



**Juvenile Huntington's disease:  
an epidemiological study based on the Clinical Practice  
Research Datalink**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002085
Article Type:	Research
Date Submitted by the Author:	08-Sep-2012
Complete List of Authors:	Douglas, Ian; London School of Hygiene and Tropical Medicine, Epidemiology Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases Wexler, Nancy; Columbia University, Neurology and Psychiatry
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS

SCHOLARONE™  
Manuscripts

# Juvenile Huntington's disease: an epidemiological study based on the Clinical Practice Research Datalink

Ian Douglas PhD<sup>1</sup>, Stephen Evans MSc<sup>1</sup>, Michael D Rawlins FMedSci<sup>1</sup>, Liam Smeeth MD<sup>1</sup>, Sarah J. Tabrizi MD<sup>2</sup>, and Nancy S Wexler PhD<sup>3</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT; <sup>2</sup>University College London, Institute of Neurology, Queens Square, London WC1N 3BG; <sup>3</sup>Columbia University, 1051 Riverside Drive, Unit 6, PI Annex 371, New York, NY 10032; and Hereditary Disease Foundation, 3960 Broadway, New York, NY 10032.

Correspondence: Michael Rawlins, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT. email: [michael.rawlins@nice.org.uk](mailto:michael.rawlins@nice.org.uk)

## Abstract

**Objectives:** The juvenile form of Huntington's disease (HD) is a rare condition. There are no published estimates of either its incidence or prevalence. The present study was undertaken to estimate the frequency of diagnosed juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

**Design:** Cross-sectional study

**Setting:** Community-based multicentre study using the medical records of general practitioners contributing to the Central Practice Research Datalink (CPRD).

**Participants:** Patients with recorded diagnoses of Huntington's disease, under the age of 21 years, were retrieved from the CPRD for 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

**Results:** 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum estimate of incidence was 0.7 (95% CI 0.4 to 1.2) per million patient-years. The minimum estimate of prevalence was 6.8 (95% 5.6 to 8.1) per million population aged under 21. Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

**Conclusions:** Juvenile HD is, indeed, a very rare disorder. Its clinical management is undertaken with no formal evidence base for the efficacy or safety of the products used. Future studies of appropriate treatments are urgent. They will require multinational collaboration if trials are to enrol sufficient numbers of patients. The immediate initiation of smaller exploratory studies would be invaluable in designing larger, definitive trials. In the meantime it is imperative that those planning services for people with juvenile HD – and their families – ensure appropriate resources for their medical and social care are available.

1  
2  
3  
4  
5  
6  
7  
8 Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder  
9 associated with abnormal movements, psychiatric disturbances and cognitive  
10 decline<sup>1,2</sup>. HD segregates as an autosomal trait located on chromosome  
11 4p16.3 and the HD gene encodes the huntingtin protein<sup>2</sup>. The HD  
12 abnormality is an expanded CAG repeat on exon 1 of the HD gene. This  
13 leads to a corresponding expression of an expanded polyglutamine repeat in  
14 the huntingtin protein. Alleles with 40 or more CAG repeats invariably give  
15 rise to HD provided that individuals live a normal lifespan<sup>1</sup>. Alleles with 60 or  
16 more CAG repeats result in the juvenile form of the disease. Juvenile HD is  
17 defined as HD an onset of 20 years or younger.

18  
19  
20 In adult HD the movement disorder is typically chorea. In juvenile HD the  
21 movement disorder, rather than chorea, is primarily tremor, bradykinesia and  
22 dystonia<sup>3,4,5</sup>. In juvenile HD cerebellar signs, epilepsy, myoclonus and  
23 spasticity may also occur. As in adult HD, psychiatric disturbances and  
24 progressive cognitive decline are invariably present<sup>4,5</sup>.

25  
26 Although there have been various published estimates of the incidence and  
27 prevalence of adult HD there has been no attempt to investigate either the  
28 population incidence, or prevalence, of the juvenile form. This study was  
29 designed to obtain an estimate of the incidence and prevalence, in the UK, of  
30 diagnosed juvenile HD using the General Practice Research Database  
31 (GPRD) as well as to examine the range of specific treatments used in its  
32 management.

## 33 34 35 36 **Methods**

### 37 38 *Study design and setting*

39 The CPRD (formerly the General Practice Research database) is a  
40 computerised database containing anonymised electronic patient records  
41 from UK primary care. It covers around 6% of the UK population at any one  
42 time and both its unique features, as well as the high quality of the data  
43 contained within it, have been described elsewhere<sup>6</sup>.

### 44 45 46 *Participants*

47 The source population was all patients, under 21 years of age, registered with  
48 general practices contributing to the CPRD, between 1990 and 2010. Eligible  
49 cases were defined as any person, under the age of 21 years, with one or  
50 more diagnoses of Huntington's disease or Huntington's chorea in their  
51 medical record. The last date for each record was the earliest of the either the  
52 date of death, the date of patients' de-registration from the practice if still  
53 alive, the date the practice left the CPRD, or the end of the observation period  
54 (2010). The Read codes used to identify cases in the database were  
55 F134.00 (Huntington's chorea) and Eu2200 (dementia in Huntington's  
56 disease).

### *Biases*

In order to ensure that prevalent cases were not wrongly identified as incident ones, two additional criteria for inclusion as incident cases were applied: 1) they had to have been registered with the practice for 12 months or longer by the date the diagnosis was recorded; and 2) they had to have had at least one other recorded contact, with the practice, during the preceding 12 month period.

### *Prescription data*

The medicines prescribed for incident and prevalent patients were retrieved from CPRD. Medications commonly prescribed for children and adolescents, and not specific for those with juvenile HD (including antibiotics, antifungal agents, emollients, and routine vaccinations), were not analysed further. Specific treatments for the symptoms and signs of jHD were examined in detail. Those treatments prescribed more than twice, for a particular patient, were categorised as “regular” treatments.

### *Statistical methods*

Incidence was calculated from the numbers of incident cases (as defined above under Biases), within 5-year age-bands, in relation to the total number of patient-years within that age-band. Prevalence was calculated, for each year during the study period (1990-2010), from the numbers of patients with recorded juvenile HD divided by the total numbers of patients in the database aged less than 21 years during that year. For estimates of both incidence and prevalence binomial 95% confidence intervals were calculated.

## **Results**

### *Main findings: incidence*

There were 12 records (4 females, 8 males) of patients fulfilling the criteria for inclusion as incident cases of juvenile HD. Their ages at diagnosis ranged from 5 years to 20 years (median 15 years). The overall incidence was 0.7 (95% CI 0.4 to 1.2) per million patient-years. The estimates of incidence in 5 year age-bands (Table 1) ranged from 0 (95% CI 0 to 1.1) per million patient-years at age 0 to 4 years, to 1.3 (95% CI 0.5 to 2.7) per million patient-years at aged 15 to 20 years.

Eight of the 12 incident cases had records of potential prodromal diagnoses, suggestive of juvenile HD, up to 3 years before a formal diagnosis was entered into their records. These included sleep disorders (3 cases), psychiatric referrals (2 cases), movement disorders (2 cases) and referral for genetic counselling (1 case). The remaining cases had no obvious prodromal reported diagnoses.

### *Main findings: prevalence*

There were 21 records (8 females, 13 males) of individuals contributing to the database, aged less than 21 years, with a diagnosis of HD. They provided a

total of 116 patient years within the database. The average annual prevalence of juvenile HD, between 1990 and 2010, was 6.8 per million (95% CI 5.6 to 8.1) but fluctuated year by year (Table 2).

### *Prescription data*

Prescription data for the treatment relevant to the symptoms and signs of juvenile HD among prevalent cases are summarised in Table 3. One patient had no prescriptions recorded during the observation period and 6 were prescribed products for intercurrent conditions (mainly antimicrobial agents, oral contraceptives, antiasthma products and vaccines) which were assumed to be unrelated to HD.

Fourteen patients were prescribed regular treatments apparently for the specific management of their HD symptomatology (Table 3). Simultaneous prescriptions for more than one therapeutic category were common. The products most commonly prescribed included antidepressants (particularly fluoxetine and citalopram), a wide variety of treatments for motor disorders (including baclofen, levodopa, amantidine and tetrabenazine), hypnotics, antipsychotics (risperidone and olanzepine) and anticonvulsants (especially valproate and clobazam). Because of the small numbers of patients it would be inappropriate to use these data to infer the relative frequencies of the phenotypic variations, in the clinical manifestations of juvenile HD. Nevertheless, the data correspond – at least qualitatively – with the phenotypic patterns observed in reports of juvenile HD<sup>5</sup>.

## **Discussion**

Our results, extrapolated to the entire UK population under 211,, suggests that there are – at a minimum – 100 children and adolescents living with a diagnosis of juvenile HD. Ten more children are being diagnosed annually with juvenile HD.

The estimates of incidence and prevalence of diagnosed juvenile HD, reported here, are the first to provide population-based epidemiological data on the frequency of this condition both for the UK or worldwide. The apparent increase in the age-specific incidence of juvenile HD, in Table 1, is intuitively appropriate but because of the small numbers involved it is impossible to be certain.

Our estimates of both the incidence and prevalence of juvenile HD are, however, likely to underestimate of the true frequency of juvenile HD. First, it is possible that some general practitioners failed to record their patients' HD diagnoses for reasons of confidentiality<sup>8</sup>. Second, the dates of onset of past diagnoses are not always reliably recorded. In some instances past diagnoses may be recorded either without a date or as occurring at the date of registration. Such cases would have been excluded from our analysis of incidence. Thirdly, the strict criteria we applied in defining incident cases might have resulted in omitting some who should have been assigned to this category. However, only two prevalent cases were excluded as incident

1  
2  
3 cases (one aged 12 years and the other aged 19 years) on the basis of these  
4 criteria. They were excluded because their records failed to include any other  
5 contact with the practice, one of our exclusion criteria, in the 12 months prior  
6 to the entry of a diagnosis of HD.  
7

8  
9 Most of the potential prodromal diagnoses, reported for incident cases, were  
10 typical of the clinical features of juvenile HD including motor disturbances and  
11 psychiatric problems. It is striking, however, that in three instances patients  
12 complained of sleep disturbances. This has not previously, to our knowledge,  
13 been reported in association with juvenile HD. Furthermore, hypnotics were  
14 prescribed to a significant proportion of prevalent patients with diagnosed  
15 juvenile HD.  
16

17  
18 The symptomatology of juvenile HD is complex and causes suffering in all  
19 domains of quality of life. Even though a wide range of therapies are used,  
20 often simultaneously, there are no studies to guide the current trial-and-error  
21 “experimental” approach to the treatment of juvenile HD. Most of the  
22 treatments for the motor manifestations of juvenile HD are those shown to be  
23 effective in Parkinson’s disease but none have ever been formally assessed  
24 in juvenile HD. There are no studies of the effectiveness of antidepressants,  
25 antipsychotics or anticonvulsants specifically in the treatment of the juvenile  
26 form of HD. In clinical medicine there is general concern about prescribing  
27 antidepressants to children<sup>9</sup>. Studies are urgently required of the efficacy and  
28 safety of selective serotonin re-uptake inhibitors in treating depression in  
29 children and adolescents with juvenile HD.  
30

31  
32 The present investigation also demonstrates that it is imperative to assess the  
33 comparative effectiveness of other treatment options in juvenile HD. Because  
34 the numbers of children and adolescents with juvenile HD are small, in any  
35 single country such as the UK, only multinational trials are likely to produce  
36 the most reliable answers. In the meantime, small exploratory studies will  
37 guide the design of larger trials.  
38

39  
40 The humane care of children and adolescents with juvenile HD requires  
41 appropriate health and other forms of supportive care to be provided by the  
42 UK’s health and social services. It is imperative that those responsible for  
43 planning the provision of such care meet the compelling needs of both these  
44 young people and of their families.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Authors**

All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by all the other contributors. MDR is the guarantor.

**Source of funding**

The authors are grateful to the Hereditary Disease Foundation and the Huntington's Disease Association for their support for this study. LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

**Conflicts of Interest**

None of the authors have any conflicts of interest to declare.

peer review only



## References

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Annual Review of Medicine* 2012; 63: 1-22.
3. Van Dijk JG, van der Velde EA, Roos RAC, Bruyn GW. Juvenile Huntington's disease. *Human Genetics* 1986; 73: 235-239.
4. Ribai P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Legout A, Dode C, Brice A, Durr A. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology* 2007;64:813-819.
5. Quarrell OWJ, Brewer HM, Squitieri F, Barker RA, Nance MA, Landwehrmeyer GB. *Juvenile Huntington's Disease (and other trinucleotide repeat disorders)*. Oxford University Press: Oxford, 2009.
6. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database. *British Journal of Clinical Pharmacology* 2010; 69:4-14.
7. Connecting for Health. Read Codes. <http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes> (accessed 5.9.12)
8. Evans S, Ian Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *Lancet* (submitted for publication).
9. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. National Institute for Health and Clinical Excellence: London, 2005. <http://guidance.nice.org.uk/CD28>. (Accessed 5.9.12)

## Article Summary

### Article focus:

- A study of the incidence and prevalence of the juvenile form of Huntington's disease, in the UK, based on general practitioner's records in the Clinical Practice Research Datalink (CPRD).
- An analysis of symptomatic treatments prescribed for children and adolescents with juvenile Huntington's disease

### Key messages:

- The juvenile form of Huntington's disease is very rare with an incidence of 0.7 (95% CI 0.4 to 1.2) per million patient-years and a prevalence of 6.8 (95% 5.6 to 8.1) per million population aged under 21 years.
- Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities but no formal studies of the efficacy and safety of these medicines have ever been undertaken.

### Strengths and weaknesses:

- This is the first attempt to assess, in any population in the world, the incidence and prevalence of the juvenile form of Huntington's disease;
- The study emphasises the weakness of the evidence base to support its clinical management.
- The study relies on the recording, by general practitioners contributing to the CPRD, of a Huntington's disease diagnosis.

**Table 1**  
**Incidence estimates of juvenile Huntington's disease in UK**

<b>Age group (years)</b>	<b>Incident cases</b>	<b>Population (patient-years)</b>	<b>Incidence per million patient-years (95%CI)</b>
0-4	0	4,097,551	0 (0 to 1·1)
5-9	3	4,156,414	0·7 (0·2 to 2·1)
10-14	3	4,115,431	0·7 (0·2 to 2·1)
15-20	6	4,762,455	1·3 (0·5 to 2·7)

**Table 2**  
**Prevalence estimates of juvenile Huntington's disease in the UK**

<b>Year</b>	<b>Prevalent cases</b>	<b>Numbers in GPRG aged less than 21 years</b>	<b>Prevalence per million (95% CI)</b>
1990	1	248,518	4.0 (0.1 to 22.4)
1991	1	304,836	3.3 (0.1 to 18.3)
1992	1	350,401	2.9 (0.1 to 15.9)
1993	5	376,180	13.3 (4.3 to 31.0)
1994	5	406,351	12.3 (4.0 to 28.7)
1995	6	434,286	13.8 (5.1 to 30.1)
1996	6	524,798	11.4 (4.2 to 24.9)
1997	6	605,201	9.9 (3.6 to 21.6)
1998	6	708,142	8.5 (3.1 to 18.4)
1999	7	850,823	8.2 (3.3 to 17.0)
2000	6	946,889	6.3 (2.3 to 13.8)
2001	6	1,016,667	5.9 (2.2 to 12.9)
2002	7	1,075,286	6.5 (2.6 to 13.4)
2003	8	1,104,342	7.2 (3.1 to 14.3)
2004	10	1,133,156	8.8 (4.2 to 16.2)
2005	8	1,153,294	6.9 (3.0 to 13.7)
2006	6	1,176,419	5.1 (1.9 to 11.1)
2007	7	1,188,555	5.9 (2.4 to 12.1)
2008	8	1,184,231	6.8 (2.9 to 13.3)
2009	3	1,175,793	2.6 (0.5 to 7.5)
2010	3	1,167,683	2.6 (0.5 to 7.5)

**Table 3**  
**Prescriptions for the specific management of patients with juvenile Huntington's disease**

<b>Therapeutic category</b>	<b>Number of patients having products prescribed (regular prescriptions<sup>a</sup>)</b>
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

<sup>a</sup>Regular prescriptions are those prescribed to a particular patient more than twice



**Juvenile Huntington's disease:  
a population-based study using the General Practice  
Research Database**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002085.R1
Article Type:	Research
Date Submitted by the Author:	16-Nov-2012
Complete List of Authors:	Douglas, Ian; London School of Hygiene and Tropical Medicine, Epidemiology Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases Wexler, Nancy; Columbia University, Neurology and Psychiatry
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# Juvenile Huntington's disease: a population-based study using the General Practice Research Database

Ian Douglas PhD<sup>1</sup>, Stephen Evans MSc<sup>1</sup>, Michael D Rawlins FMedSci<sup>1</sup>, Liam Smeeth MD<sup>1</sup>, Sarah J Tabrizi MD<sup>2</sup>, and Nancy S Wexler PhD<sup>3</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT; <sup>2</sup>University College London, Institute of Neurology, Queens Square, London WC1N 3BG; <sup>3</sup>Columbia University, 1051 Riverside Drive, Unit 6, PI Annex 371, New York, NY 10032; and Hereditary Disease Foundation, 3960 Broadway, New York, NY 10032.

Correspondence: Michael Rawlins, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT. email: [michael.rawlins@nice.org.uk](mailto:michael.rawlins@nice.org.uk)

## Article Summary

### Article focus

This population-based study, using primary care data, was designed to:

- estimate the incidence and prevalence of juvenile Huntington's disease (HD) in the UK; and
- examine the range of pharmaceutical treatments used in its management.

### Key messages

- The minimum estimate of the incidence of juvenile HD is 0.70 (0.36 to 1.22) per million patient-years
- The minimal estimate of the prevalence of juvenile HD is 6.77 (5.60 to 8.12) per million patient-years
- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

### Strengths and limitations

- The study, based on primary care data for the UK as a whole, provides the first population-based estimates of incidence and prevalence of juvenile HD
- The study indicates that the pharmacological treatments used for the management of juvenile HD are used in the absence of a formal evidence base.
- The study's major limitation is the extent to which, because of the stigma associated with the condition, primary care physicians are reluctant to include an HD diagnosis in patients' records.



## Summary

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder. There are no population-based estimates of either its incidence or prevalence in any population in the world. The present study was undertaken to estimate the frequency of juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

*Method:* The records of individuals under the age of 21 who had recorded diagnoses of HD were retrieved from the General Practice Research Database from 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

*Results:* 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum population-based estimate of incidence is 0.70 (95% CI 0.36 to 1.22) per million-patient years. The minimum estimate of prevalence is 6.77 per million (95% 5.60 to 8.12) per million patient-years. Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

*Conclusions:* In the UK, juvenile HD is an extremely rare and complex disorder. The prescribing data demonstrate that the clinical management of juvenile HD is undertaken with no formal evidence base for the efficacy or safety of the treatments used. Research into the safety and efficacy of appropriate therapies is urgently required to offset the haphazard nature of prescribing. Multinational collaboration will be necessary to enrol sufficient numbers. Exploratory studies, though, should begin now.

1  
2  
3  
4  
5  
6  
7  
8 Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder  
9 associated with abnormal movements, psychiatric disturbances and cognitive  
10 decline<sup>1,2</sup>. HD segregates as an autosomal trait located on chromosome  
11 4p16.3. The HD gene encodes the huntingtin protein<sup>2</sup>. The HD abnormality  
12 is an expanded CAG repeat on exon 1 of the HD gene leading to the  
13 corresponding expression of an expanded polyglutamine repeat in the  
14 huntingtin protein. Alleles with 40 or more CAG repeats invariably give rise to  
15 HD provided that individuals live a normal lifespan<sup>1</sup>. Alleles with 60 or more  
16 CAG repeats usually result in the juvenile form of the disease.

17  
18  
19 In adult HD the movement disorder is typically chorea. In juvenile HD the  
20 movement disorder, rather than chorea, is primarily tremor, bradykinesia and  
21 dystonia<sup>3,4,5</sup>. In juvenile HD cerebellar signs, epilepsy, myoclonus and  
22 spasticity may also occur. As in adult HD, psychiatric disturbances and  
23 cognitive decline are also present<sup>4,5</sup>.

24  
25 Although there have been various published estimates of the incidence and  
26 prevalence of adult HD there has been no attempt to estimate the population-  
27 based incidence, or prevalence, of the juvenile form. This study was  
28 designed to obtain an estimate of the incidence and prevalence of juvenile HD  
29 using the General Practice Research Database (GPRD) as well as to examine  
30 the range of specific treatments used in its management.

## 31 32 33 **Methods**

### 34 35 *Study design and setting*

36 The GPRD is a computerised database containing anonymised electronic  
37 patient records from UK primary care. It covers around 6% of the UK  
38 population at any one time and both its unique features, as well as the high  
39 quality of the data contained within it, have been described elsewhere<sup>6</sup>. The  
40 database is now included under the umbrella of the Clinical Practice Research  
41 Datalink that brings together data from across the United Kingdom's National  
42 Health Service.

### 43 44 45 *Participants*

46 The source population was all patients, under 21 years of age, registered with  
47 general practices contributing to the GPRD, between 1990 and 2010. Eligible  
48 cases were defined as any person, under the age of 21 years, with one or  
49 more diagnoses of Huntington's disease or Huntington's chorea in their  
50 medical record. The last date for each record was the earliest of the either the  
51 date of death, the date of patients' de-registration from the practice if still  
52 alive, the date the patient achieved the age of 21 years, the date the practice  
53 left the GPRD, or the end of the observation period (2010). The Read codes  
54 used to identify cases in the database were F134.00 (Huntington's chorea)  
55 and Eu2200 (dementia in Huntington's disease).

### *Biases*

In order to ensure that incident cases were not wrongly identified as prevalent ones, two additional criteria for inclusion as incident cases were applied: 1) they must have been registered with the practice for 12 months or longer by the date the diagnosis was recorded; and 2) they had to have had at least one other recorded contact, with the practice, during the preceding 12 month period.

### *Prescription data*

The medicines prescribed for incident and prevalent patients were also retrieved from the GPRD. Medications commonly prescribed for children and adolescents, and not specific for those with juvenile HD (including antibiotics, antifungal agents, emollients, and routine vaccinations), were not examined further. Specific treatments for the symptoms and signs of jHD were analysed in detail. Those treatments prescribed more than twice in a particular patient were categorised as “regular” treatments.

### *Statistical methods*

Incidence was calculated from the numbers of incident cases (as defined above under biases), within 5-year age-bands, in relation to the total number of patient-years within the same age-band. Prevalence was calculated, for each year during the study period (1990-2010), from the numbers of patients with recorded juvenile HD divided by the total numbers of patients aged less than 21 years during that year. For estimates of both incidence and prevalence binomial 95% confidence intervals were calculated.

## **Results**

### *Main findings: incidence*

There were 12 records (4 females, 8 males) of patients fulfilling the criteria for inclusion as incident cases of juvenile HD. Their ages, at diagnosis, ranged from 5 years to 20 years (median 15 years). The overall incidence was 0.70 (95% confidence intervals 0.36 to 1.22) per million patient-years. The estimates of incidence in 5 year age-bands (Table 1) ranged from 0 (95% confidence interval 0 to 1.1) per million patient-years at age 0 to 4 years, to 1.26 (95% confidence interval 0.46 to 2.74) per million patient-years at aged 15 to 20 years.

Eight of the 12 incident cases had records of potential prodromal diagnoses, suggestive of juvenile HD, up to 3 years before a formal diagnosis of HD was entered into their records. These included sleep disorders (3 cases), psychiatric referrals (2 cases), movement disorders (2 cases) and referral for genetic counselling (1 case). The remaining cases had no obvious prodromal reported diagnoses.

### *Main findings: prevalence*

There were 21 records (8 females, 13 males) of individuals contributing to the database, aged less than 21 years, with a diagnosis of HD. They provided a total of 116 patient years within the database. These 21 prevalent cases included the 12 incident cases. The average annual prevalence of juvenile HD, between 1990 and 2010, was 6.77 per million (95% confidence interval 5.60 to 8.12 per million) but fluctuated year by year (Table 2).

### *Prescription data*

Prescription data for the treatment relevant to the symptoms and signs of juvenile HD among prevalent cases are summarised in Table 3. One patient had no prescriptions recorded during the observation period and 6 were prescribed products for intercurrent conditions (mainly antimicrobial agents, oral contraceptives, antiasthma products and vaccines) which were assumed to be unrelated to HD.

Fourteen patients were prescribed regular treatments apparently for the specific management of their HD symptomatology. Simultaneous prescriptions of more than one therapeutic category were common. The products most commonly prescribed included antidepressants (particularly fluoxetine and citalopram), a wide variety of treatments for motor disorders (including baclofen, levodopa, amantidine and tetrabenazine), hypnotics, antipsychotics (risperidone and olanzepine) and anticonvulsants (especially valproate and clobazam). Because of the small numbers of patients it would be inappropriate to use these data to infer the relative frequencies of the phenotypic variations, in the clinical manifestations of juvenile HD. Nevertheless, the data correspond – at least qualitatively – to the phenotypic patterns observed in reports of juvenile HD<sup>5</sup>.

## **Discussion**

There have been a number of population based studies of the prevalence of HD that have provided information about the proportion of cases with the juvenile form of the condition<sup>7,8</sup>. It is not possible to infer from these reports the prevalence of juvenile HD, because none provide estimates of the relevant population under 21 years of age. The estimates of incidence and prevalence of juvenile HD, reported here, are therefore the first to provide population-based epidemiological data on the frequency of this condition, either in the UK or worldwide. The apparent increase in the incidence of juvenile HD with age, in Table 1, is intuitively appropriate. However, because of the small numbers involved it is impossible to be certain.

Our estimates of both the incidence and prevalence of juvenile HD, almost certainly underestimate the true frequency of juvenile HD. First, it is possible that some general practitioners chose not to record their patients' HD diagnoses for reasons of confidentiality. Secondly, the dates of onset of past diagnoses are not always reliably recorded. Past diagnoses may be recorded either without a date or as occurring at the date of registration. These cases were excluded from our analysis of incidence. Thirdly, we

1  
2  
3 report the dates of recorded diagnoses. Possibly, some patients diagnosed in  
4 adulthood began showing symptoms in childhood or adolescence. These  
5 cases were also excluded. Finally, the strict criteria we applied in defining  
6 incident cases might have resulted in omitting some who should have been  
7 assigned to this category. However, only two prevalent cases were  
8 excluded as incident cases (one aged 12 years and the other aged 19 years)  
9 because their records failed to include any other contact with the practice in  
10 the 12 months prior to the entry of a diagnosis of HD.  
11

12  
13 Extrapolated to the entire UK population our results suggest that at a  
14 minimum, there are 100 children and adolescents living with juvenile HD. Ten  
15 new cases are diagnosed annually.  
16

17  
18 Most of the potential prodromal diagnoses, reported for incident cases, were  
19 typical of the clinical features of juvenile HD, including motor disturbances and  
20 psychiatric problems. It is striking that three patients complained of sleep  
21 disturbances. This has not previously been reported in association with  
22 juvenile HD. Furthermore, hypnotics were prescribed to a significant  
23 proportion of juvenile HD patients.  
24

25  
26 The symptomatology of juvenile HD is complex and causes suffering in all  
27 domains of life. The range of pharmacological products prescribed (Table 3)  
28 for our cohort of people with juvenile HD are similar to that recently reported  
29 by Robertson and colleagues<sup>9</sup>. Most of the treatments for the motor  
30 manifestations of juvenile HD are those shown to be effective in Parkinson's  
31 disease but none have ever been formally assessed in juvenile HD. Even  
32 though a wide range of other therapies are used, often simultaneously, there  
33 are no studies to guide the current trial-and-error "experimental" approach to  
34 the treatment of juvenile HD. No studies of the effectiveness of  
35 antidepressants, antipsychotics or anticonvulsants have ever been done to  
36 assess the effectiveness of these treatments in juvenile HD. In particular, in  
37 view of current anxieties about the potential hazards of using  
38 antidepressants in children<sup>8</sup>, clinical trials of the effectiveness of specific  
39 serotonin re-uptake inhibitors, are especially urgent. The present  
40 investigation also suggests that there is a critical need to assess the  
41 comparative effectiveness of other treatment options in juvenile HD. Because  
42 the numbers of children and adolescents with juvenile HD are small, in any  
43 one country such as the UK, only multinational trials are likely to produce the  
44 most rigorous answers. Small exploratory studies should be initiated  
45 immediately to guide the design of larger trials **as well as provide some early**  
46 **answers.**  
47  
48

49  
50 The humane and supportive care of children and adolescents with HD  
51 requires the availability of appropriate resources to be provided by the UK's  
52 health and social services. These resources are complex and  
53 multidisciplinary. It is incumbent on those planning the provision of such care  
54 that the needs of these young people – and their families – are met.  
55  
56  
57  
58  
59  
60

**Authors**

All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by the other contributors. MDR is the guarantor.

**Source of funding**

The authors are grateful to the Hereditary Disease Foundation and the Huntington's Disease Association for their support for this study. LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

**Conflicts of Interest**

None of the authors have any conflicts of interest to declare.

peer review only

## References

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Annual Review of Medicine* 2012; 63: 1-22.
3. Van Dijk JG, van der Velde EA, Roos RAC, Bruyn GW. Juvenile Huntington's disease. *Human Genetics* 1986; 73: 235-239.
4. Ribai P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Legout A, Dode C, Brice A, Durr A. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology* 2007;64:813-819.
5. Quarrell OWJ, Brewer HM, Squitieri F, Barker RA, Nance MA, Landwehrmeyer GB. *Juvenile Huntington's Disease (and other trinucleotide repeat disorders)*. Oxford University Press: Oxford, 2009.
6. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database. *British Journal of Clinical Pharmacology* 2010; 69:4-14.
7. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington's disease in Northern Ireland. *Journal of Medical Genetics* 1995; 32:5240530
8. Quarrell O, O'Donovan KL, Bandmann O, Strong M. The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. *PLOS Currents* 2012;4:doi10.1371/418606b742ef3
9. Robertson L, Santini H, O'Donovan KL, Squitieri F, Barker R, Rakowicz M, Landwehrmeyer GB, Quarrell O. Current pharmacological management in juvenile Huntington's disease. *PLOS Currents Huntington Disease* 2012-10-30. <http://currents.plos.org/hd/article/current-pharmacological-management-in-juvenile-huntingtons-disease-2/>. (Accessed 30<sup>th</sup> October 2012)
10. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. National Institute for Health and Clinical Excellence: London, 2005. <http://guidance.nice.org.uk/CD28>. (Accessed 30th Oct 2012)

Table 1  
Incidence estimates of juvenile Huntington's disease in UK

Age group (years)	Incident cases	Population (patient-years)	Incidence per million patient-years (95%CI)
0-4	0	4,097,551	0 (0 to 1.1)
5-9	3	4,156,414	0.7 (0.2 to 2.1)
10-14	3	4,115,431	0.7 (0.2 to 2.1)
15-20	6	4,762,455	1.3 (0.5 to 2.7)



**Table 2**  
**Prevalence estimates of juvenile Huntington's disease in the UK**

<b>Year</b>	<b>Prevalent cases</b>	<b>Numbers in GPRG aged less than 21 years</b>	<b>Prevalence per million (95% CI)</b>
1990	1	248,518	4.0 (0.1 to 22.4)
1991	1	304,836	3.28 (0.1 to 18.3)
1992	1	350,401	2.9 (0.1 to 15.9)
1993	5	376,180	13.3 (4.3 to 31.0)
1994	5	406,351	12.3 (4.0 to 28.7)
1995	6	434,286	13.8 (5.1 to 30.1)
1996	6	524,798	11.4 (4.2 to 24.9)
1997	6	605,201	9.9 (3.6 to 21.6)
1998	6	708,142	8.5 (3.1 to 18.4)
1999	7	850,823	8.2 (3.3 to 17.0)
2000	6	946,889	6.3 (2.3 to 13.8)
2001	6	1,016,667	5.9 (2.2 to 12.9)
2002	7	1,075,286	6.5 (2.6 to 13.4)
2003	8	1,104,342	7.2 (3.1 to 14.3)
2004	10	1,133,156	8.8 (4.2 to 16.2)
2005	8	1,153,294	6.9 (3.0 to 13.7)
2006	6	1,176,419	5.1 (1.9 to 11.1)
2007	7	1,188,555	5.9 (2.4 to 12.1)
2008	8	1,184,231	6.8 (2.9 to 13.3)
2009	3	1,175,793	2.6 (0.5 to 7.5)
2010	3	1,167,683	2.6 (0.5 to 7.5)

**Table 3**  
**Prescriptions for the specific management of patients with juvenile Huntington's disease**

<b>Therapeutic category</b>	<b>Number of patients having products prescribed (regular prescriptions<sup>a</sup>)</b>
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

<sup>a</sup>Regular prescriptions are those prescribed to a particular patient more than twice

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# Juvenile Huntington's disease: a population-based study using based on the General Practice Research Database

Ian Douglas PhD<sup>1</sup>, Stephen Evans MSc<sup>1</sup>, Michael D Rawlins FMedSci<sup>1</sup>, Liam Smeeth MD<sup>1</sup>, Sarah J Tabrizi MD<sup>2</sup>, and Nancy S Wexler PhD<sup>3</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT; <sup>2</sup>University College London, Institute of Neurology, Queens Square, London WC1N 3BG; <sup>3</sup>Columbia University, 1051 Riverside Drive, Unit 6, PI Annex 371, New York, NY 10032; and Hereditary Disease Foundation, 3960 Broadway, New York, NY 10032.

Correspondence: Michael Rawlins, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT. email: [michael.rawlins@nice.org.uk](mailto:michael.rawlins@nice.org.uk)

Formatted: Centered

## Article Summary

Formatted: Font: Bold

### Article focus

This population-based study, using primary care data, was designed to:

- estimate the incidence and prevalence of juvenile Huntington's disease (HD) in the UK; and
- examine the range of pharmaceutical treatments used in its management.

### Key messages

- The minimum estimate of the incidence of juvenile HD is 0.70 (0.36 to 1.22) per million patient-years
- The minimal estimate of the prevalence of juvenile HD is 6.77 (5.60 to 8.12) per million patient-years
- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

### Strengths and limitations

- The study, based on primary care data for the UK as a whole, provides the first population-based estimates of incidence and prevalence of juvenile HD
- The study indicates that the pharmacological treatments used for the management of juvenile HD are used in the absence of a formal evidence base.
- The study's major limitation is the extent to which, because of the stigma associated with the condition, primary care physicians are reluctant to include an HD diagnosis in patients' records.

Formatted: Centered

## Summary

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder, a unusual condition ~~but there are have been no population-based estimates of either its incidence or prevalence in any population in the world.~~ The present study was undertaken to estimate the frequency of juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

*Method:* ~~The records of individuals under the age of 21 who had recorded diagnoses of HD. Patients with recorded diagnoses of Huntington's disease, under the age of 21 years,~~ were retrieved from the General Practice Research Database ~~from~~ 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

*Results:* 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum population-based estimates of incidence is 0.70 (95% CI 0.36 to 1.22) per million-patient years. ~~The minimum estimate of and prevalence is were 0.70 (95% CI 0.36 to 1.22) per million patient years and 6.77 per million (95% 5.60 to 8.12) per million patient-years (respectively).~~ Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

*Conclusions:* ~~In the UK, juvenile HD is an extremely, indeed, a very rare and complex disorder. The prescribing data demonstrate that the condition and its clinical management of juvenile HD is undertaken with no formal evidence base for the efficacy or safety of the treatments products used. Research into the safety and efficacy of appropriate therapies is urgently required to offset the haphazard nature of prescribing. Future studies of appropriate treatments are urgent but would be likely to require Mmultinational collaboration will be necessary if trials are to enrol sufficient numbers. Exploratory studies, though, should begin now. of patients.~~

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline<sup>1,2</sup>. HD segregates as an autosomal trait located on chromosome 4p16.3. ~~T and~~ the HD gene encodes the huntingtin protein<sup>2</sup>. The HD ~~abnormality~~mutation is an expanded CAG repeat on exon 1 of the HD gene leading to the corresponding expression of an expanded polyglutamine repeat in the huntingtin protein. Alleles with 40 or more CAG repeats invariably give rise to HD provided that individuals live a normal lifespan<sup>1</sup>. Alleles with 60 or more CAG repeats usually result in the juvenile form of the disease.

Comment [MR1]: With great respect to the referees, this sentence is, I think, now correct

In adult HD the movement disorder is typically chorea. In juvenile HD the movement disorder, rather than chorea, is primarily tremor, bradykinesia and dystonia<sup>3,4,5</sup>. In juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present<sup>4,5</sup>.

Although there have been various published estimates of the incidence and prevalence of adult HD there has been no attempt to ~~estimate~~ investigate ~~either~~ the population-based incidence, or prevalence, of the juvenile form. This study was designed to obtain an estimate of the incidence and prevalence of juvenile HD using the ~~General~~General Practice Research Databasebase (GGPRD) as well as to examine the range of specific treatments used in its management.

## Methods

### *Study design and setting*

The GGPRD is a computerised database containing anonymised electronic patient records from UK primary care. It covers around 6% of the UK population at any one time and both its unique features, as well as the high quality of the data contained within it, have been described elsewhere<sup>6</sup>. The database is now included under the umbrella of the Clinical Practice Research Datalink that brings together data from across the United Kingdom's National Health Service.

Formatted: Not Superscript/ subscript

### *Participants*

The source population was all patients, under 21 years of age, registered with general practices contributing to the GGPRD, between 1990 and 2010. Eligible cases were defined as any person, under the age of 21 years, with one or more diagnoses of Huntington's disease or Huntington's chorea in their medical record. The last date for each record was the earliest of the either the date of death, the date of patients' de-registration from the practice if still alive, the date the patient achieved the age of 21 years, the date the practice left the GGPRD, or the end of the observation period (2010). The Read

codes used to identify cases in the database were F134.00 (Huntington's chorea) and Eu2200 (dementia in Huntington's disease).

### *Biases*

In order to ensure that incident cases were not wrongly identified as prevalent ones, two additional criteria for inclusion as incident cases were applied: 1) they ~~must~~ have been registered with the practice for 12 months or longer by the date the diagnosis was recorded; and 2) they had to have had at least one other recorded contact, with the practice, during the preceding 12 month period.

### *Prescription data*

The medicines prescribed for incident and prevalent patients were also retrieved from [the GGPRD](#). Medications commonly prescribed for children and adolescents, and not specific for those with juvenile HD (including antibiotics, antifungal agents, emollients, and routine vaccinations), were not ~~examined~~ ~~analysed~~ further. Specific treatments for the symptoms and signs of jHD were ~~analysed~~ ~~examined~~ in detail. Those treatments prescribed more than twice in a particular patient were categorised as "regular" treatments.

### *Statistical methods*

Incidence was calculated from the numbers of incident cases (as defined above [under biases](#)), within 5-year age-bands, in relation [to](#) the total number of patient-years within the [same](#) age-band. Prevalence was calculated, for each year during the study period (1990-2010), from the numbers of patients with recorded juvenile HD divided by the total numbers of patients aged less than 21 years during that year. For estimates of both incidence and prevalence binomial 95% confidence intervals were calculated.

## **Results**

### *Main findings: incidence*

There were 12 records (4 females, 8 males) of patients fulfilling the criteria for inclusion as incident cases of juvenile HD. ~~A~~ ~~Their~~ ~~ages~~ ~~at~~ ~~diagnosis~~ ~~t~~ ~~Their~~ ~~ages~~ ~~at~~ ~~diagnosis~~ ~~ages~~ ranged from 5 years to 20 years (median 15 years). The overall incidence was 0.70 (95% confidence intervals 0.36 to 1.22) per million patient-years. The estimates of incidence in 5 year age-bands (Table 1) ranged from 0 (95% confidence interval 0 to 1.1) per million patient-years at age 0 to 4 years, to 1.26 (95% confidence interval 0.46 to 2.74) per million patient-years at aged 15 to 20 years.

Eight of the 12 incident cases had records of potential prodromal diagnoses, suggestive of juvenile HD, up to 3 years before a formal diagnosis [of HD](#) was entered into their records. These included sleep disorders (3 cases), psychiatric referrals (2 cases), movement disorders (2 cases) and referral for genetic counselling (1 case). The remaining cases had no obvious prodromal reported diagnoses.

### Main findings: prevalence

There were 21 records (8 females, 13 males) of individuals contributing to the database, aged less than 21 years, with a diagnosis of HD. They provided a total of 116 patient years within the database. [These 21 prevalent cases included the 12 incident cases.](#) The average annual prevalence of juvenile HD, between 1990 and 2010, was 6.77 per million (95% confidence interval 5.60 to 8.12 per million) but fluctuated year ~~by~~ year (Table 2).

### Prescription data

Prescription data for the treatment relevant to the symptoms and signs of juvenile HD among prevalent cases are summarised in Table 3. One patient had no prescriptions recorded during the observation period and 6 were prescribed products for intercurrent conditions (mainly antimicrobial agents, oral contraceptives, antiasthma products and vaccines) which were assumed to be unrelated to HD.

Fourteen patients were prescribed regular treatments apparently for the specific management of their HD symptomatology (~~Table 3~~). ~~Simultaneous~~ ~~p~~Prescriptions of more than one therapeutic category ~~were~~ common. The products most commonly prescribed included antidepressants (particularly fluoxetine and citalopram), a wide variety of treatments for motor disorders (including baclofen, levodopa, amantidine and tetrabenazine), hypnotics, antipsychotics (risperidone and olanzepine) and anticonvulsants (especially valproate and clobazam). Because of the small numbers of patients it would be inappropriate to use these data to infer the relative frequencies of the phenotypic variations, in the clinical manifestations of juvenile HD. Nevertheless, the data correspond – at least qualitatively – ~~to~~with the phenotypic patterns observed in reports of juvenile HD<sup>5</sup>.

### Discussion

~~There have been a number of many population based studies of the prevalence of HD that have provided information about the proportion of cases with the juvenile form of the condition<sup>7,8</sup>. It is not possible to infer from these reports the prevalence of juvenile HD, because none provide estimates of the relevant population under 21 years of age.~~ The estimates of incidence and prevalence of juvenile HD, reported here, are ~~therefore we believe~~ the first to provide population-based epidemiological data on the frequency of this condition, ~~both~~ either ~~in for~~ the UK or, ~~indeed, for anywhere else in the world wide.~~ – The apparent increase in the incidence of juvenile HD ~~with age~~, in Table 1, is intuitively appropriate. ~~However, but~~ because of the small numbers involved it is impossible to be certain.

Our estimates of both the incidence and prevalence of juvenile HD ~~are~~, ~~however~~, almost certainly underestimate ~~of~~ the true frequency of juvenile HD. First, it is possible that some general practitioners ~~chose not~~failed to record



1  
2  
3  
4  
5  
6 their patients' HD diagnoses for reasons of confidentiality<sup>7</sup>. Secondly, the  
7 dates of onset of past diagnoses are not always be reliably recorded, ~~and in~~  
8 ~~Sometimes instances p~~ Past diagnoses may be recorded either without a  
9 date or as occurring at the date of registration. ~~These Such~~ cases ~~were~~  
10 ~~excluded from our would have been excluded from~~ our analysis of incidence.  
11 ~~Thirdly, we report the dates of recorded diagnoses. and it is p~~ Possibly, ~~that~~  
12 ~~some patients diagnosed in adulthood began showing started to develop~~  
13 ~~symptoms in childhood or adolescence. These cases were also excluded.~~  
14 ~~Finally~~ Thirdly, the strict criteria we applied in defining incident cases might  
15 have resulted in omitting some who should have been assigned to this  
16 category. However, only two prevalent cases were excluded as incident  
17 cases (one aged 12 years and the other aged 19 years) because their records  
18 failed to include any other contact with the practice in the 12 months prior to  
19 the entry of a diagnosis of HD.

20  
21 ~~Our results, e~~ Extrapolated to the ~~entire UK whole~~ population, ~~would our results~~  
22 suggests that, ~~in the UK, there are~~ at a minimum, ~~there are~~ at least around  
23 100 children and adolescents living with ~~with~~ juvenile HD. ~~We also estimate~~  
24 ~~that and that 10. Ten~~ new cases ~~are diagnosed present~~ annually.

Formatted: Font: Italic

Formatted: Font: Not Italic

Formatted: Font: Italic

25  
26 Most of the potential prodromal diagnoses, reported for incident cases, were  
27 typical of the clinical features of juvenile HD, including motor disturbances and  
28 psychiatric problems. It is striking, ~~however,~~ that ~~in~~ three ~~instances~~ patients  
29 complained of sleep disturbances. This has not previously, ~~to our knowledge,~~  
30 been reported in association with juvenile HD. Furthermore, hypnotics were  
31 prescribed to a significant proportion of ~~juvenile HD prevalent~~ patients, ~~with~~  
32 ~~diagnosed juvenile HD.~~

33  
34 The symptomatology of juvenile HD is complex and causes suffering in  
35 ~~all most every~~ domains ~~of the quality~~ of life. ~~The range of pharmacological~~  
36 ~~products prescribed (Table 3) for our cohort of people with juvenile HD are~~  
37 ~~similar to that recently reported by Robertson and colleagues<sup>9</sup>.~~ Most of the  
38 treatments for the motor manifestations of juvenile HD are those shown to be  
39 effective in Parkinson's disease but none have ever been formally assessed  
40 in juvenile HD. Even though a wide range of other therapies are used,  
41 ~~often sometimes~~ simultaneously, there are no studies to guide the current trial-  
42 and-error "experimental" approach to the treatment of juvenile HD. No  
43 studies, ~~for example,~~ of the effectiveness of antidepressants, antipsychotics or  
44 anticonvulsants have ever been ~~specifically~~ done ~~to assess the effectiveness of~~  
45 ~~these treatments~~ in ~~the~~ juvenile ~~form of~~ HD. In particular, ~~and~~ in view of  
46 current anxieties about the ~~potential hazards of use using~~ antidepressants  
47 ~~generally~~ in children<sup>8</sup>, clinical trials of the effectiveness of specific serotonin  
48 re-uptake inhibitors, are especially urgent. The present investigation also  
49 suggests that there is ~~an~~ **critical** need to assess the comparative effectiveness  
50 of other treatment options in juvenile HD. Because the numbers of children  
51 and adolescents with juvenile HD are small, in any one country such as the  
52 UK, only multinational trials are likely to produce the most ~~rigorous expeditious~~  
53 answers. ~~S but, in the meantime,~~ small exploratory studies ~~should be~~  
54 ~~initiated immediately to would~~ guide the design of larger trials ~~as well as~~  
55 ~~provide some early answers.~~

1  
2  
3  
4  
5  
6  
7 The humane and supportive care of children and adolescents with HD  
8 requires the availability of appropriate resources, ~~for supportive care~~, to be  
9 provided by the UK's health and social services. These resources are  
10 complex and multidisciplinary. It is incumbent on those planning the provision  
11 of such care that the needs of these young people – and ~~of~~ their families – are  
12 met.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Authors**

All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by the other contributors. MDR is the guarantor.

**Source of funding**

The authors are grateful to the Hereditary Disease Foundation and the Huntington's Disease Association for their support for this study. LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

**Conflicts of Interest**

None of the authors have any conflicts of interest to declare.

## References

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Annual Review of Medicine* 2012; 63: 1-22.
3. Van Dijk JG, van der Velde EA, Roos RAC, Bruyn GW. Juvenile Huntington's disease. *Human Genetics* 1986; 73: 235-239.
4. Ribai P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Legout A, Dode C, Brice A, Durr A. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology* 2007;64:813-819.
5. Quarrell OWJ, Brewer HM, Squitieri F, Barker RA, Nance MA, Landwehrmeyer GB. *Juvenile Huntington's Disease (and other trinucleotide repeat disorders)*. Oxford University Press: Oxford, 2009.
6. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database. *British Journal of Clinical Pharmacology* 2010; 69:4-14.
7. Morrison PJ, Johnston WP, Nevin NC. [The epidemiology of Huntington's disease in Northern Ireland. \*Journal of Medical Genetics\* 1995; 32:5240530](#)
8. Quarrell O, O'Donovan KL, Bandmann O, Strong M. [The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. \*PLOS Currents\* 2012;4:doi10.1371/418606b742ef3](#)
9. Robertson L, Santini H, O'Donovan KL, Squitieri F, Barker R, Rakowicz M, Landwehrmeyer GB, Quarrell O. [Current pharmacological management in juvenile Huntington's disease. \*PLOS Currents Huntington Disease\* 2012-10-30. <http://currents.plos.org/hd/article/current-pharmacological-management-in-juvenile-huntingtons-disease-2/>. \(Accessed 30<sup>th</sup> October 2012\)](#)
7. ~~Evans S, Ian Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *Lancet* (submitted for publication).~~
108. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. National Institute for Health and Clinical Excellence: London, 2005. <http://guidance.nice.org.uk/CD28>. (Accessed 30<sup>th</sup> Oct 4<sup>th</sup> May 2012)

Formatted: Superscript

**Table 1**  
**Incidence estimates of juvenile Huntington's disease in UK**

<b>Age group (years)</b>	<b>Incident cases</b>	<b>Population (patient-years)</b>	<b>Incidence per million patient-years (95%CI)</b>
0-4	0	4,097,551	0 (0 to 1.1)
5-9	3	4,156,414	0.7 (0.2 to 2.1)
10-14	3	4,115,431	0.7 (0.2 to 2.1)
15-20	6	4,762,455	1.3 (0.5 to 2.7)

**Table 2**  
**Prevalence estimates of juvenile Huntington's disease in the UK**

Year	Prevalent cases	Numbers in GPRG aged less than 21 years	Prevalence per million (95% CI)
1990	1	248,518	4.0 (0.1 to 22.4)
1991	1	304,836	3.28 (0.1 to 18.3)
1992	1	350,401	2.9 (0.1 to 15.9)
1993	5	376,180	13.3 (4.3 to 31.0)
1994	5	406,351	12.3 (4.0 to 28.7)
1995	6	434,286	13.8 (5.1 to 30.1)
1996	6	524,798	11.4 (4.2 to 24.9)
1997	6	605,201	9.9 (3.6 to 21.6)
1998	6	708,142	8.5 (3.1 to 18.4)
1999	7	850,823	8.2 (3.3 to 17.0)
2000	6	946,889	6.3 (2.3 to 13.8)
2001	6	1,016,667	5.9 (2.2 to 12.9)
2002	7	1,075,286	6.5 (2.6 to 13.4)
2003	8	1,104,342	7.2 (3.1 to 14.3)
2004	10	1,133,156	8.8 (4.2 to 16.2)
2005	8	1,153,294	6.9 (3.0 to 13.7)
2006	6	1,176,419	5.1 (1.9 to 11.1)
2007	7	1,188,555	5.9 (2.4 to 12.1)
2008	8	1,184,231	6.8 (2.9 to 13.3)
2009	3	1,175,793	2.6 (0.5 to 7.5)
2010	3	1,167,683	2.6 (0.5 to 7.5)

**Table 3**  
**Prescriptions for the specific management of patients with juvenile Huntington's disease**

<b>Therapeutic category</b>	<b>Number of patients having products prescribed (regular prescriptions<sup>a</sup>)</b>
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

<sup>a</sup>Regular prescriptions are those prescribed to a particular patient more than twice



**Juvenile Huntington's disease:  
a population-based study using the General Practice  
Research Database**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002085.R2
Article Type:	Research
Date Submitted by the Author:	05-Dec-2012
Complete List of Authors:	Douglas, Ian; London School of Hygiene and Tropical Medicine, Epidemiology Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases Wexler, Nancy; Columbia University, Neurology and Psychiatry
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Neurology, Genetics and genomics
Keywords:	Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS

SCHOLARONE™  
Manuscripts



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# Juvenile Huntington's disease: a population-based study using the General Practice Research Database

Ian Douglas PhD<sup>1</sup>, Stephen Evans MSc<sup>1</sup>, Michael D Rawlins FMedSci<sup>1</sup>, Liam Smeeth MD<sup>1</sup>, Sarah J Tabrizi MD<sup>2</sup>, and Nancy S Wexler PhD<sup>3</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT; <sup>2</sup>University College London, Institute of Neurology, Queens Square, London WC1N 3BG; <sup>3</sup>Columbia University, 1051 Riverside Drive, Unit 6, PI Annex 371, New York, NY 10032; and Hereditary Disease Foundation, 3960 Broadway, New York, NY 10032.

Correspondence: Michael Rawlins, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT. email: [michael.rawlins@nice.org.uk](mailto:michael.rawlins@nice.org.uk)

## Article Summary

### Article focus

This population-based study, using primary care data, was designed to:

- estimate the incidence and prevalence of juvenile Huntington's disease (HD) in the UK; and
- examine the range of pharmaceutical treatments used in its management.

### Key messages

- The minimum estimate of the incidence of juvenile HD is 0.70 (0.36 to 1.22) per million patient-years
- The minimal estimate of the prevalence of juvenile HD is 6.77 (5.60 to 8.12) per million patient-years
- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

### Strengths and limitations

- The study, based on primary care data for the UK as a whole, provides the first population-based estimates of incidence and prevalence of juvenile HD
- The study indicates that the pharmacological treatments used for the management of juvenile HD are used in the absence of a formal evidence base.
- The study's major limitation is the extent to which, because of the stigma associated with the condition, primary care physicians are reluctant to include an HD diagnosis in patients' records.

## Summary

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder. There are no population-based estimates of either its incidence or prevalence in any population in the world. The present study was undertaken to estimate the frequency of juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

*Method:* The records of individuals under the age of 21 who had recorded diagnoses of HD were retrieved from the General Practice Research Database from 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

*Results:* 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum population-based estimate of incidence is 0.70 (95% CI 0.36 to 1.22) per million-patient years. The minimum estimate of prevalence is 6.77 per million (95% 5.60 to 8.12) per million patient-years. Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

*Conclusions:* In the UK, juvenile HD is an extremely rare and complex disorder. The prescribing data demonstrate that the clinical management of juvenile HD is undertaken with no formal evidence base for the efficacy or safety of the treatments used. Research into the safety and efficacy of appropriate therapies is urgently required to offset the haphazard nature of prescribing. Multinational collaboration will be necessary to enrol sufficient numbers. Exploratory studies, though, should begin now.

1  
2  
3  
4  
5  
6  
7  
8 Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder  
9 associated with abnormal movements, psychiatric disturbances and cognitive  
10 decline<sup>1,2</sup>. HD segregates as an autosomal trait located on chromosome  
11 4p16.3. The HD gene encodes the huntingtin protein<sup>2</sup>. The HD abnormality  
12 is an expanded CAG repeat on exon 1 of the HD gene leading to the  
13 corresponding expression of an expanded polyglutamine repeat in the  
14 huntingtin protein. Alleles with 40 or more CAG repeats invariably give rise to  
15 HD provided that individuals live a normal lifespan<sup>1</sup>.  
16

17  
18 The juvenile form of HD is characterised by onset in childhood or  
19 adolescence. Alleles with 60 or more CAG repeats usually result in the  
20 juvenile HD although it may occur in patients with less than 60 repeats. In  
21 adult HD the movement disorder is typically chorea. In juvenile HD the  
22 movement disorder, rather than chorea, is primarily tremor, bradykinesia and  
23 dystonia<sup>3,4,5</sup>. In juvenile HD cerebellar signs, epilepsy, myoclonus and  
24 spasticity may also occur. As in adult HD, psychiatric disturbances and  
25 cognitive decline are also present<sup>4,5</sup> but seizures are very unusual.  
26

27  
28 Although there have been various published estimates of the incidence and  
29 prevalence of adult HD there has been no attempt to estimate the population-  
30 based incidence, or prevalence, of the juvenile form. This study was  
31 designed to obtain an estimate of the incidence and prevalence of juvenile HD  
32 using the General Practice Research Database (GPRD) as well as to examine  
33 the range of specific treatments used in its management.  
34

## 35 36 **Methods**

### 37 38 *Study design and setting*

39 The GPRD is a computerised database containing anonymised electronic  
40 patient records from UK primary care. It covers around 6% of the UK  
41 population at any one time and both its unique features, as well as the high  
42 quality of the data contained within it, have been described elsewhere<sup>6</sup>. The  
43 database is now included under the umbrella of the Clinical Practice Research  
44 Datalink that brings together data from across the United Kingdom's National  
45 Health Service.  
46

### 47 48 *Participants*

49 For the purposes of this study juvenile HD was defined as onset before the  
50 age of 21 years. The source population was therefore all patients, under 21  
51 years of age, registered with general practices contributing to the GPRD,  
52 between 1990 and 2010. Eligible cases were defined as any person, under  
53 the age of 21 years, with one or more diagnoses of Huntington's disease or  
54 Huntington's chorea in their medical record. The last date for each record was  
55 the earliest of the either the date of death, the date of patients' de-registration  
56 from the practice if still alive, the date the patient achieved the age of 21  
57  
58  
59  
60

1  
2  
3 years, the date the practice left the GPRD, or the end of the observation  
4 period (2010). The Read codes used to identify cases in the database were  
5 F134.00 (Huntington's chorea) and Eu2200 (dementia in Huntington's  
6 disease).  
7  
8  
9

### 10 *Biases*

11 In order to ensure that incident cases were not wrongly identified as prevalent  
12 ones, two additional criteria for inclusion as incident cases were applied: 1)  
13 they must have been registered with the practice for 12 months or longer by  
14 the date the diagnosis was recorded; and 2) they had to have had at least one  
15 other recorded contact, with the practice, during the preceding 12 month  
16 period.  
17  
18

### 19 *Prescription data*

20 The medicines prescribed for incident and prevalent patients were also  
21 retrieved from the GPRD. Medications commonly prescribed for children and  
22 adolescents, and not specific for those with juvenile HD (including antibiotics,  
23 antifungal agents, emollients, and routine vaccinations), were not examined  
24 further. Specific treatments for the symptoms and signs of jHD were  
25 analysed in detail. Those treatments prescribed more than twice in a  
26 particular patient were categorised as "regular" treatments.  
27  
28

### 29 *Statistical methods*

30 Incidence was calculated from the numbers of incident cases (as defined  
31 above under biases), within 5-year age-bands, in relation to the total number  
32 of patient-years within the same age-band. Prevalence was calculated, for  
33 each year during the study period (1990-2010), from the numbers of patients  
34 with recorded juvenile HD divided by the total numbers of patients aged less  
35 than 21 years during that year. For estimates of both incidence and  
36 prevalence binomial 95% confidence intervals were calculated.  
37  
38

## 39 **Results**

### 40 *Main findings: incidence*

41 There were 12 records (4 females, 8 males) of patients fulfilling the criteria for  
42 inclusion as incident cases of juvenile HD. Their ages, at diagnosis, ranged  
43 from 5 years to 20 years (median 15 years). The overall incidence was 0.70  
44 (95% confidence intervals 0.36 to 1.22) per million patient-years. The  
45 estimates of incidence in 5 year age-bands (Table 1) ranged from 0  
46 (95% confidence interval 0 to 1.1) per million patient-years at age 0 to 4  
47 years, to 1.26 (95% confidence interval 0.46 to 2.74) per million patient-years  
48 at aged 15 to 20 years.  
49  
50  
51  
52

53 Eight of the 12 incident cases had records of potential prodromal diagnoses,  
54 suggestive of juvenile HD, up to 3 years before a formal diagnosis of HD was  
55 entered into their records. These included sleep disorders (3 cases),  
56 psychiatric referrals (2 cases), movement disorders (2 cases) and referral for  
57  
58  
59  
60

1  
2  
3 genetic counselling (1 case). The remaining cases had no obvious prodromal  
4 reported diagnoses.  
5  
6  
7

### 8 *Main findings: prevalence*

9  
10 There were 21 records (8 females, 13 males) of individuals contributing to the  
11 database, aged less than 21 years, with a diagnosis of HD. They provided a  
12 total of 116 patient years within the database. These 21 prevalent cases  
13 included the 12 incident cases. The average annual prevalence of juvenile  
14 HD, between 1990 and 2010, was 6.77 per million (95% confidence interval  
15 5.60 to 8.12 per million) but fluctuated year by year (Table 2).  
16

### 17 *Prescription data*

18 Prescription data for the treatment relevant to the symptoms and signs of  
19 juvenile HD among prevalent cases are summarised in Table 3. One patient  
20 had no prescriptions recorded during the observation period and 6 were  
21 prescribed products for intercurrent conditions (mainly antimicrobial agents,  
22 oral contraceptives, antiasthma products and vaccines) which were assumed  
23 to be unrelated to HD.  
24  
25

26  
27 Fourteen patients were prescribed regular treatments apparently for the  
28 specific management of their HD symptomatology. Simultaneous prescriptions  
29 of more than one therapeutic category were common. The products most  
30 commonly prescribed included antidepressants (particularly fluoxetine and  
31 citalopram), a wide variety of treatments for motor disorders (including  
32 baclofen, levodopa, amantidine and tetrabenazine), hypnotics, antipsychotics  
33 (risperidone and olanzepine) and anticonvulsants (especially valproate and  
34 clobazam). Because of the small numbers of patients it would be  
35 inappropriate to use these data to infer the relative frequencies of the  
36 phenotypic variations, in the clinical manifestations of juvenile HD.  
37 Nevertheless, the data correspond – at least qualitatively – to the phenotypic  
38 patterns observed in reports of juvenile HD<sup>5</sup>.  
39  
40

## 41 **Discussion**

42  
43 There have been a number of population based studies of the prevalence of  
44 HD that have provided information about the proportion of cases with the  
45 juvenile form of the condition<sup>7,8</sup>. It is not possible to infer from these reports  
46 the prevalence of juvenile HD, because none provide estimates of the  
47 relevant population under 21 years of age. The estimates of incidence and  
48 prevalence of juvenile HD, reported here, are therefore the first to provide  
49 population-based epidemiological data on the frequency of this condition,  
50 either in the UK or worldwide. The apparent increase in the incidence of  
51 juvenile HD with age, in Table 1, is intuitively appropriate. However, because  
52 of the small numbers involved it is impossible to be certain.  
53  
54

55  
56 Our estimates of both the incidence and prevalence of juvenile HD, almost  
57 certainly underestimate the true frequency of juvenile HD. First, it is possible  
58  
59  
60

1  
2  
3 that some general practitioners chose not to record their patients' HD  
4 diagnoses for reasons of confidentiality. Secondly, the dates of onset of past  
5 diagnoses are not always be reliably recorded. Past diagnoses may be  
6 recorded either without a date or as occurring at the date of registration.  
7 These cases were excluded from our our analysis of incidence. Thirdly, we  
8 report the dates of recorded diagnoses. Possibly, some patients diagnosed in  
9 adulthood began showing symptoms in childhood or adolescence These  
10 cases were also excluded. Finally, the strict criteria we applied in defining  
11 incident cases might have resulted in omitting some who should have been  
12 assigned to this category. However, only two prevalent cases were  
13 excluded as incident cases (one aged 12 years and the other aged 19 years)  
14 because their records failed to include any other contact with the practice in  
15 the 12 months prior to the entry of a diagnosis of HD.  
16  
17

18  
19 Extrapolated to the entire UK population our results suggest that at a  
20 minimum, there are 100 children and adolescents living with juvenile HD. This  
21 does not of course include patients, over the age of 20 years, during the  
22 period of the study, who were originally diagnosed as juvenile HD. Again,  
23 extrapolating to the UK as a whole, we estimate that 10 new cases are  
24 diagnosed annually.  
25

26  
27 Most of the potential prodromal diagnoses, reported for incident cases, were  
28 typical of the clinical features of juvenile HD, including motor disturbances and  
29 psychiatric problems. It is striking that three patients complained of sleep  
30 disturbances. This has not previously been reported in association with  
31 juvenile HD. Furthermore, hypnotics were prescribed to a significant  
32 proportion of juvenile HD patients.  
33

34  
35 The symptomatology of juvenile HD is complex and causes suffering in all  
36 domains of life. The range of pharmacological products prescribed (Table 3)  
37 for our cohort of people with juvenile HD are similar to that recently reported  
38 by Robertson and colleagues<sup>9</sup>. Most of the treatments for the motor  
39 manifestations of juvenile HD are those shown to be effective in Parkinson's  
40 disease but none have ever been formally assessed in juvenile HD. Even  
41 though a wide range of other therapies are used, often simultaneously, there  
42 are no studies to guide the current trial-and-error "experimental" approach to  
43 the treatment of juvenile HD. No studies of the effectiveness of  
44 antidepressants, antipsychotics or anticonvulsants have ever been done to  
45 assess the effectiveness of these treatments in juvenile HD. In particular, in  
46 view of current anxieties about the potential hazards of using  
47 antidepressants in children<sup>8</sup>, clinical trials of the effectiveness of specific  
48 serotonin re-uptake inhibitors, are especially urgent. The present  
49 investigation also suggests that there is a critical need to assess the  
50 comparative effectiveness of other treatment options in juvenile HD. Because  
51 the numbers of children and adolescents with juvenile HD are small, in any  
52 one country such as the UK, only multinational trials are likely to produce the  
53 most rigorous answers. Small exploratory studies should be initiated  
54 immediately to guide the design of larger trials **as well as provide some early**  
55 **answers.**  
56  
57  
58  
59  
60

1  
2  
3  
4 The humane and supportive care of children and adolescents with HD  
5 requires the availability of appropriate resources to be provided by the UK's  
6 health and social services. These resources are complex and  
7 multidisciplinary. It is incumbent on those planning the provision of such care  
8 that the needs of these young people – and their families – are met.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



**Authors**

All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by the other contributors. MDR is the guarantor.

**Source of funding**

The authors are grateful to the Hereditary Disease Foundation and the Huntington's Disease Association for their support for this study. LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

**Conflicts of Interest**

None of the authors have any conflicts of interest to declare.

## References

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Annual Review of Medicine* 2012; 63: 1-22.
3. Van Dijk JG, van der Velde EA, Roos RAC, Bruyn GW. Juvenile Huntington's disease. *Human Genetics* 1986; 73: 235-239.
4. Ribai P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Legout A, Dode C, Brice A, Durr A. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology* 2007;64:813-819.
5. Quarrell OWJ, Brewer HM, Squitieri F, Barker RA, Nance MA, Landwehrmeyer GB. *Juvenile Huntington's Disease (and other trinucleotide repeat disorders)*. Oxford University Press: Oxford, 2009.
6. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database. *British Journal of Clinical Pharmacology* 2010; 69:4-14.
7. Morrison PJ, Johnston WP, Nevin NC. The epidemiology of Huntington's disease in Northern Ireland. *Journal of Medical Genetics* 1995; 32:5240530
8. Quarrell O, O'Donovan KL, Bandmann O, Strong M. The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. *PLOS Currents* 2012;4:doi10.1371/418606b742ef3
9. Robertson L, Santini H, O'Donovan KL, Squitieri F, Barker R, Rakowicz M, Landwehrmeyer GB, Quarrell O. Current pharmacological management in juvenile Huntington's disease. *PLOS Currents Huntington Disease* 2012-10-30. <http://currents.plos.org/hd/article/current-pharmacological-management-in-juvenile-huntingtons-disease-2/>. (Accessed 30<sup>th</sup> October 2012)
10. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. National Institute for Health and Clinical Excellence: London, 2005. <http://guidance.nice.org.uk/CD28>. (Accessed 30th Oct 2012)

**Table 1**  
**Incidence estimates of juvenile Huntington's disease in UK**

<b>Age group (years)</b>	<b>Incident cases</b>	<b>Population (patient-years)</b>	<b>Incidence per million patient-years (95%CI)</b>
0-4	0	4,097,551	0 (0 to 1.1)
5-9	3	4,156,414	0.7 (0.2 to 2.1)
10-14	3	4,115,431	0.7 (0.2 to 2.1)
15-20	6	4,762,455	1.3 (0.5 to 2.7)

**Table 2**  
**Prevalence estimates of juvenile Huntington's disease in the UK**

<b>Year</b>	<b>Prevalent cases</b>	<b>Numbers in GPRG aged less than 21 years</b>	<b>Prevalence per million (95% CI)</b>
1990	1	248,518	4.0 (0.1 to 22.4)
1991	1	304,836	3.28 (0.1 to 18.3)
1992	1	350,401	2.9 (0.1 to 15.9)
1993	5	376,180	13.3 (4.3 to 31.0)
1994	5	406,351	12.3 (4.0 to 28.7)
1995	6	434,286	13.8 (5.1 to 30.1)
1996	6	524,798	11.4 (4.2 to 24.9)
1997	6	605,201	9.9 (3.6 to 21.6)
1998	6	708,142	8.5 (3.1 to 18.4)
1999	7	850,823	8.2 (3.3 to 17.0)
2000	6	946,889	6.3 (2.3 to 13.8)
2001	6	1,016,667	5.9 (2.2 to 12.9)
2002	7	1,075,286	6.5 (2.6 to 13.4)
2003	8	1,104,342	7.2 (3.1 to 14.3)
2004	10	1,133,156	8.8 (4.2 to 16.2)
2005	8	1,153,294	6.9 (3.0 to 13.7)
2006	6	1,176,419	5.1 (1.9 to 11.1)
2007	7	1,188,555	5.9 (2.4 to 12.1)
2008	8	1,184,231	6.8 (2.9 to 13.3)
2009	3	1,175,793	2.6 (0.5 to 7.5)
2010	3	1,167,683	2.6 (0.5 to 7.5)

**Table 3**  
**Prescriptions for the specific management of patients with juvenile Huntington's disease**

<b>Therapeutic category</b>	<b>Number of patients having products prescribed (regular prescriptions<sup>a</sup>)</b>
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

<sup>a</sup>Regular prescriptions are those prescribed to a particular patient more than twice

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# Juvenile Huntington's disease: a population-based study using based on the General Practice Research Database

Ian Douglas PhD<sup>1</sup>, Stephen Evans MSc<sup>1</sup>, Michael D Rawlins FMedSci<sup>1</sup>, Liam Smeeth MD<sup>1</sup>, Sarah J Tabrizi MD<sup>2</sup>, and Nancy S Wexler PhD<sup>3</sup>

<sup>1</sup>London School of Hygiene and Tropical Medicine, University of London, Keppel St, London WC1E 7HT; <sup>2</sup>University College London, Institute of Neurology, Queens Square, London WC1N 3BG; <sup>3</sup>Columbia University, 1051 Riverside Drive, Unit 6, PI Annex 371, New York, NY 10032; and Hereditary Disease Foundation, 3960 Broadway, New York, NY 10032.

Correspondence: Michael Rawlins, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT. email: [michael.rawlins@nice.org.uk](mailto:michael.rawlins@nice.org.uk)

Formatted: Centered

## Article Summary

Formatted: Font: Bold

### Article focus

This population-based study, using primary care data, was designed to:

- estimate the incidence and prevalence of juvenile Huntington's disease (HD) in the UK; and
- examine the range of pharmaceutical treatments used in its management.

### Key messages

- The minimum estimate of the incidence of juvenile HD is 0.70 (0.36 to 1.22) per million patient-years
- The minimal estimate of the prevalence of juvenile HD is 6.77 (5.60 to 8.12) per million patient-years
- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

### Strengths and limitations

- The study, based on primary care data for the UK as a whole, provides the first population-based estimates of incidence and prevalence of juvenile HD
- The study indicates that the pharmacological treatments used for the management of juvenile HD are used in the absence of a formal evidence base.
- The study's major limitation is the extent to which, because of the stigma associated with the condition, primary care physicians are reluctant to include an HD diagnosis in patients' records.

Formatted: Centered

## Summary

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder, a unusual condition ~~but there are have been no population-based estimates of either its incidence or prevalence in any population in the world.~~ The present study was undertaken to estimate the frequency of juvenile HD in the UK and to examine the range of pharmacological treatments used in its management.

*Method:* ~~The records of individuals under the age of 21 who had recorded diagnoses of HD. Patients with recorded diagnoses of Huntington's disease, under the age of 21 years,~~ were retrieved from the General Practice Research Database ~~from~~ 1990 through 2010. From these data estimates of incidence and prevalence were made as well as the specific treatments used in the treatment of its physical and psychological manifestations.

*Results:* 12 incident and 21 prevalent patients with juvenile HD were identified. The 21 prevalent cases included the 12 incident cases. The minimum population-based estimates of incidence is 0.70 (95% CI 0.36 to 1.22) per million-patient years. ~~The minimum estimate of and prevalence is were 0.70 (95% CI 0.36 to 1.22) per million patient years and 6.77 per million (95% 5.60 to 8.12) per million patient-years (respectively).~~ Patients were most frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormalities.

*Conclusions:* ~~In the UK, juvenile HD is an extremely, indeed, a very rare and complex disorder. The prescribing data demonstrate that the condition and its clinical management of juvenile HD is undertaken with no formal evidence base for the efficacy or safety of the treatments products used. Research into the safety and efficacy of appropriate therapies is urgently required to offset the haphazard nature of prescribing. Future studies of appropriate treatments are urgent but would be likely to require Mmultinational collaboration will be necessary if trials are to enrol sufficient numbers. Exploratory studies, though, should begin now. of patients.~~



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline<sup>1,2</sup>. HD segregates as an autosomal trait located on chromosome 4p16.3. ~~T and~~ the HD gene encodes the huntingtin protein<sup>2</sup>. The HD ~~abnormality~~mutation is an expanded CAG repeat on exon 1 of the HD gene leading to the corresponding expression of an expanded polyglutamine repeat in the huntingtin protein. Alleles with 40 or more CAG repeats invariably give rise to HD provided that individuals live a normal lifespan<sup>1</sup>.

The juvenile form of HD is characterised by onset in childhood or adolescence. Alleles with 60 or more CAG repeats usually result in the juvenile HD form of the disease although it may occur in patients with less than 60 repeats-

In adult HD the movement disorder is typically chorea. In juvenile HD the movement disorder, rather than chorea, is primarily tremor, bradykinesia and dystonia<sup>3,4,5</sup>. In juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present<sup>4,5</sup> but seizures are very unusual.-

Although there have been various published estimates of the incidence and prevalence of adult HD there has been no attempt to estimate investigate either the population-based incidence, or prevalence, of the juvenile form. This study was designed to obtain an estimate of the incidence and prevalence of juvenile HD using the GeneralGeneral Practice Research Databasebase (GGPRD) as well as to examine the range of specific treatments used in its management.

## Methods

### *Study design and setting*

The GGPRD is a computerised database containing anonymised electronic patient records from UK primary care. It covers around 6% of the UK population at any one time and both its unique features, as well as the high quality of the data contained within it, have been described elsewhere<sup>6</sup>. The database is now included under the umbrella of the Clinical Practice Research Datalink that brings together data from across the United Kingdom's National Health Service.

### *Participants*

For the purposes of this study juvenile HD was defined as onset before the age of 21 years. The source population was therefore all patients, under 21 years of age, registered with general practices contributing to the GGPRD, between 1990 and 2010. Eligible cases were defined as any person, under the age of 21 years, with one or more diagnoses of Huntington's disease or Huntington's chorea in their medical record. The last date for each record was

1  
2  
3  
4  
5  
6 the earliest of the either the date of death, the date of patients' de-registration  
7 from the practice if still alive, [the date the patient achieved the age of 21](#)  
8 [years](#), the date the practice left the GGPRD, or the end of the observation  
9 period (2010). The Read codes used to identify cases in the database were  
10 F134.00 (Huntington's chorea) and Eu2200 (dementia in Huntington's  
11 disease).

### 12 13 14 15 *Biases*

16 In order to ensure that incident cases were not wrongly identified as prevalent  
17 ones, two additional criteria for inclusion as incident cases were applied: 1)  
18 they ~~must have~~ had to have been registered with the practice for 12 months or  
19 longer by the date the diagnosis was recorded; and 2) they had to have had at  
20 least one other recorded contact, with the practice, during the preceding 12  
21 month period.

### 22 23 *Prescription data*

24 The medicines prescribed for incident and prevalent patients were also  
25 retrieved from [the GGPRD](#). Medications commonly prescribed for children  
26 and adolescents, and not specific for those with juvenile HD (including  
27 antibiotics, antifungal agents, emollients, and routine vaccinations), were not  
28 ~~examined~~ ~~analysed~~ further. Specific treatments for the symptoms and signs  
29 of jHD were ~~analysed~~ ~~examined~~ in detail. Those treatments prescribed more  
30 than twice in a particular patient were categorised as "regular" treatments.

### 31 32 *Statistical methods*

33 Incidence was calculated from the numbers of incident cases (as defined  
34 above [under biases](#)), within 5-year age-bands, in relation [to](#) the total number  
35 of patient-years within the [same](#) age-band. Prevalence was calculated, for  
36 each year during the study period (1990-2010), from the numbers of patients  
37 with recorded juvenile HD divided by the total numbers of patients aged less  
38 than 21 years during that year. For estimates of both incidence and  
39 prevalence binomial 95% confidence intervals were calculated.

## 40 41 **Results**

### 42 43 *Main findings: incidence*

44 There were 12 records (4 females, 8 males) of patients fulfilling the criteria for  
45 inclusion as incident cases of juvenile HD. ~~A~~ ~~Their ages at diagnosis~~ ~~t~~ ~~Their~~  
46 ~~ages-~~ ~~at diagnosis,~~ ~~ages~~ ranged from 5 years to 20 years (median 15 years).  
47 The overall incidence was 0.70 (95% confidence intervals 0.36 to 1.22) per  
48 million patient-years. The estimates of incidence in 5 year age-bands (Table  
49 1) ranged from 0  
50 (95% confidence interval 0 to 1.1) per million patient-years at age 0 to 4  
51 years, to 1.26 (95% confidence interval 0.46 to 2.74) per million patient-years  
52 at aged 15 to 20 years.

53  
54 Eight of the 12 incident cases had records of potential prodromal diagnoses,  
55 suggestive of juvenile HD, up to 3 years before a formal diagnosis [of HD](#) was  
56

1  
2  
3  
4  
5  
6 entered into their records. These included sleep disorders (3 cases),  
7 psychiatric referrals (2 cases), movement disorders (2 cases) and referral for  
8 genetic counselling (1 case). The remaining cases had no obvious prodromal  
9 reported diagnoses.

#### 11 12 13 *Main findings: prevalence*

14 There were 21 records (8 females, 13 males) of individuals contributing to the  
15 database, aged less than 21 years, with a diagnosis of HD. They provided a  
16 total of 116 patient years within the database. [These 21 prevalent cases](#)  
17 [included the 12 incident cases.](#) The average annual prevalence of juvenile  
18 HD, between 1990 and 2010, was 6.77 per million (95% confidence interval  
19 5.60 to 8.12 per million) but fluctuated year ~~by~~ year (Table 2).

#### 20 21 *Prescription data*

22 Prescription data for the treatment relevant to the symptoms and signs of  
23 juvenile HD among prevalent cases are summarised in Table 3. One patient  
24 had no prescriptions recorded during the observation period and 6 were  
25 prescribed products for intercurrent conditions (mainly antimicrobial agents,  
26 oral contraceptives, antiasthma products and vaccines) which were assumed  
27 to be unrelated to HD.

28  
29 Fourteen patients were prescribed regular treatments apparently for the  
30 specific management of their HD symptomatology ([Table 3](#)). ~~Simultaneous~~  
31 ~~Prescriptions of~~ more than one therapeutic category ~~were~~ common. The  
32 products most commonly prescribed included antidepressants (particularly  
33 fluoxetine and citalopram), a wide variety of treatments for motor disorders  
34 (including baclofen, levodopa, amantidine and tetrabenazine), hypnotics,  
35 antipsychotics (risperidone and olanzepine) and anticonvulsants (especially  
36 valproate and clobazam). Because of the small numbers of patients it  
37 would be inappropriate to use these data to infer the relative frequencies of  
38 the phenotypic variations, in the clinical manifestations of juvenile HD.  
39 Nevertheless, the data correspond – at least qualitatively – ~~to~~ with the  
40 phenotypic patterns observed in reports of juvenile HD<sup>5</sup>.

#### 41 42 **Discussion**

43  
44 [There have been a number of many population based studies of the](#)  
45 [prevalence of HD that have provided information about the proportion of](#)  
46 [cases with the juvenile form of the condition<sup>7,8</sup>. It is not possible to infer from](#)  
47 [these reports the prevalence of juvenile HD, because none provide estimates](#)  
48 [of the relevant population under 21 years of age.](#) The estimates of incidence  
49 and prevalence of juvenile HD, reported here, are ~~therefore we believe~~ the  
50 first to provide population-based epidemiological data on the frequency of this  
51 condition, ~~both~~ either ~~in for~~ the UK or, ~~indeed, for anywhere else in the~~  
52 world ~~wide~~. ~~–~~ The apparent increase in the incidence of juvenile HD ~~with age~~,  
53 in Table 1, is intuitively appropriate. ~~However, but~~ because of the small  
54 numbers involved it is impossible to be certain.

Our estimates of both the incidence and prevalence of juvenile HD ~~are, however,~~ almost certainly underestimate ~~of~~ the true frequency of juvenile HD. First, it is possible that some general practitioners ~~chose not~~ failed to record their patients' HD diagnoses for reasons of confidentiality<sup>7</sup>. Secondly, the dates of onset of past diagnoses are not always be reliably recorded ~~;~~ ~~and in~~ ~~Sometimes instances p~~ Past diagnoses may be recorded either without a date or as occurring at the date of registration. ~~These Such~~ cases ~~were excluded from our would have been excluded from~~ our analysis of incidence. ~~Thirdly, we report the dates of recorded diagnoses, and it is p~~ Possibly, ~~that some patients diagnosed in adulthood began showing started to develop symptoms in childhood or adolescence. These cases were also excluded.~~ ~~Finally~~ ~~Thirdly~~, the strict criteria we applied in defining incident cases might have resulted in omitting some who should have been assigned to this category. However, only two prevalent cases were excluded as incident cases (one aged 12 years and the other aged 19 years) because their records failed to include any other contact with the practice in the 12 months prior to the entry of a diagnosis of HD.

~~Our results, e~~ Extrapolated to the ~~entire UK whole~~ population, ~~would our results~~ suggests that, ~~in the UK, there are~~ at a minimum, ~~there are~~ ~~at least around~~ 100 children and adolescents living with ~~with~~ juvenile HD. ~~This does not of course include patients, over the age of 20 years, during the period of the study, who were originally diagnosed as juvenile HD. We also estimate that and that 10~~ Again, extrapolating to the UK as a whole, we estimate that 10 ~~Ten~~ new cases ~~are diagnosed present~~ annually.

Most of the potential prodromal diagnoses, reported for incident cases, were typical of the clinical features of juvenile HD, including motor disturbances and psychiatric problems. It is striking, ~~however,~~ that ~~in~~ three ~~instances~~ patients complained of sleep disturbances. This has not previously, ~~to our knowledge,~~ been reported in association with juvenile HD. Furthermore, hypnotics were prescribed to a significant proportion of ~~juvenile HD prevalent~~ patients, ~~with diagnosed juvenile HD.~~

The symptomatology of juvenile HD is complex and causes suffering in ~~all~~ ~~most every~~ domains ~~of the quality~~ of life. ~~The range of pharmacological products prescribed (Table 3) for our cohort of people with juvenile HD are similar to that recently reported by Robertson and colleagues<sup>9</sup>.~~ Most of the treatments for the motor manifestations of juvenile HD are those shown to be effective in Parkinson's disease but none have ever been formally assessed in juvenile HD. Even though a wide range of other therapies are used, ~~often~~ ~~sometimes~~ simultaneously, there are no studies to guide the current trial-and-error "experimental" approach to the treatment of juvenile HD. No studies, ~~for example,~~ of the effectiveness of antidepressants, antipsychotics or anticonvulsants have ever been ~~specifically~~ done ~~to assess the effectiveness of these treatments~~ in ~~the~~ juvenile ~~form of~~ HD. In particular, ~~and~~ in view of current anxieties about the ~~potential hazards of use using~~ antidepressants ~~generally~~ in children<sup>8</sup>, clinical trials of the effectiveness of specific serotonin re-uptake inhibitors, are especially urgent. The present investigation also

Formatted: Font: Italic

Formatted: Font: Not Italic

Formatted: Font: Italic

1  
2  
3  
4  
5  
6 | suggests that there is an **critical** need to assess the comparative effectiveness  
7 of other treatment options in juvenile HD. Because the numbers of children  
8 and adolescents with juvenile HD are small, in any one country such as the  
9 UK, only multinational trials are likely to produce the most **rigorous** **expedient**  
10 answers. ~~S but, in the meantime,~~ small exploratory studies **should be**  
11 **initiated immediately to would** guide the design of larger trials **as well as**  
12 **provide some early answers.**  
13

14  
15 | The humane **and supportive** care of children and adolescents with HD  
16 requires the availability of appropriate resources ~~ss, for supportive care,~~ to be  
17 provided by the UK's health and social services. **These resources are**  
18 **complex and multidisciplinary.** It is incumbent on those planning the provision  
19 of such care that the needs of these young people – and **of** their families – are  
20 met.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Authors**

All the authors were involved in the design and analysis of the study. ID and SE were responsible for the extraction of the data and undertook the statistical analyses. MDR and NSW wrote the first draft of the paper which was then edited and approved by the other contributors. MDR is the guarantor.

**Source of funding**

The authors are grateful to the Hereditary Disease Foundation and the Huntington's Disease Association for their support for this study. LS is supported by a Senior Clinical Fellowship from the Wellcome Trust and ID by a fellowship from the Medical Research Council.

**Conflicts of Interest**

None of the authors have any conflicts of interest to declare.

## References

1. Novak MJ, Tabrizi SJ. Huntington's disease. *BMJ* 2010;c3109.
2. Wexler NS. Huntington's disease: advocacy driving science. *Annual Review of Medicine* 2012; 63: 1-22.
3. Van Dijk JG, van der Velde EA, Roos RAC, Bruyn GW. Juvenile Huntington's disease. *Human Genetics* 1986; 73: 235-239.
4. Ribai P, Nguyen K, Hahn-Barma V, Gourfinkel-An I, Legout A, Dode C, Brice A, Durr A. Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology* 2007;64:813-819.
5. Quarrell OWJ, Brewer HM, Squitieri F, Barker RA, Nance MA, Landwehrmeyer GB. *Juvenile Huntington's Disease (and other trinucleotide repeat disorders)*. Oxford University Press: Oxford, 2009.
6. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database. *British Journal of Clinical Pharmacology* 2010; 69:4-14.
7. Morrison PJ, Johnston WP, Nevin NC. [The epidemiology of Huntington's disease in Northern Ireland. \*Journal of Medical Genetics\* 1995; 32:5240530](#)
8. Quarrell O, O'Donovan KL, Bandmann O, Strong M. [The prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. \*PLOS Currents\* 2012;4:doi10.1371/418606b742ef3](#)
9. Robertson L, Santini H, O'Donovan KL, Squitieri F, Barker R, Rakowicz M, Landwehrmeyer GB, Quarrell O. [Current pharmacological management in juvenile Huntington's disease. \*PLOS Currents Huntington Disease\* 2012-10-30. <http://currents.plos.org/hd/article/current-pharmacological-management-in-juvenile-huntingtons-disease-2/>. \(Accessed 30<sup>th</sup> October 2012\)](#)
- ~~7. Evans S, Ian Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. [Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. \*Lancet\* \(submitted for publication\).](#)~~
108. National Institute for Health and Clinical Excellence. *Depression in children and young people: identification and management in primary, community and secondary care*. National Institute for Health and Clinical Excellence: London, 2005. <http://guidance.nice.org.uk/CD28>. (Accessed 30<sup>th</sup> Oct 4<sup>th</sup> May 2012)

Formatted: Superscript

**Table 1**  
**Incidence estimates of juvenile Huntington's disease in UK**

<b>Age group (years)</b>	<b>Incident cases</b>	<b>Population (patient-years)</b>	<b>Incidence per million patient-years (95%CI)</b>
0-4	0	4,097,551	0 (0 to 1.1)
5-9	3	4,156,414	0.7 (0.2 to 2.1)
10-14	3	4,115,431	0.7 (0.2 to 2.1)
15-20	6	4,762,455	1.3 (0.5 to 2.7)



**Table 2**  
**Prevalence estimates of juvenile Huntington's disease in the UK**

Year	Prevalent cases	Numbers in GPRG aged less than 21 years	Prevalence per million (95% CI)
1990	1	248,518	4.0 (0.1 to 22.4)
1991	1	304,836	3.28 (0.1 to 18.3)
1992	1	350,401	2.9 (0.1 to 15.9)
1993	5	376,180	13.3 (4.3 to 31.0)
1994	5	406,351	12.3 (4.0 to 28.7)
1995	6	434,286	13.8 (5.1 to 30.1)
1996	6	524,798	11.4 (4.2 to 24.9)
1997	6	605,201	9.9 (3.6 to 21.6)
1998	6	708,142	8.5 (3.1 to 18.4)
1999	7	850,823	8.2 (3.3 to 17.0)
2000	6	946,889	6.3 (2.3 to 13.8)
2001	6	1,016,667	5.9 (2.2 to 12.9)
2002	7	1,075,286	6.5 (2.6 to 13.4)
2003	8	1,104,342	7.2 (3.1 to 14.3)
2004	10	1,133,156	8.8 (4.2 to 16.2)
2005	8	1,153,294	6.9 (3.0 to 13.7)
2006	6	1,176,419	5.1 (1.9 to 11.1)
2007	7	1,188,555	5.9 (2.4 to 12.1)
2008	8	1,184,231	6.8 (2.9 to 13.3)
2009	3	1,175,793	2.6 (0.5 to 7.5)
2010	3	1,167,683	2.6 (0.5 to 7.5)

1  
2  
3  
4  
5  
6  
7  
8 **Table 3**  
9 **Prescriptions for the specific management of patients with juvenile**  
10 **Huntington's disease**

Therapeutic category	Number of patients having products prescribed (regular prescriptions <sup>a</sup> )
Antidepressants	8 (6)
Motor abnormalities	7 (5)
Hypnotics	7 (3)
Antipsychotics	6 (3)
Anticonvulsants	5 (5)
Anxiolytics	3 (0)
Food supplements	2 (2)
Wound dressings	2 (2)

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25 <sup>a</sup>Regular prescriptions are those prescribed to a particular patient more than  
26 twice  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60