Prevalence of Huntington Disease in Italy: a systematic review and meta-analysis

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Summary. Worldwide prevalence of Huntington’s disease (HD) is quite heterogenous. As Italy is characterized by significant genetic heterogeneity, with presumptive differences between Italian regions, this review was undertaken to define available data of HD prevalence in Italy, to assess geographic heterogeneity, and reconcile possible variation in HD prevalence rates with the availability of genetic testing. Methods. In total, 14 relevant studies were identified from Medline/Embase, and analysis of available Italian regional reports on rare diseases. Results. A cumulative prevalence of 3.9/100,000 inhabitants (95% Confidence Interval 3.0 – 5.0) was identified, with apparently higher rates in the last decades (4.1/100,000 vs. 3.0/100,000). The lowest rates were among the resident of the Oristano province in Sardinia, while the highest were reported in three mountainous and rather isolated areas (i.e. Molise, San Marino, Varese; all well over 10 cases/100,000 inhabitants). These differences cannot be not fully explained by varying approaches to case-ascertainment or diagnosis, and a possible “founder effect” may therefore be extensively advocated. Discussion. The prevalence of HD in retrieved Italian reports varied up to almost tenfold between different geographical regions. Even though such variation can in part be attributed to differences in case-ascertainment and/or diagnostic criteria, there is consistent evidence of significant founder effects in certain areas such as the provinces of Varese, the Republic of San Marino, and the region od Molise – all of them with estimates > 10/100,000 cases. As our estimates suggest that up to half of Italian HD cases may be still waiting, Public Health approach should improve diagnostic rates in order to guaranteeing palliative and symptomatic interventions (antidepressants, antipsychotics, anti-choreiform medications) to all individuals and their families.

Key words: Huntington’s disease, Prevalence, Neurodegenerative disorders, Analyses, genetic linkage, Italy

Introduction

Huntington’s disease (HD) is a monogenic, autosomal-dominant, incurable and slowly progressive neurodegenerative disorder characterized by chorea, dystonia, cognitive decline, and psychiatric manifestations, as well as dementia (1,2). The hereditary nature of HD was identified since 19th century, and the discovery of the causal HD gene (i.e. the huntingtin gene, HTT; chromosome 4) has established HD as triggered by a CAG triplet repeat expansion (HTT), which leads to an expanded polyglutamine stretch in the huntingtin protein, and subsequent protein misfolding (1,3,4). While the average CAG tract length in the general population ranges 16 to 20 repeats, in HD cases it usually exceeds 36 repeats (1,2,5). Interestingly, both severity of clinical features and disease progression are well correlated with the range of CAG tract length: longer the tract (i.e. > 40 repeats), earlier are the manifestations of HD, with a similarly shorter
survival. However, prognosis of HD remains relatively dismal: after the onset of the symptoms, usually between 35 and 55 years of age, life expectancy rarely exceeds 15 to 20 years (2,5–7), following complications such as aspiration pneumonia, myocardial infarction, opportunistic infections (8). As a consequence, people affected by HD can conceive offspring unaware of their status, ultimately maintaining the burden of disease in the general population (2,7–9). Unsurprisingly, HD shows a stable prevalence in population groups of European origin, with rates ranging 5 to 7 cases per 100,000, but clusters of higher prevalence rates have been extensively described, particularly where the population can be traced to a few founders (2). Still, the discovery of the genetic basis of HD has hinted towards a possible underestimate of actual prevalence of this disorder in earlier reports (4,7,9,10). In facts, as before 1993 diagnosis of HD was purely based on the recognition of extrapyramidal clinical features (i.e. chorea, dystonia, bradykinesia, or incoordination) in individuals from a favorable background, whereas people with typical neurological features, but without a family history compatible with the HD diagnosis may have remained largely undiagnosed (7,9,10).

Italy, with its quite heterogenous genetic background, is suspected to be similarly heterogenous in terms of HD prevalence (10,11), but epidemiological reports are substantially lacking, particularly after the introduction of genetic testing (10). Interestingly, while recent estimates from the Italian National Health Institute have reported around 1188 prevalent cases in 2014, prevalence estimates from Squitieri et al. pointed out towards a possible HD burden of around 6500 cases (10,12). Our study will therefore attempt to:
1) Identify the published measurement of HD prevalence in Italy;
2) Ascertain geographic heterogeneity, and reconcile possible variation in HD prevalence rates with the availability of genetic testing.

Materials and Methods

This systematic review has been conducted following the PRISMA (Prepared Items for Systematic Reviews and Meta-Analysis) guidelines (13). We searched into two different settings. On the one hand, we searched conventional scientific databases (i.e. PubMed and EMBASE) for relevant studies until 31/12/2019, without any chronological restriction. The search strategy was a combination of the following keywords (free text and Medical Subject Heading [MeSH] terms): («Huntington* disease» OR «Huntington* chorea») AND («Italy» OR «Italian») AND («epidemiology» OR «prevalence» OR «frequency» OR «occurrence») (Figure 1). On the other hand, we searched Institutional Web Sites of Italian Regional Health Services for reports on rare diseases, identifying prevalence estimates for medical exemptions RF0080 (i.e. diagnosis of HD). Records were handled using a references management software (Mendeley Desktop Version 1.19.5, Mendeley Ltd 2019), and duplicates were removed.

Documents eligible for review were original research publications available online or through interlibrary loan. Articles had to be written in Italian, English, German, French or Spanish, the languages spoken by the investigators. Studies included were national and international reports, case studies, cohort studies, case-control studies and cross-sectional studies. Only article reporting diagnostic criteria for PD cases, the number of prevalent cases, or crude prevalence rates, were eligible for the full review. Retrieved documents were excluded if: (1) full text was not available; (2) articles were written in a language not understood by reviewers; (3) reports lacked significant timeframe (i.e. the prevalence year); (4) reports lacked definition of the geographical settings, or it was only vaguely defined.

Two independent reviewers reviewed titles, abstracts, and articles. Titles were screened for relevance to the subject. Any articles reporting original studies, which did not meet one or more of the exclusion criteria, were retained for full-text review. The investigators independently read full-text versions of eligible articles. Disagreements were resolved by consensus between the two reviewers; where they did not reach consensus, input from a third investigator (MR) was obtained. Further studies were retrieved from reference lists of relevant articles and consultation with experts in the field.

Data abstracted included:
1) Settings of the study: prevalence year, Italian region, level of assessment (i.e. community, province, region);
2) Screening procedures (i.e. clinical assessment vs. clinical assessment assisted by genetic testing)
3) Total number of prevalent PD cases;
4) Number of reference population.

We first performed a descriptive analysis to report the characteristics of the included studies. Crude HD prevalence figures were initially calculated: if a study did not include raw data, either as number of prevalent cases, or referent population (either in general or by age groups), such figures were either reverse-calculated from available data, or obtained from the Italian National Institute of Statistics (ISTAT) site DEMO (http://demo.istat.it/). DEMO includes Italian demographic data for the timeframe 1974 – 2019, at various geographical levels (i.e. national, regional, provincial, local communities).

Pooled prevalence (as prevalent cases/100,000 inhabitants) estimates were then calculated by means of a random effect model (in order to cope with the presumptive heterogeneity in study design). I² statistic was then calculated to quantify the amount of inconsistency between included studies; it estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I² values ranging from 0 to 25% were considered to represent low heterogeneity, from 26% to 50% as moderate heterogeneity and above 50% as substantial heterogeneity, being pooled using a fixed-effects model because of the reduced number of samples eventually included. To investigate publication bias, funnel plots were initially generated: publication bias was evaluated by testing the null hypothesis that publication bias does not exist by means of the regression test for funnel plot asymmetry. The null hypothesis was rejected if the p-value is less than 0.10.

All calculations were performed in R (version 3.6.1; R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and RStudio (version 1.2.5019) software by means of meta package (version 4.9-9), functions metaprop for pooling of HD prevalence. The meta package is an open-source add-on for conducting meta-analyses.

Results

Initially, 252 entries were identified, including a total of 230 abstracts from MedLine/EMBASE and 22 Regional reports: as 6 of them were duplicated across the sources, 246 entries were initially screened. After applying the inclusion and exclusion criteria (Figure 1), 14 articles were included in the analyses and summarized, including 5 regional reports (14–18) and 9 scientific reports (8,10,11,19–25)(Table 1).

The majority of the reports (10 out of 14, 71.4%) were published after 1993. Overall, 8 reports included data retrieved at regional level (57.1%), while 6 studies reported figures at provincial level (42.9%). As two reports included figures both at regional level and provincial level, only discrete provincial figures were included in the final analyses. Eventually, the final sample included a total of 1244 cases (total sample size: 35,105,567 inhabitants), that were retrieved from the region of Lombardy, Friuli Venezia Giulia, Toscana, Lazio, Molise, Apulia, Toscana, with 4 provinces of Emilia Romagna (including San Marino Republic), whose total population includes 47.9% of total Ital-

![Figure 1. PRISMA flow diagram including keywords employed for the inquiry (i.e «Huntington" disease OR «Huntington" chorea») AND («Italy» OR «Italian») AND («epidemiology» OR «prevalence» OR «frequency» OR «occurrence»), integrated by analysis of regional reports on rare diseases).](https://www.R-project.org/)
Table 1. Retrieved prevalence studies on Huntington’s disease (HD) in Italy. Notes: DRG = diagnosis related groups; * = San Marino Republic, while an independent State, is actually a small enclave in the Emilia Romagna Region.

| Study                        | Year  | Level of ascertain | Case finding method                                                                 | Diagnostic criteria               | No. of cases | Reference Population | Raw prevalence |
|------------------------------|-------|--------------------|-------------------------------------------------------------------------------------|-----------------------------------|--------------|----------------------|-----------------|
| Groppi et al. (1)            | 1979  | Provincial, Florence | Analysis of medical records from medical facilities of the Florence area; interview of 47 neurologists/psychiatrists practicing in the Florence area (years 1970 – 1979) | Clinical only                      | 37           | 1,202,013            | 3.1             |
| Frontali et al. 1990 (2)     | 1981  | Regional, Lazio     | Analysis of medical records from medical facilities of the Lazio region; interview of neurologists/psychiatrists practicing in the Lazio region (years 1975 – 1990); analysis of families with at least one HD case | Clinical analysis, genetic testing (not specific for HTT), CT study of Central Nervous System | 128          | 5,001,684            | 2.6             |
| Mainini et al. 1982 (3)      | 1982  | Provincial, Parma & Reggio Emilia | Records of neurological and psychiatric institutions in the area; interview of neurologists/psychiatrists practicing in the Parma & Reggio Emilia areas; analysis of families with at least one HD case | Clinical only                      | 39           | 812,581              | 4.8             |
| Pavoni et al. 1990 (4)       | 1987  | Provincial, Ferrara | Analysis of medical records from medical facilities of the Ferrara area; interview of neurologists/psychiatrists practicing in the Ferrara area; analysis of families with at least one HD case | Clinical only                      | 7            | 370,375              | 1.9             |
| Community of Trieste - Regional Health Service 2013 (5) | 2011  | Regional, Friuli Venezia Giulia | Analysis of the institutional database of the Regional Health Service; identification of Medical Exemption code RF0080 | N/A                               | 23           | 1,229,363            | 1.9             |
| Reverberi et al. 2014 (6)    | 2013  | Provincial, Reggio Emilia & Modena | Analysis of medical records (DRG) from the Local Health Units + Hospitals of Reggio Emilia and Modena | Clinical assessment + Genetic testing | 30           | 1,210,844            | 2.5             |
| Squitieri et al. 2015 (7)    | 2013  | Regional, Molise    | Report from the Italian Network of Rare disease; analysis of all families (N = 31) with at least one case of HD in the pedigree residing in Molise region | Clinical assessment + Genetic testing | 34           | 313,341              | 10.9            |
| Carrassi et al. 2017 (8)     | 2014  | Provincial, Ferrara | Analysis of medical records (DRG) from the Local Health Units + Hospitals of Ferrara province, identification of Medical Exemption code RF0080 | Clinical assessment + Genetic testing | 15           | 354,673              | 4.2             |
| Regional Registry of Toscana Region, 2015 (9) | 2014  | Regional, Toscana   | Analysis of the institutional database of the Regional Health Service; identification of Medical Exemption code RF0080 | N/A                               | 169          | 3,750,511            | 4.5             |
| ReLMaR 2015 (10)             | 2015  | Regional, Lombardy; includes provincial estimates | Analysis of the institutional database of the Regional Health Service; identification of Medical Exemption code RF0080 | N/A                               | 442          | 10,008,348           | 4.4             |
ian residents (2019 estimates). Interestingly, while all scientific entries published after 1993 included HTT analysis in the case definition, reports published by the Regional Health Services estimated HD prevalence only by means of reported medical exemption code RF0080, without any hints whether the diagnosis was achieved by a clinical assessment or was assisted by genetic testing.

Pooled estimates for HD prevalence are reported in Figure 2. Briefly, individual estimates ranged from 0.6/100,000 inhabitants (95%CI 0.0 to 3.5) in Oristano 2019, peaking to 31.8/100,000 in San Marino Republic 2016. More precisely, while half of the estimates reported substantially low prevalence rates (i.e. < 5/100,000 inhabitants), four estimates were included in the usual range for Western Countries (i.e. 5 to 7 cases/100,000 inhabitants), all of them from Lombardy in 2015 (i.e. Brescia: 5.7/100,000, 95%CI 4.5 to 7.2; Milan: 5.2/100,000, 95%CI 4.4 to 6.0; Pavia: 5.3/100,000, 95%CI 3.5 to 7.6; and Sondrio: 5.0/100,000, 95%CI 2.3 to 9.4), with three areas characterized by high or even very high rates, including the regional estimate for Molise (10.9/100,000 inhabitants, 95%CI 7.5 to 15.2), and provincial estimates for Varese 2015 (29.2/100,000 inhabitants, 95%CI 19.1 to 42.8) and San Marino.

Based on the random-effect model, a pooled estimate of 3.9/100,000 inhabitants (95%CI 3.0 to 5.0) was obtained: focusing on the geographical level of ascertain, a significant difference was identified, with an estimate of 3.4/100,000 inhabitants (95%CI 2.1 to 5.4) calculated from regional records, and 4.1/100,000 inhabitants (95%CI 3.0 to 5.5) for studies performed...
at a provincial level (chi squared test p value < 0.001). Heterogeneity was substantial, not only for the summary estimate ($I^2 = 95\%$, p < 0.001), but also for the subgroup analyses (97\% for studies performed at regional level, 92\% for studies performed at provincial level).

Interestingly, also when studies were grouped by publication date (i.e. before vs. after 1993; Figure 3), a significant difference was identified, with a pooled prevalence of 3.0/100,000 (95\%CI 2.3 to 4.0) vs. 4.1/100,000 (95\%CI 3.1 to 5.5) (chi squared test p value < 0.001). Studies performed after 1993 were affected by high heterogeneity values ($I^2 = 95\%$), while in earlier studies a lower but still substantial heterogeneity value ($I^2 = 68\%$). However, in a meta-regression model, the effect of the study year on the residual heterogeneity $Q$ was not statistically significant ($Q = 0.4495$, p = 0.480).

The presence of publication bias was evaluated using funnel plots and regression test for funnel plot asymmetry, separately for studies performed at regional and provincial level. Each point in funnel plots represents a separate study and asymmetrical distribution indicates the presence of publication bias. First, studies’ effect sizes were plotted against their standard errors and the visual evaluation of the funnel plot suggested a significant publication bias only for studies performed at regional level, as the graph appeared slightly asymmetrical (Figure 4b). Still, such subjective evidence from the funnel plot was rejected after the regression test ($t = -0.62672$, p-value = 0.5539 for regional estimates; $t = -1.0009$, p-value = 0.3283 for provincial estimates).

![Figure 3](image-url) **Figure 3.** Pooled prevalence of reported studies, with estimates by the year of publication, i.e. pre-1993 vs. post-1993 (Note: ReLMaR = Registro Lombardo Malattie Rare, Regional registry of Lombardy for rare diseases; “San Marino Republic, while an independent State, is actually a small enclave in the Emilia Romagna Region).”

![Figure 4](image-url) **Figure 4.** Funnel plots of available studies on the Italian prevalence of Huntington’s disease, at regional level (a), and at provincial level (b).
Discussion

HD is a relatively rare disease, whose prevalence rates are, at the same time, stable overtime, strictly population-specific, and possible affected by the “founder effect”, with possible clusters of higher prevalence even in areas otherwise of normal or low prevalence (2,3,6,7,9,26).

As a consequence, while usual prevalence rates of 5 to 7/100,000 inhabitants have been diffusely reported (2,9), more recently Rawlins et al. (7) have suggested that such figures may result from a very heterogeneous evidence, even focusing on European countries and/or geographical areas inhabited by individuals of European origin. In facts, prevalence rate for continental Western European Countries would be somewhat lower than previously reported, i.e. 3.6/100,000 (95%CI 3.5 – 3.7), with higher figures for United Kingdom (6.7/100,000, 95%CI 6.5 to 7.0), North America (7.3/100,000, 95%CI 6.9 to 7.7), and Oceania (5.6/100,000, 95%CI 5.6 to 6.3), i.e. geographical areas that in the past centuries were involved in significant migratory fluxes from British Islands, with a possible magnification role of the founder effect, particularly in Eastern US (2,7,9).

Available evidence suggests that actual Italian prevalence rates may be somewhat intermediate between those reported in continental Western European Countries and United Kingdom (i.e. 3.9/100,000, 95%CI 3.0 to 5.0), particularly when focusing on more recent studies (i.e. 4.1/100,000, 95%CI 3.1 to 5.5). However, the estimates are quite heterogeneous in terms of quality, as derived from studies of strikingly different design (i.e. clinical assessment vs. genetic-based assessment), and databases whose case definition is often unclear. For instance, all regional reports derived their estimates from the total medical exemption for HD (i.e. code RF0080) among regional residents, but it remains unclear how such diagnosis was performed (14–18). In other words, even for reports published after 1993, a possible underestimate remains possible, being of difficult ascertain. Not coincidentally, while the field study of Frontali et al. in 1990 suggested a possible prevalence of 2.6/100,000 for the Lazio Region (11), a more recent estimate of 1.9/100,000 was reported by the National Health Agency in 2017 (17).

Despite such preventive caveats, available figures apparently stress the well-known Italian genetic heterogeneity, with areas characterized by prevalence rates well-below estimates for Western European Countries (for example: Oristano, 0.6/100,000; Mantua, 1.5/100,000; Friuli-Venezia-Giulia, 1.9/100,000) (14,18,21), coexisting in the same region in the same timeframe with areas of relatively high prevalence (e.g. South Sardinia, 4.8/100,000; Brescia 5.7/100,000), and even with some significant possible clusters as the province of Varese (29.2./100,000). Possible clusters were also reported in the Molise region (10), as well as in the San Marino Republic (19): all of them are areas characterized by a mountainous and/or somewhat geographically segregated nature, and again – likewise to the Eastern United States, founder effect may have played a prominent role in increasing actual rates. For these reasons, a comparison with other areas from the Alpine Region would be of particular interest, but data are still unavailable.

As a consequence, our estimates suggest that around 2354 HD cases may be prevalent in Italy in 2020 (95%CI 1811 to 3018), or even 2474 (95%CI 1871 to 3320) assuming as a reference only estimates reported after 1993. Such figures are somehow intermediate between the 6500 cases suggested by the report of Squitieri et al. on the Molise region (10), and the 1188 actual cases identified in the National Report on Rare Disease (12), and should be cautiously interpreted, for several reasons. First at all, raw data stratified by sex and age at the prevalence date are scarcely reported in retrieved estimates. Therefore, not only a standardization of HD prevalence rates, but even the actual raw figures are hardly obtainable.

Secondly, our data encompassed only half of Italian population, with the notable exception of Alpine regions: reports on other neurodegenerative diseases extensively suggest that such antiquely quasi-segregated area may largely diverge from national estimates because of the specific genetic composition of original residents (27). Moreover, around half of the total sample included cases from two Italian regions (i.e. Lazio e Lombardy), that have been characterized by large migratory fluxes, from both Southern Italian Regions and Foreign countries. As a consequence, both regions are possibly characterized by a higher number of resi-
dent from areas at low or even very low risk for HD, and that would possibly impair the generalizability of reported estimates (7,9,28).

Despite its potential interest, our study is affected by several limitations.

In first place, we addressed a topic (i.e. prevalence of HD), that rarely achieved a full publication on peer-review journals. Therefore, the majority of the possible evidence included in this report is drawn either from other scientific publications (i.e. abstracts and scientific reports), or from regional record, whose reliability has been often discussed.

Second, we explored a relatively large timeframe, starting with 1982: between the earlier reports of Reverberi et al. (24) and the more recent report of Muroni et al. (21), not only genetic counseling was introduced, but also clinical diagnostic criteria have progressively evolved, being progressively refined. However, the meta-regression model hinted towards a non-significant effect of the study year on the residual heterogeneity Q. Therefore, the differences we identified in the estimates between pre- and post-1993 studies may rather found their roots in other factors, such as the different geographical settings, or the heterogenous sampling strategy.

In summary, notwithstanding potential bias and aforementioned limitations, it should be stressed that our crude prevalence estimates hint towards a HD burden of disease that is nearly the double of that more recently acknowledged by the National Report on Rare Diseases (i.e. 1188 cases for 2014) (12,29). In other words, despite all its limitation, our study suggests that up to half of all Italian cases of HD may have failed to receive an appropriate diagnosis, possibly because of a mixture of low suspicion in subjects from non-symptomatic families (1,2,6,9), and unfamiliarity with rare diseases and their diagnosis in the main Health-care providers (e.g. Pediatrician for early onset cases, General Practitioners, Internists, but also figures potentially able to identify early signs/symptoms likewise the occupational physician) (30–32), the latter being a shared problem for several less common clinical conditions and infectious diseases (33–36).

In other words, available estimates suggest that Italian Health Service would actually fail in guaranteeing appropriate services for all HD cases. Even though a curative therapy for HD still does not exist, palliative and symptomatic interventions (antidepressants, antipsychotics, anti-choleform medications) should be ensured to all individuals and their families.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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