (N = 462, 8.3 cases [7.6–9.1]).

Annual prevalence steadily increased throughout the study period, with prevalence estimates ranging from 4.3 cases (3.6–5.1) per 100,000 in 2000 to 9.2 cases (8.1–10.5) per 100,000 people in 2018 ($\beta = 0.27$, $p < 0.001$).

There were 586 incident cases of HD from a total at-risk population of 10,756,901 persons (corresponding to 80,048,926 PY) during the study period (Table 1). There was no evidence that incidence increased over time ($\beta = 0.004$, $p = 0.4$), with 16–44 newly diagnosed cases per year identified. In 2018, incidence of HD was 0.8 (0.5–1.19) per 100,000 PY.

Demographics

Of the overall incident HD population in the UK (N = 586), 54% were female. The median age at first recorded diagnosis was 54 years (interquartile range [IQR] 44–66) and the majority (44.9%) of individuals were aged 45–64 years at the time of HD index. Of these, 264 HD patients were eligible for inclusion in the matched comparative analysis. Gender (50% male) and age distribution were similar to their overall cohort and exactly matched to non-HD controls (Table 2, S3).

Prevalence of clinical diagnoses

At HD index, depression (9% vs. 3%, 4.34, 1.90–8.68, $p < 0.001$), falls (6% vs. 2%, 2.19, 0.79–5.09, $p = 0.09$), and fractures/breaks/sprains (5% vs. 2%, 2.5, 0.83–5.96, $p = 0.09$) were more prevalent in HD cases than controls; only depression exceeded $p < 0.05$ after model adjustment. Controls were more prevalent than individual with HD for hypertension (6% vs. 11%, 0.43, 0.23–0.89, $p < 0.05$) and diabetes (4% vs. 7%, 0.39, 1.9–8.68, $p < 0.05$) (%, OR_{adj}, 95% CI) (Table S4).

Three months before death, anxiety (11% vs. 5%, 2.11, 0.7–5.6, $p = 0.15$), depression (28% vs. 6%, 4.28, 1.72–8.67, $p < 0.001$), falls (25% vs. 8%, 2.5, 1.18–4.73, $p < 0.05$), insomnia (25% vs. 4%, 8.82, 3.62–20.19, $p < 0.001$), and fractures/breaks/sprains (20% vs. 10%, 1.83, 0.85–3.35, $p = 0.09$) were more prevalent in HD cases. Cardiovascular disease was more prevalent in controls than in individuals with HD (48% vs. 27%, 0.49, 0.29–0.79, $p < 0.01$) (%, OR_{adj}, 95% CI) (Table S4).

Incidence of Other Clinical Diagnoses in HD Cases versus Controls

Incident rates of the following were statistically higher in individuals with HD cases than controls: psychotic disorders, psychosis, insomnia, dementia, depression, pneumonia, weight loss and falls. Incidence of cardiovascular disease, hypertension and diabetes was higher in matched controls. Cases per 1,000 PY, IRR, 95% CI and P-values are shown in Table 3. Data summarising the number of individuals at risk and person time used to calculate IRRs can be found in Table S5.

Prevalence of healthcare interventions

At HD index, homecare/domestic visits (9% vs. 3%, 2.64, 1.24–5.29) and physiotherapy (6% vs. 3%, 1.38, 0.55–2.90) were more prevalent in the HD cohort (%, OR_{adj}, 95% CI). After model adjustment, homecare/domestic visits were more than twice as prevalent in individuals than controls (OR_{adj} = 2.64, $p = 0.03$) (Table S6).

Three months before death, individuals with HD generally received more interventions than controls; however, in most cases the number of records was not powered to perform significance testing. Homecare and domestic visits were >4 times more prevalent in individuals with HD at the time point 3 months prior to death compared with controls (OR_{adj} = 4.39, p < 0.001).

Molecular pathology procedures (including coded interactions with geneticists and genetic counselling) were more common in HD than controls at index (11% vs. 0%) and close to death (14% vs. 0%). Statistical modelling was not conducted due to zero events in the control cohort (Table S6).

Prevalence of medication records

At index, antipsychotics (11% vs. 3%, 3.71, 1.70–6.83), antidepressants (33% vs. 14%, 3.04, 2.04–4.53), sleep medication (19% vs. 7%, 3.01, 1.75–4.99), and diazepam (9% vs. 3%, 2.79, 1.29–5.81) were more common in individuals with HD compared with controls (%, OR_{adj}, 95% CI).

Three months before death, antipsychotics (58% vs. 11%, 7.08, 3.88–12.00), sleep medications (53% vs. 19%, 3.71, 2.23–5.70), antidepressants (63 vs. 22%, 3.38, 2.12–5.33), and diazepam (24 vs. 9%, 2.62, 1.18–4.81) was higher in HD after model adjustment use of the following medications (%, OR_{adj}, 95% CI).

Tetrabenazine was higher than controls at HD index (6% vs. 0%) and close to death (39% vs. 0%) but was not modelled (Table S7).

Mortality

Of the incident cohort, 106 HD cases (40%) and 114 controls (14%) died during the study period. KM survival curve (Figure. 1) shows a median survival time of 12.4 years (95% CI 10.6–15.2). Median age at death in individuals with HD and controls was 71 (IQR 59–79) and 81 (IQR 73–86) years, respectively. Individuals with HD were at 4.5 times greater risk of death than controls (HR 4.51, 95% CI 3.36–6.06, p < 0.001) after multivariable adjustment of baseline covariates (Figure S1).

The most common underlying cause of death in the HD cohort was HD (n = 62; 59.6%). The most commonly mentioned causes of death (any mention) were HD (78.3%), bronchopneumonia (unspecified) (15.9%), pneumonitis due to food and vomiting (10.4%), unspecified dementia (6.6%), and sepsis (6.6%) (Table S8).

DISCUSSION

This is the first study to explore the burden of HD in UK EMRs and provides updated epidemiological estimates on the prevalence, incidence and mortality of HD in the UK/England. In addition to expanding upon prior observations, our study uniquely introduces a control comparator arm which is absent in many population-based studies.

Overall, 881 prevalent and 586 incident cases of HD were identified in the UK CPRD-GOLD database between 2000 and 2018. A strength of the CPRD database compared with patient registries such as Enroll-HD (NCT01574053) is that it includes all individuals seen by GPs in the UK, not just those participating in long-term clinical trials where they are seen by HD specialists. Prevalence doubled from 4.3 cases per 100,000 in 2000 to 9.2 cases per 100,000 in 2018. These figures align with a global systematic review (12) and when considering studies only conducted in the UK, our results fall within the range (5.96–12.3 cases per 100,000 people) of those reported previously (8, 13). Increased prevalence was not explained by an increased incidence of HD, whereby our findings corroborate prior evidence that incidence of HD in the UK does not increase steadily over time (9). Increasing life

expectancy of the UK general population or better symptomatic treatments that prolong longevity in individuals with HD may explain the increased prevalence observed. The UK is known for its active clinical research in the field of HD which may contribute to a higher case ascertainment compared with other European countries, rather than a difference in the underlying epidemiology across European countries.

Global variation in HD prevalence is partly explained by the average cytosine adenine guanine (CAG) repeat lengths and frequency of different huntingtin gene haplotypes across individuals. For example, prevalence is 10–100 times lower in East Asian populations (12, 14) whose HD chromosomes are typically found on haplotype C, compared with Western European populations who are typically haplotype A. Genetic factors that may influence prevalence could not be accounted for in this study since genetic data are not available in CPRD. Prevalence varied across the UK, with the highest prevalence in Scotland, which may be attributed to better case ascertainment due to higher underlying genetic susceptibility in the ancestral populations, increased disease awareness and education, and access to world-leading specialist HD care. Lower prevalence in London may be attributed to the higher cost of living and the high population density which would decrease the numerator and denominator respectively, leading to a lower net prevalence in the capital.

Median age of first recorded diagnosis was 54 years and 56 years in the UK-wide cohort and incident-matched cohort, respectively, which was higher than the age of motor symptom onset typically reported in the literature (3, 15). Identifying the exact point at which a patient is diagnosed with manifest HD can be hard to determine in regular healthcare settings. It may be that GP reporting of HD diagnosis may be delayed, since a clinical diagnosis itself is commonly given in a specialist neurology setting prior to informing the GP. Conversely, some patients, particularly in rural populations, may not be known to specialists, and GPs may manage the diagnosis and management of disease in the early stages. Since the GP acts as the gatekeeper to NHS specialist services, we consider the first GP recorded diagnosis as useful index definition for public health planning.

A later primary care diagnosis may also contribute to the shorter survival time (~12 years) observed in our study compared with other global studies, which report survival of 15–25 years (16-20). This may be partly attributed to index definition (e.g. first recorded diagnosis vs. motor symptom onset) and/or the methods used. For example, a retrospective chart review by Roos et al, 1993, (18) reported a median survival time of 16.2 years, however onset of choreatic movements (aged 40 ± 12 years) was used to define index in this study, and data from this specialist centre have biased findings towards earlier detection and longer life expectancy due to better specialist management. To our knowledge, this is the first study to report HD-related mortality in the UK; using this robust death registry and our findings demonstrate a ~4 times increased risk of death compared with the general population. The most common underlying cause of death was 'Huntington's disease', demonstrating the fatal effects of HD, although unfortunately the immediate cause of death, such as pneumonia, infections or suicide (21), which may be useful for treating professionals, was not captured.

Our findings describe a picture of high psychiatric burden in individuals with HD compared with the general population, including a higher incidence rate of psychosis, depression and sleep disturbances after diagnosis. In line with other reports, it was noted that depression is the most prevalent clinical diagnosis associated with HD (22). The high rate of sleep disturbances in those closer to death reflects the progressive disruption in circadian rhythms which is a progressive phenotype of HD (23). Beyond the psychiatric symptoms of HD, we also report on the rate of other physical comorbidities, including higher prevalence of falls. Increased falls are often one of the earliest signs of HD,

preceding a clinical diagnosis of HD, and are explained by loss of muscle control and gait disturbances typical of HD, which occur more frequently as the disease progresses.

Not all comorbidities were higher in HD, for example, diabetes and hypertension were lower in individuals with HD than controls at the time of diagnosis. A study using data from the Enroll-HD database attributed lower prevalence of hypertension to antihypertensive medication use, although the causal relationship is not clear (24). Both diabetes and hypertension are well-established risk factors for cardiovascular disease, which might explain the lower prevalence of cardiovascular disease in individuals with HD than matched controls at the later time point.

There are no disease-modifying treatments currently available for HD. Symptomatic treatments may influence survival, for instance by reducing suicidality or improving mobility. We found that the odds of taking antidepressants, diazepam and other sleep medications were up to 4 times higher in HD and use of antipsychotics was up to 8 times. Together these findings are in line with the incidence of psychiatric and motor diagnoses reported in this cohort and demonstrate the importance of these symptomatic therapies in standard clinical care. Our findings also describe increased homecare/domestic visits in HD patients, particularly those closer to death, thereby demonstrating the increasing burden on the UK healthcare system, particularly later in the disease course.

Limitations

CPRD only captures clinical diagnoses recorded by primary care physicians and therefore diagnoses and drugs/interventions given in a hospital setting are not captured. This may be particularly important for understanding more progressed patients. Unlike registry studies like Enroll-HD, data on the causative CAG repeat expansion and established Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996) (25) are not captured in CPRD. Furthermore, we cannot rule out the possibility of misclassification (e.g. where pre-manifest HD gene carriers were falsely coded as manifest HD gene carriers after receiving a positive genetic test) and/or miscoding errors, since the quality of case ascertainment depends on multiple factors including whether the team enters them, the clinician's IT skills, time, certainty of diagnosis, how important they believe coding is and organisational issues (26). A proxy for late-stage disease was used here to demonstrate increased burden at more advanced stages, however alternative ways of staging HD in routine clinical care data warrant investigation.

CONCLUSIONS

Prevalence of HD continued to increase throughout the UK, though not because of increased incidence, which remained stable throughout the study period. Median survival from first GP record to death was 12.4 years. Psychiatric burden was higher in individuals with HD compared with controls and increased in those closer to death. Incidence rates of psychotic disorders, insomnia, dementia, depression, pneumonia, weight loss and falls were also higher in individuals with HD, whilst incidence of cardiovascular disease, hypertension and diabetes were higher in the matched controls without HD. This study provides updated epidemiological estimates on the prevalence and incidence of, and mortality in, HD, which together, increase our understanding of the physical, psychiatric and public health burden of HD.

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CONFLICT OF INTEREST

Hannah Furby – Full-time employee of Roche Products Ltd. Shareholder in F. Hoffmann-La Roche Ltd.

Athanasios Siadimas – Full-time employee of F. Hoffmann-La Roche Ltd. Shareholder in F. Hoffmann-La Roche Ltd.

Loes Rutten-Jacobs – Full-time employee of F. Hoffmann-La Roche Ltd. Shareholder in F. Hoffmann-La Roche Ltd.

Filipe B. Rodrigues – Full-time employee of University College London. Has provided consultancy to F. Hoffmann-La Roche Ltd and GLG.

Edward J. Wild – Consultancies and/or advisory board memberships with F. Hoffmann-La Roche Ltd, Triplet Therapeutics, Takeda Pharmaceuticals, PTC Therapeutics, Annexon Biosciences, Roche Products Ltd, Vico Therapeutics, Spark Therapeutics (via Huntington Study Group) and EcoR1 Capital. Full-time employee of University College London and an honorary employee of University College London Hospitals NHS Foundation Trust. Editor-in-chief of HDBuzz, a registered charity. Received research grants from CHDI Foundation, European Huntington's Disease Network, University College London and F. Hoffmann-La Roche Ltd.

AUTHOR CONTRIBUTIONS

Hannah Furby: Research project conception, organization and execution. Statistical analysis design, review and critique. Manuscript first draft development and critique.

Athanasios Siadimas: Research project execution. Statistical analysis design and execution. Manuscript first draft development, review and critique.

Loes Rutten-Jacobs: Research project conception. Statistical analysis review and critique. Manuscript review and critique.

Filipe B. Rodrigues: Statistical analysis review and critique. Manuscript review and critique.

Edward J. Wild: Statistical analysis review and critique. Manuscript review and critique.

DATA AVAILABILITY STATEMENT

This study (17_144) is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Office for National Statistics (ONS) data: This study is based in part on data from the ONS. The interpretation and conclusions contained in this study are those of the author/s alone.

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FIGURE AND TABLE CAPTIONS

Figure 1. Kaplan–Meier curve showing survival probability in individuals with HD and non-HD controls

HD, Huntington's disease.

TABLE 1. Annual prevalence and incidence of HD between 2000 and 2018

CI, confidence interval; HD, Huntington's disease

† Individuals ≥18 years of age with ≥1 Read code indicating a diagnosis of HD during that year.

‡ Total number of persons ≥18 years in each calendar year (prior to 31 December) with ≥1 day of eligible data during that year.

§ Individuals ≥18 years of age with ≥1 Read code indicating a diagnosis of HD by a physician at any time during or prior to that year who is alive and contributing ≥1 day of eligible data during that year.

¶ Total person time (years), from 1st Jan of the given year, until the first recorded diagnosis of HD, end of eligible data or the end of that year (whichever occurs first), summed across all individuals in the at-risk population (i.e. no previous diagnosis of HD and eligible for ≥1 day during the study period).

TABLE 2. Key demographics of the overall and restricted cohorts at the time of first recorded diagnosis of HD (HD index)

CCI, Charlson comorbidity index; GP, general practitioner; HD, Huntington's disease; IQR, interquartile range; NA, not applicable; SD, standard deviation.

TABLE 3. Clinical diagnoses with the largest IRR between HD cases and controls

CI, confidence interval; HD, Huntington's disease; IR, incidence rate; IRR, incidence rate ratio.

IRR was calculated as the IR in HD cases divided by the IR in controls and was corrected for multiple comparisons. *P*-values were adjusted for multiple comparisons testing using the Benjamini–Hochberg method.

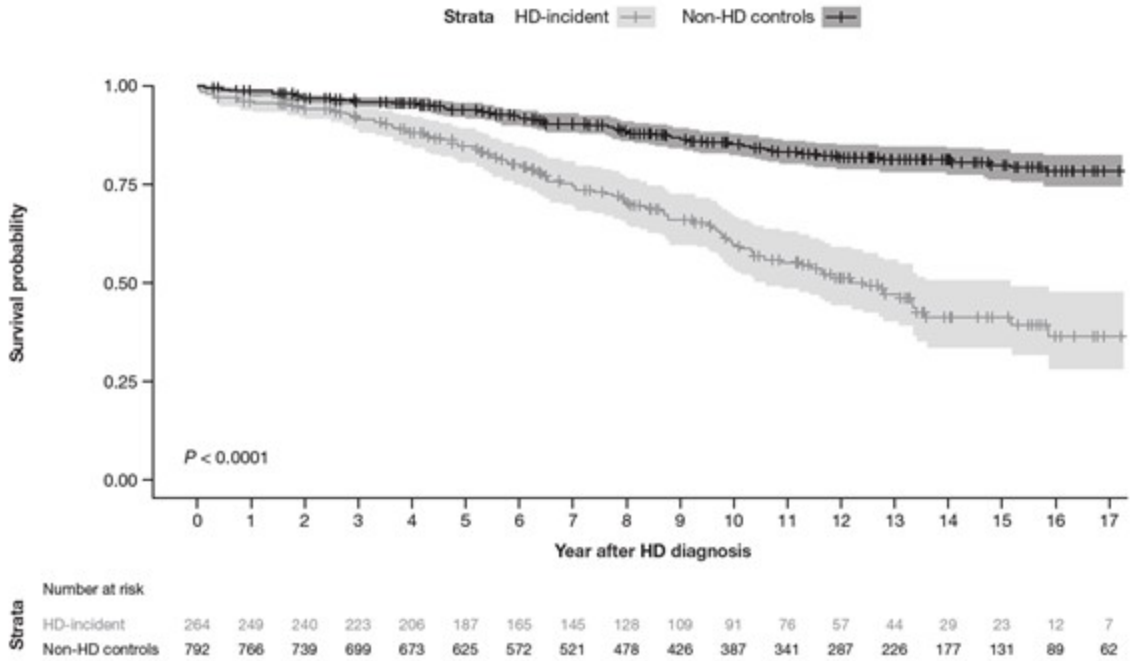
	Annual prevalence			Annual incidence		
Year	Prevalent HD cases†	Total population‡	Prevalence per 100,000 persons (95% CI)	Incident HD cases§	Person years¶	Incidence rate (per 100,000 person years [95% CI])
2000	135	3,129,421	4.3 (3.6–5.1)	23	3,129,160	0.7 (0.49–1.10)
2001	157	3,596,005	4.4 (3.7–5.1)	24	3,595,685	0.7 (0.45–0.99)
2002	171	3,995,208	4.3 (3.7–5.0)	22	3,994,836	0.6 (0.36–0.83)
2003	200	4,373,088	4.6 (4.0–5.3)	29	4,372,677	0.7 (0.46–0.95)
2004	231	4,609,702	5.0 (4.4–5.7)	34	4,609,238	0.7 (0.53–1.03)

2005	260	4,722,313	5.5 (4.9–6.2)	39	4,721,803	0.8 (0.60–1.13)
2006	280	4,827,097	5.8 (5.2–6.5)	37	4,826,562	0.8 (0.56–1.06)
2007	305	4,890,036	6.2 (5.6–7.0)	44	4,889,487	0.9 (0.67–1.21)
2008	305	4,872,637	6.3 (5.6–7.0)	31	4,872,045	0.6 (0.45–0.90)
2009	313	4,892,957	6.4 (5.7–7.2)	30	4,892,354	0.6 (0.43–0.88)
2010	323	4,887,786	6.6 (5.9–7.4)	40	4,887,175	0.8 (0.60–1.11)
2011	326	4,797,035	6.8 (6.1–7.6)	33	4,796,420	0.7 (0.49–0.97)
2012	337	4,728,123	7.1 (6.4–7.9)	38	4,727,505	0.8 (0.59–1.10)
2013	335	4,679,927	7.2 (6.4–8.0)	30	4,679,300	0.6 (0.45–0.92)
2014	332	4,419,097	7.5 (6.8–8.4)	35	4,418,502	0.8 (0.57–1.10)
2015	312	3,946,409	7.9 (7.1–8.8)	28	3,945,852	0.7 (0.49–1.03)
2016	280	3,246,514	8.6 (7.7–9.7)	33	3,246,061	1.0 (0.72–1.43)
2017	251	2,851,811	8.8 (7.8–10.0)	16	2,851,397	0.6 (0.35–0.91)
2018	239	2,593,243	9.2 (8.1–10.5)	20	2,592,867	0.8 (0.50–1.19)

Clinical diagnoses	HD cases		Controls		IRR		
	Cases per 1,000 person years	95% CI	Cases per 1,000 person years	95% CI	IRR	95% CI	*P*-value
Psychotic disorders	3.98	1.69–9.24	0.22	0.04–1.25	18.00	2.10–154.05	< 0.001
Psychosis	6.40	3.22–12.49	0.67	0.23–1.95	9.62	2.55–36.25	< 0.001
Insomnia	36.33	25.85–47.39	9.01	6.54–12.18	4.03	2.59–6.27	< 0.001
Dementia	17.47	11.26–26.11	4.69	3.06–7.13	3.72	2.03–6.82	< 0.001
Depression	53.87	38.88–66.94	15.43	11.90–19.40	3.49	2.40–5.07	< 0.001
Pneumonia	7.93	4.28–14.42	2.44	1.36–4.35	3.25	1.38–7.65	< 0.01
Weight loss	15.07	9.41–23.35	4.73	3.08–7.18	3.19	1.70–5.99	< 0.001
Falls	42.43	30.56–54.03	14.86	11.44–18.73	2.86	1.95–4.19	< 0.001
Cardiovascular disease	41.87	29.76–54.07	81.81	66.66–85.68	0.51	0.37–0.71	< 0.001
Hypertension	20.00	12.98–29.51	45.24	37.00–50.57	0.44	0.28–0.69	< 0.001
Diabetes	3.27	1.27–8.34	13.02	9.82–16.82	0.25	0.09–0.69	< 0.01

		Overall HD-incident cohort	**Restricted HD-incident cohort**
		***N* (%)**	***N* (%)**
Total		586	264 (100.0)
Sex	Female	317 (54.1)	133 (50.4)
Age group	18–34	60 (10.2)	29 (11.0)

	35–44	101 (17.2)	42 (15.9)
	45–54	137 (23.4)	55 (20.8)
	55–64	126 (21.5)	54 (20.5)
	65–74	100 (17.1)	51 (19.3)
	75+	62 (10.6)	33 (12.5)
	Mean (SD)	54.40 (15.26)	55.30 (15.81)
	Median (IQR)	54 (44–66)	56 (44–67)
Region	East Midlands	14 (2.4)	11 (4.2)
	East of England	43 (7.3)	34 (12.9)
	London	23 (3.9)	18 (6.8)
	North East	6 (1.0)	6 (2.3)
	North West	57 (9.7)	43 (16.3)
	Northern Ireland	11 (1.9)	NA
	Scotland	132 (22.5)	NA
	South Central	52 (8.9)	35 (13.3)
	South East Coast	56 (9.6)	33 (12.5)
	South West	47 (8.0)	38 (14.4)
	Wales	82 (14.0)	NA
	West Midlands	52 (8.9)	38 (14.4)
	Yorkshire & the Humber	11 (1.9)	8 (3.0)
Body mass index	Underweight (<18.5)	40 (6.8)	19 (7.2)
	Normal (18.5–24.9)	267 (45.6)	133 (50.4)
	Overweight (25.0–25.9)	140 (23.9)	60 (22.7)
	Obese (30.0+)	54 (9.2)	16 (6.1)
	Missing	85 (14.5)	36 (13.6)
CCI group	0	474 (80.9)	220 (83.3)
	1	74 (12.6)	28 (10.6)
	2	30 (5.1)	12 (4.5)
	3	6 (1.0)	3 (1.1)
	4 +	2 (0.3)	1 (0.4)


Strata HD-incident Non-HD controls
Survival probability
1.00
0.75
0.50
0.25
0.00
P < 0.0001
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Year after HD diagnosis
Number at risk
Strata
HD-incident 264 249 240 223 206 187 165 145 128 109 91 76 57 44 29 23 12 7
Non-HD controls 792 766 739 699 673 625 572 521 478 426 387 341 287 226 177 131 89 62