**The Prevalence of Huntington’s Disease:
A Systematic Review**

Michael D Rawlins1, Nancy S Wexler2,3, Alice R Wexler2, Sarah J Tabrizi4, Ian Douglas1, Stephen JW Evans1, Liam Smeeth1.

1Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine; 2Hereditary Disease Foundation, New York, USA; 3Columbia University, New York, USA; 4Institute of Neurology, University College London, London, UK.

**Corresponding author:** Michael Rawlins, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK.

e-mail:michael.rawlins@nice.org.uk. Tel +07739809006 Fax: +44 (0)20 7436 5389

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**Abstract**

**Background:** Reviews of the epidemiology of Huntington’s disease (HD) suggest that its worldwide prevalence varies widely. This review was undertaken to confirm these observations, to assess the extent to which differences in case-ascertainment and/or diagnosis might be responsible, and to investigate whether prevalence has changed over the past 50 years**. Methods:**82 relevant studies were identified from Medline and Embase, previous reviews, scrutiny of references from included and excluded studies and enquiry among those interested in the field. **Results:** The lowest rates were among Asians and the highest among Caucasians. The differences are not fully explained by varying approaches to case-ascertainment or diagnosis. There was evidence of an increasing prevalence of between 15% and 20% per decade in studies from Australia, North America and Western Europe.

**Conclusions:** The prevalence of Huntington’s disease (HD) varies more than ten-fold between different geographical regions. This variation can in part be attributed to differences in case-ascertainment and/or diagnostic criteria but there is consistent evidence of a lower incidence in Asian populations. There is also evidence that in Australia, North America and in Western Europe (including the UK) prevalence has increased over the past 50 plus years.

**Introduction**

Huntington’s disease (HD) is a hereditary neurological disorder inherited as an autosomal dominant trait [1,2] as a result of an expanded trinucleotide repeat in a gene on chromosome 4p16.3 [3]. Although there is an unusually rare juvenile form of the condition [4], HD usually presents in early middle life with abnormal movements (particularly chorea) together with psychiatric symptoms including psychosis, depression and obsessive-compulsive disorder together with progressive cognitive impairment [1,2].

Estimates of the prevalence of HD suggest a more than ten-fold difference between regions across the world. Three systematic reviews of the prevalence of HD appear to have been published. Of these one was confined to sub-Saharan Africa [5], one only included studies conducted in the UK [6] after 1988, and the third [7] was confined to estimates undertaken between 1985 and 2010. The present systematic review was undertaken to identify all published estimates of the prevalence of HD between January 1930 and June 2015; to assess the heterogeneity of these estimates within and between geographical regions; and to determine the extent to which this might be explained by differences in case-ascertainment and/or approaches to diagnosis and/or other factors. The review also sought to establish whether the apparent increase in the prevalence of HD, recently reported in the UK [8], occurs in other geographical regions.

**Methods**

The criteria for inclusion in the systematic review were that studies should have attempted to identify patients with manifest HD amongst a population of more than 150,000 persons between 1930 and June 2015. This population exclusion criterion was introduced for two reasons. First, prevalence in smaller populations would provide unreliable estimates. Second, such studies include “clusters” of HD families often living in small isolated communities some of which may possibly be descended from a single “founder”. These reports were therefore excluded from the main review but descriptions of them have been included in “discrete populations” (Supplementary Material Annex 2).

Relevant publications (including published Abstracts) were sought from a search of Medline and Embase databases (Supplementary Material Annex 1). Publications were also sought from scrutiny of the references quoted in reviews of the epidemiology of HD [9-14] and by examining the reference lists of publications meeting the inclusion criteria. Reports described as “personal communications” to the author of one review [11] were not, however, included. No studies were excluded by virtue of their date, or because of the approach taken to either case ascertainment or the diagnosis of HD. There were no language restrictions.

Relevant details included in publications that met the inclusion criteria were transcribed by MDR and ARW onto specially devised forms. The transcribed data recorded the following:

* The full reference.
* The geographical location of the study.
* The prevalence date(s).
* The source and size of the base population data.
* Case ascertainment methodology.
* Method(s) used in the diagnosis of HD.
* Number of HD patients identified.
* The authors’ estimate of the prevalence including confidence intervals where these were provided.

For all included studies the estimates of prevalence were recalculated together with their 95% binomial confidence intervals (CIs). In some instances, although studies provided estimates of prevalence, they failed to indicate either the base population size or the number of HD patients. In these circumstances the missing values were determined by back extrapolation.

The heterogeneity of different estimates of prevalence was estimated from the I2 test [15]. Relationships between study years, and the prevalence rates for those years, were assessed by Poisson regression analysis and trends were expressed as the percentage increase per decade. To avoid undue emphasis in favour of studies with estimates of prevalence rates covering more than one year, only the rate in the final year was used in the assessment of heterogeneity and in the trend analyses. Reporting follows, where appropriate, the PRISMA guidelines [16].

**Results**

The removal of duplicate publications, irrelevant reports and reports among discrete populations yielded 83 studies with population estimates of the prevalence of HD. Further details of the studies in discrete populations are in Supplementary Material Annexes 2 and 3. Other excluded studies are shown in Supplementary Material Annexes 4 and 5. The study by Panse [17], carried out in the Rhineland between 1936 and 1937, met the prespecified inclusion criteria but was excluded on ethical grounds. Friedrich Panse, a German psychiatrist, was deeply involved in the Nazi eugenics program that carried out coercive sterilization and extermination of persons with a wide range of psychiatric and neurological conditions including HD [18].  We consider that his participation in such a programme compromises his study on both ethical and scientific grounds and urge that future reviews of the epidemiology of HD also consider excluding this publication. Exclusion of this study left 82 publications for scrutiny and analysis (Figure 1, Table 1). A summary of the geographical distribution of the included studies is shown in Table 1.

The methods used for case ascertainment and the diagnosis of HD, for each included study, are shown in the Supplementary Material (Annexes 6 to 12). A variety of approaches have been adopted in identifying patients with HD in defined populations. Some have been based on a scrutiny of the records of hospitals and nursing homes. Others sought information from individual physicians. In some instances, cases were also identified by enquiry of the families of affected individuals. More recent studies based case ascertainment on the records of medical genetics laboratories. We were unable, however, to devise a method that would have allowed quantitative analyses of various approaches to case ascertainment for this study.

In the majority of studies, the diagnosis of HD was based on clinical features supplemented, in more recent years, by the results of genetic analysis. Again, however, we were unable to develop an approach that would have provided a quantitative assessment of the reliability of the diagnostic approaches used in individual studies.

The estimates of prevalence across the 81 studies shows marked heterogeneity (I2= 99.0%, CIs 98.9% to 99.1%). Forest plots of prevalence rates by geographical region are shown in Figures 3 to 9. In all figures, the size of the point estimates of each study reflects their power. Further details of the studies, themselves, can be found in the Supplementary Material (Annexes 13 to 19). Summary results of the Poisson regression analyses of prevalence rates by study year (expressed in decades), for each geographical region, are shown in Table 2. This does not, however, include the three studies carried out in Africa as the number is too few (Table 2) for reliable conclusions to be drawn.

*Africa*

Figure 2 (Supplementary Material Annex 13) shows the prevalence of HD from studies undertaken in Africa. In the forest plot (Figure 2) the “total” prevalence estimate by Hayden [19], combining rates among Cape coloured, white and black communities, has been omitted but is shown in Web-extra Annex 13. The data suggest that in South Africa the prevalence of HD is similar among Cape coloureds and whites but appears to be substantially less in blacks [19]. The prevalence amongst the Bantu population of Zimbabwe [20]is reported to be greater than that among black South Africans.

*Americas*

Figure 3 (Supplementary Material Annex 14) shows marked heterogeneity between estimates of prevalence in the Americas. The study by Paradisi and colleagues [21] from Venezuela shows the lowest prevalence rates in the region (0.35 per 100,000) while the recent study by Fisher and colleagues [22], amongst Caucasians in Canada, shows the highest prevalence (17.27 per 100,000). Excluding the single study from South America [21], there still remained marked heterogeneity (I2 = 98.8%, CI = 98.6% to 99.0%) in North America. The prevalence among black Americans in the United States [23] (6.37 per 100,000) is strikingly higher than those of blacks living in South African [19] and Zimbabwe[20] (0.02 and 1.00 per 100,000 respectively). Excluding the single study from South America [21], there was a significant trend in data from North America (Table 2), between 1950 and 2012, for estimates of prevalence to increase with time (20.1%, CI 18.1% to 22.1% per decade).

*Asia*

Figure 4 (Supplementary Material Annex 15) shows prevalence rates in Hong Kong, Japan, South Korea and Taiwan. These range from 0.11 per 100,000[24] to 0.72 per 100,000[25] and are strikingly lower than those in most of Oceania, Western Europe and the United States. In addition there was substantially less heterogeneity compared to other regions (I2 = 49.0% % CI 0% to 76.6%). There was no significant trend between study years and estimates of prevalence (Table 2).

*Central and Eastern Europe*

The marked heterogeneity of the prevalence rates of HD in Central and Eastern Europe(I2 = 94.6%; 95% CI 92.1% to 96.0%) can be seen in Figure 5 (Supplementary Material Annex 16). There was, however, no significant trend between study dates and prevalence estimates (Table 2).

*Oceania*

The eight included studies from Oceania were all undertaken in Australia between 1954 and 1999. There is marked heterogeneity (Figure 6; web-extra Annex 17) in prevalence rates(I2 = 94.9% 95% CI 92.6% to 96.2%)as well as a significant trend (Table 2) with study years (15.7% CIs 11.9% to 19.6% per decade).

*United Kingdom*

Because of the large number of studies undertaken in Western Europe, as a whole, those from the UK are described separately. As can be seen from Figure 7 (Supplementary Material Annex 18) the included UK studies, conducted over a 60 year time-frame (1950 to 2013), show marked heterogeneity (I2 = 95% 95% CI 93.7% to 95.8%). Factors that contribute to the apparent discrepancies between the two most recent prevalence estimates for the UK have been discussed elsewhere [8]. It is striking that the estimate of prevalence in a study[25] confined to migrants from the Indian subcontinent (1.35 CIs 0.79 to 2.16 per 100,000 population) is substantially lower than other UK estimates of adult HD and is commensurate with the results from Asia. Excluding the studies confined to UK migrants from the Indian subcontinent[26], and those with the juvenile form of HD[**27],** there is a significant trend (Table 2) of 15.5% (CIs 11.3% to 18.0%) per decade between study dates and the estimates of prevalence.

*Western Europe (excluding the UK)*

The prevalence rates in the rest of Western Europe are shown in Figure 8 (Supplementary Material Annex 19). Again, there is marked heterogeneity (I2 = 97.5%CI 97.2% to 97.8%)with estimates ranging from 0.53 per 100,000 in Finland[28] to 10.85 per 100,000 in Italy[29]. There was, overall, a significant trend (Table 2) between the study dates and prevalence estimates (16.3% CIs 14.8% to 18.4% per decade).

*Discrete populations*

The studies of HD in discrete populations, shown in the Supplementary Material Annex 2, fall into two groups. Some[30-35] describe clusters of HD families, living in small communities, often with suggestions that affected individuals are descended from a single progenitor. The remaining studies describe estimates of prevalence in populations of less than 150,000.

**Discussion and Conclusions**

The global population prevalence of HD appears to show a more than ten-fold variation across regions. The very low prevalence rates among blacks in South Africa (0.02 CIs 0 to 0.5 per 100,000)[19] and Zimbabwe (1.00 CIs 0.48 to 1.84 per 100,000)[20] may be due to weak case-ascertainment in communities with limited healthcare provision. In North America, Folstein and her colleagues**[23]** reported prevalence among blacks of 6.37 (CIs 4.87 to 8.18) per 100,000 and in whites of 4.79 (CIs 4.06 to 5.60) per 100,000. The similarity between the estimates of prevalence among blacks and whites in North America may be due, at least in part, to mixed race ancestry. The low prevalence rates of HD in Hong Kong, Japan and Taiwan (Figure 5, Web-extra Annex 16) are very unlikely to be due to poor case ascertainment or inadequate diagnoses because all have relatively high levels of healthcare provision. The average prevalence rate since 1995 – when genetic testing came into routine use – in Asians countries (Hong Kong, Japan, South Korea and Taiwan) was 0.42 (95% CIs 0.37 to 0.47) per 100,000. By comparison, the average prevalence rate for the same period, among predominantly Caucasians populations (in Australia, Western Europe including the UK and North America) is 9.71 (95% CIs 9.32 to 10.12) per 100,000. Moreover, as discussed earlier, the UK study amongst UK immigrants from the Indian subcontinent also showed a substantially lower prevalence **[26**] than the UK as a whole. Reduced mutation rates may be responsible for the lower prevalence rates of HD in East Asians. It has been suggested[36,37] that different haplotypes, between East Asians and Europeans, may be associated with differing mutation rates. Sipla and colleagues **[38]** suggest that the lower prevalence of HD in Finland may also be due to differences in haplotype. Further research, however, is needed to explain these marked global differences in prevalence.

Our previous study of the prevalence of HD in the UK [7] showed that prevalence rates have increased more than two-fold between 1990 and 2010. The present study indicates that apparent prevalence rates of HD have increased (Table 2) by around 15% to 20% per decade in Australia (between 1954 and 1996), North America (between1950 and 2012), the UK (between 1950 and 2010) and other countries in Western Europe (between 1930 and 2007). There is no suggestion that prevalence has increased significantly in Asia or Central and Eastern Europe. This may be due to the relatively small numbers of studies reported in these two regions or, at least for Asia, because of the lower prevalence of HD more generally.

The rise in prevalence of HD in Australia, North America, the UK and Western Europe, is likely to have a number of causes. First, physicians’ better knowledge and awareness of HD, complemented by the availability of a genetic test to indicate the genetic status of individuals[2], may have increased the rates of diagnosis particularly in older patients and those with no known family history of HD [39-42]. Secondly, it is also possible that the “shame” traditionally associated with a family history[43] of HD has diminished, and that physicians have become less reluctant to record an HD diagnosis. Thirdly, the increased prevalence might be due to increased mutation rates, with a corresponding increase in incidence. A recent study by us, however, based on data from the UK[44] suggests that the incidence of HD between 1990 and 2010 has remained unchanged. Fourthly it is likely that the general increase in population survival will have had some effect on the longevity of those with HD thus increasing prevalence even in the absence of a rise in incidence. In addition, the availability of more effective symptomatic treatments for HD (including antidepressants, antipsychotics and anti-choreiform medication) may have also had an additional impact on survival.

Irrespective of the explanation it behoves healthcare systems in Australia, North America and Western Europe (including the UK) to ensure that appropriate facilities are available for the care of patients with HD. It is uncertain as to whether all the reported “clusters” of people with HD, in villages and townships in South America and Europe, have persisted as reports date back many years. Certainly many people with HD are known to still live in the “clusters” in Colombia and Venezuela. For these individuals, their families and their communities countries’ healthcare systems should strive, even further, to ensure appropriate services are available for their care.

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**Conflicts of Interest:**

None

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**Table 1**

**Summary of studies of the prevalence of HD**

|  |  |  |
| --- | --- | --- |
| **Region** | **Included prevalence studies** | **Discrete** **populations** |
| Africa | 3 | 4 |
| Americas | 7 | 5 |
| Asia | 8 | 1 |
| Central and Eastern Europe | 8 | 1 |
| Oceania | 8 | 2 |
| United Kingdom | 21 | 4 |
| Western Europe (excluding UK) | 27 | 2 |
| Totals | 82 | 19 |

 **Table 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Number of studies in estimates of rate ratios** | **Study years (range)** | **Average****Prevalence per 100,000****(95%CIs)** | **Trend (percent) by decade** |
| Asia | 7 | 1957 to 2013 | 0.40(0.36 to 0.44) | 8.9(-2.24 to +23.8) |
| C and E Europe | 8 | 1981 to 2008 | 2.17(1.95 to 2.41) | 15.4(2.70 to +38.6) |
| N America | 6 | 1950 to 2012 | 7.33(6.94 to 7.74) | 20.1(+18.1 to 22.1) |
| Oceania | 8 | 1981 to 2008 | 5.63(5.61 to 6.25) | 15.4(+11.6 to +19.3) |
| UK | 19 | 1950 to 2010 |  6.68(6.40 to 6.97) | 15.5(+11.3 to +18.0) |
| W Europe | 27 | 1930 to 2013 | 3.60(3.50 to 3.69) | 16.5(+14.9 to +18.6) |

 **Prevalence rate ratios**