BMJ open

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|---|---|
| Journal: | *BMJ Open* |
| 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<br>Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics<br>Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology<br>Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology<br>Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases<br>Wexler, Nancy; Columbia University, Neurology and Psychiatry |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS |
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# Juvenile Huntington's disease: an epidemiological study based on the Clinical Practice Research Datalink

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## 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.

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline[1,2]. HD segregates as an autosomal trait located on chromosome 4p16.3 and the HD gene encodes the huntingtin protein[2]. The HD abnormality is an expanded CAG repeat on exon 1 of the HD gene. This leads to a 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[1]. Alleles with 60 or more CAG repeats result in the juvenile form of the disease. Juvenile HD is defined as HD an onset of 20 years or younger.

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

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

## Methods

*Study design and setting*

The CPRD (formerly the General Practice Research database) 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 elswhere[6].

*Participants*

The source population was all patients, under 21 years of age, registered with general practices contributing to the CPRD, 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 practice left the CPRD, 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 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 preceding12 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 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 intercurrrent 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[5].

## 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-speciific 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, are 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[8]. 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

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

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 prevalent patients with diagnosed juvenile HD.

The symptomatology of juvenile HD is complex and causes suffering in all domains of quality of life. Even though a wide range of therapies are used, often simultaneously, there are no studies to guide the current trial-and-error "experimental" approach to the treatment of juvenile HD. 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. There are no studies of the effectiveness of antidepressants, antipsychotics or anticonvulsants specifically in the treatment of the juvenile form of HD. In clinical medicine there is general concern about prescribing antidepressants to children[9]. Studies are urgently required of the efficacy and safety of selective serotonin re-uptake inhibitors in treating depression in children and adolescents with juvenile HD.

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

The humane care of children and adolescents with juvenile HD requires appropriate health and other forms of supportive care to be provided by the UK's health and social services. It is imperative that those responsible for planning the provision of such care meet the compelling needs of both these young people and of their families.

**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.

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## 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**

| 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**

| 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 | 3·3 (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**

| Therapeutic category | Number of patients having products prescribed (regular prescriptions[a]) |
|---|---|
| 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) |

[a]Regular prescriptions are those prescribed to a particular patient more than twice

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|---|---|
| Journal: | *BMJ Open* |
| 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<br>Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics<br>Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology<br>Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology<br>Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases<br>Wexler, Nancy; Columbia University, Neurology and Psychiatry |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Epidemiology |
| Keywords: | Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS |
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# Juvenile Huntington's disease: a population-based study using the General Practice Research Database

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## 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 abnormaliries.

**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.

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline[1,2]. HD segregates as an autosomal trait located on chromosome 4p16.3. The HD gene encodes the huntingtin protein[2]. The HD abnormality 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[1]. Alleles with 60 or more CAG repeats usually result in the juvenile form of the disease.

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

Although there have been various published estimates of the incidence and prevalence of adult HD there has been no attempt to estimate 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 Practice Research Database (GPRD) as well as to examine the range of specific treatments used in its management.

## Methods

*Study design and setting*

The GPRD 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 elswhere[6]. 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*

The source population was all patients, under 21 years of age, registered with general practices contributing to the GPRD, 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 GPRD, 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 preceding12 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, emolients, 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 intercurrrent 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[5].

## 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[7,8]. 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 be 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 our analysis of incidence. Thirdly, we

report the dates of recorded diagnoses.Possibly,some patients diagnosed in adulthood began showing symptoms in childhood or adolescence These cases were also excluded. Finally, 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.

Extrapolated to the entire UK population our results suggest that at a minimum, there are100 children and adolescents living with juvenile HD. Ten new cases are diagnosed 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 that three patients complained of sleep disturbances. This has not previously been reported in association with juvenile HD. Furthermore, hypnotics were prescribed to a significant proportion of juvenile HD patients.

The symptomatology of juvenile HD is complex and causes suffering in all domains 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[9]. 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 simultaneously, there are no studies to guide the current trial-and-error "experimental" approach to the treatment of juvenile HD. No studies of the effectiveness of antidepressants, antipsychotics or anticonvulsants have ever been done to assess the effctiveness of these treatments in juvenile HD. In particular, in view of current anxieties about the potential hazards of using antidepressants in children[8], clinical trials of the effectiveness of specific serotonin re-uptake inhibitors, are especially urgent. The present investigation also suggests that there is a critical need to assess the comparative effectiveness of other treatment options in juvenile HD. Because the numbers of children and adolescents with juvenile HD are small, in any one country such as the UK, only multinational trials are likely to produce the most rigorous answers. Small exploratory studies should be initiated immediately to guide the design of larger trials as well as provide some early answers.

The humane and supportive care of children and adolescents with HD requires the availability of appropriate resources to be provided by the UK's health and social services. These resources are complex and multidisciplinary. It is incumbent on those planning the provision of such care that the needs of these young people – and their families – are met.

**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.

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**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**

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

| Therapeutic category | Number of patients having products prescribed (regular prescriptions[a]) |
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| Motor abnormalities | 7 (5) |
| Hypnotics | 7 (3) |
| Antipsychotics | 6 (3) |
| Anticonvulsants | 5 (5) |
| Anxiolytics | 3 (0) |
| Food supplements | 2 (2) |
| Wound dressings | 2 (2) |

[a]Regular prescriptions are those prescribed to a particular patient more than twice

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

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

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## 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 abnormaliries.

### 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.

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**Summary**

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder.n unusual condition T 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 fromor 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, jJuvenile 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[1,2]. HD segregates as an autosomal trait located on chromosome 4p16.3. T ~~and t~~he HD gene encodes the huntingtin protein[2]. 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[1]. 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[3,4,5]. In juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present[4,5].

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 Database~~base~~ (GG~~G~~PRD) as well as to examine the range of specific treatments used in its management.

## Methods

*Study design and setting*

The GG~~G~~PRD ~~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 elswhere[6]. 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.

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*Participants*

The source population was all patients, under 21 years of age, registered with general practices contributing to the GG~~G~~PRD, 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 GG~~G~~PRD, 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 musthad 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 preceding12 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, emolients, and routine vaccinations), were not examined analysed further. Specific treatments for the symptoms and signs of jHD were analysedexamined 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 sameat 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. ATheir ages at diagnosis tTheir 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 byon 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 intercurrrent 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 pPrescriptions of more than one therapeutic category wereas 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 – towith the phenotypic patterns observed in reports of juvenile HD[5].

## 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[7,8]. 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 worldwide. – 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 notfailed to record

their patients' HD diagnoses for reasons of confidentiality[7]. Secondly, the dates of onset of past diagnoses are not always be reliably recorded.; and in Ssometimes instances pPast 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 pPossiblye, that some patients diagnosed in adulthood began showing started to develop symptoms in childhood or adolescence. These cases were also excluded. FinallyThirdly, 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, eExtrapolated to the entire UKwhole 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. ;We also estimate that and that 10 Ten new cases are diagnosedpresent 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 allmost 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[9]. 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, oftensometimes 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 effctiveness 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[8], clinical trials of the effectiveness of specific serotonin re-uptake inhibitors, are especially urgent. The present investigation also suggests that there is an critical need to assess the comparative effectiveness of other treatment options in juvenile HD. Because the numbers of children and adolescents with juvenile HD are small, in any one country such as the UK, only multinational trials are likely to produce the most rigorousexpeditious answers. S but, in the meantime, small exploratory studies should be initiated immediately to would guide the design of larger trials as well as provide some early answers.

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The humane and supportive care of children and adolescents with HD requires the availability of appropriate resources~~s, for supportive care,~~ to be provided by the UK's health and social services. These resources are complex and multidisciplinary. It is incumbent on those planning the provision of such care that the needs of these young people – and ~~of~~ their families – are met.

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BMJ open

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|---|---|
| Journal: | *BMJ Open* |
| 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<br>Evans, Stephen; London School of Hygiene and Tropical Medicine, Medical Statistics<br>Rawlins, Michael; London School of Hygiene and Tropical Medicine, Epidemiology<br>Smeeth, Liam; London School of Hygiene and Tropical Medicine, Epidemiology<br>Tabrizi, Sarah; Institute of Neurology, neurodegenerative diseases<br>Wexler, Nancy; Columbia University, Neurology and Psychiatry |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Neurology, Genetics and genomics |
| Keywords: | Paediatric neurology < NEUROLOGY, PUBLIC HEALTH, THERAPEUTICS, Paediatric clinical genetics & dysmorphology < GENETICS |
| | |

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

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## 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
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- Patients were frequently prescribed antidepressants, hypnotics, antipsychotics and treatments for motor abnormaliries.

**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.

Huntington's disease (HD) is a progressive, fatal neurodegenerative disorder associated with abnormal movements, psychiatric disturbances and cognitive decline[1,2]. HD segregates as an autosomal trait located on chromosome 4p16.3. The HD gene encodes the huntingtin protein[2]. The HD abnormality 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[1].

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 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[3,4,5]. In juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present[4,5] 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 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 Practice Research Database (GPRD) as well as to examine the range of specific treatments used in its management.

## Methods

*Study design and setting*

The GPRD 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 elswhere[6]. 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 GPRD, 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 GPRD, 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 preceding12 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, emolients, 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 intercurrrent 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[5].

## 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[7,8]. 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 be 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 our analysis of incidence. Thirdly, we report the dates of recorded diagnoses.Possibly,some patients diagnosed in adulthood began showing symptoms in childhood or adolescence These cases were also excluded. Finally, 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.

Extrapolated to the entire UK population our results suggest that at a minimum, there are100 children and adolescents living 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.Again, extrapolating to the UK as a whole, we estimate that 10 new cases are diagnosed 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 that three patients complained of sleep disturbances. This has not previously been reported in association with juvenile HD. Furthermore, hypnotics were prescribed to a significant proportion of juvenile HD patients.

The symptomatology of juvenile HD is complex and causes suffering in all domains 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[9]. 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 simultaneously, there are no studies to guide the current trial-and-error "experimental" approach to the treatment of juvenile HD. No studies of the effectiveness of antidepressants, antipsychotics or anticonvulsants have ever been done to assess the effctiveness of these treatments in juvenile HD. In particular, in view of current anxieties about the potential hazards of using antidepressants in children[8], clinical trials of the effectiveness of specific serotonin re-uptake inhibitors, are especially urgent. The present investigation also suggests that there is a critical need to assess the comparative effectiveness of other treatment options in juvenile HD. Because the numbers of children and adolescents with juvenile HD are small, in any one country such as the UK, only multinational trials are likely to produce the most rigorous answers. Small exploratory studies should be initiated immediately to guide the design of larger trials as well as provide some early answers.

The humane and supportive care of children and adolescents with HD requires the availability of appropriate resources to be provided by the UK's health and social services. These resources are complex and multidisciplinary. It is incumbent on those planning the provision of such care that the needs of these young people – and their families – are met.

**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.

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**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**

| 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**

| Therapeutic category | Number of patients having products prescribed (regular prescriptions[a]) |
|---|---|
| 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) |

[a]Regular prescriptions are those prescribed to a particular patient more than twice

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

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## 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 abnormaliries.

### 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.

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**Summary**

*Background:* The juvenile form of Huntington's disease (HD) is a rare disorder.~~n unusual condition~~ ~~T~~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~~or~~ 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~~s~~ 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, j~~J~~uvenile 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~~ M~~m~~ultinational 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[1,2]. HD segregates as an autosomal trait located on chromosome 4p16.3. T ~~and t~~he HD gene encodes the huntingtin protein[2]. 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[1].

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[3,4,5]. In juvenile HD cerebellar signs, epilepsy, myoclonus and spasticity may also occur. As in adult HD, psychiatric disturbances and cognitive decline are also present[4,5] 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 General~~General~~ Practice Research Database~~base~~ (GG~~G~~PRD) as well as to examine the range of specific treatments used in its management.

## Methods

*Study design and setting*

The GG~~G~~PRD ~~is~~ 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 elswhere[6]. 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.

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*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 GG~~G~~PRD, 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 musthad 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 preceding12 month period.

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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, emolients, and routine vaccinations), were not examined analysed further. Specific treatments for the symptoms and signs of jHD were analysedexamined 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 sameat 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. ATheir ages at diagnosis tTheir 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~~on~~ year (Table 2).

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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 intercurrrent 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~~P~~rescriptions of more than one therapeutic category were~~as~~ 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[5].

## 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[7,8]. 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~~ worldwide. – 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 their patients' HD diagnoses for reasons of confidentiality[7]. Secondly, the dates of onset of past diagnoses are not always be reliably recorded.~~; and in~~ ~~Ssometimes instances~~ pPast 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~~e, 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 suggest~~s~~ 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 a~~llmost 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[9]. 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 effctiveness 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[8], clinical trials of the effectiveness of specific serotonin re-uptake inhibitors, are especially urgent. The present investigation also

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**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.

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**Conflicts of Interest**
None of the authors have any conflicts of interest to declare.

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**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**

| 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**

| Therapeutic category | Number of patients having products prescribed (regular prescriptions[a]) |
|---|---|
| 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) |

[a]Regular prescriptions are those prescribed to a particular patient more than twice