

This is a repository copy of *Prevalence and incidence of Huntington's disease*.

White Rose Research Online URL for this paper: <u>https://eprints.whiterose.ac.uk/200988/</u>

Version: Accepted Version

# Article:

Strong, M. orcid.org/0000-0003-1486-8233 and Quarrell, O. (2023) Prevalence and incidence of Huntington's disease. Movement Disorders, 38 (8). pp. 1570-1572. ISSN 0885-3185

https://doi.org/10.1002/mds.29532

© 2023 The Authors. Except as otherwise noted, this author-accepted version of a journal article published in Movement Disorders is made available via the University of Sheffield Research Publications and Copyright Policy under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/

## Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: https://creativecommons.org/licenses/

## Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk https://eprints.whiterose.ac.uk/

#### Prevalence and Incidence of Huntington's Disease comment on Medina et al (2022). DOI: 10.1002/mds.29

Mark Strong PhD CStat<sup>1</sup> Oliver W Quarrell MD FRCP<sup>2</sup>

Professor of Public Health
School of Health and Related Research (ScHARR),
University of Sheffield, Sheffield, UK,
S1 4DA.

ORCID id 0000-0003-1486-8233 m.strong@sheffield.ac.uk

2. Honorary Consultant, Sheffield Children's Hospital, Sheffield, UK.

Honorary Clinical Lecturer, Department of Neuroscience, University of Sheffield, Sheffield, UK, S10 2HQ.

ORCID id 0000-0002-3818-9051 oliverguarrell@nhs.net ~441142717000

Word Count 553

Financial Disclosures: None. No Financial Support

Authors' roles

- 1. Design, analysis, writing, editing of the final version of the manuscript.
- 2. Design, writing, editing of the final version of the manuscript.

## Prevalence and Incidence of Huntington's Disease comment on Medina et al (2022). DOI: 10.1002/mds.29

We read with interest the updated review of the epidemiology of Huntington's disease (HD) by Medina *et al.*[1] In their paper, the authors present results from a series of meta-analyses of prevalence and incidence studies conducted in populations in Africa, Asia, Europe and the Americas between 2011 and 2022. World-wide pooled estimates are reported for prevalence and for incidence, along with separate pooled incidence estimates for each continent where there was more than a single study. In each case, estimates were derived from a random-effects meta-analysis.

As is common in systematic reviews of prevalence and incidence, the included studies are heterogeneous in terms of their methodology, data source and population. For example, whilst the majority of studies in the review reported prevalence and incidence for all ages, Gavrielov-Yusim *et al* [2] provided results only for those  $\geq$ 18 years and Evans *et al* [3], only for those  $\geq$ 21 years. These two studies derived their estimates from administrative and research databases whereas Kounidas *et al* [4] used genetic laboratory, clinic and hospital records. These differences in population and data source matter; the epidemiology of HD in children and adolescents is not the same as in adults, and different data sources are derived from populations with different disease risk.

Significant heterogeneity in a meta-analysis results in pooled estimates that are difficult to interpret, and this is very much the case here. The pooled prevalence and incidence estimates reported by Medina *et al* do not in any meaningful sense represent the prevalence or incidence in a defined population. However, this is exactly how the pooled estimates reported in a previous meta-analysis study [5] have been used [6-9].

This misinterpretation is made even more likely due to an error in the reporting of the key measures of study heterogeneity, Q (which follows a chi-squared distribution and therefore allows us to test the significance of the heterogeneity) and  $l^2$ . The values of Q and  $l^2$  reported in Tables 1 and 2 of Medina *et al* suggest that heterogeneity is very small or absent. However, this is not actually the case. Unfortunately, the software that the authors used, *Comprehensive Meta-Analysis Software*, rather confusingly reports a " $Q^*$  statistic" (along with an  $l^2$  value calculated from this value of  $Q^*$ ) which should be used "*only* for the analysis of variance, to partition  $Q^*$  into its various components", and it is these values that appear in the paper. The software authors note that these statistics are not measures of heterogeneity and state that "[r]ather, the Q statistic computed using *fixed-effect weights* [our emphasis] is the one that reflects the between-studies dispersion" [10].

We have calculated the correct values of Q and  $l^2$  and, in contrast to the values reported in the paper, the results suggest a very high degree of heterogeneity (table 1).

The high degree of heterogeneity can be also be seen clearly in forest plots generated from the data presented in the paper. See Figure 1 for an example (European prevalence studies).

In conclusion, we caution against interpreting the pooled estimates of prevalence and incidence reported in Medina *et al* as meaningful for any population. We would also encourage authors of meta-analysis studies to publish forest plots, either in the body of the paper or as a supplementary file, so that readers can visually assess the degree of heterogeneity in the study estimates.

## References

1. Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. Mov Disord 2022;37:2327-2335.

2. Gavrielov-Yusim N, Barer Y, Martinec M, et al. Huntington's disease in Israel: a population-based study using 20 years of routinely collected healthcare data. J Huntington's Dis 2021;10:469–477.

3. Evans SJ, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry 2013;84:1156–1160.

4. Kounidas G, Cruickshank H, Kastora S, Sihlabela S, Miedzybrodzka Z. The known burden of Huntington disease in the north of Scotland: prevalence of manifest and identified pre-symptomatic gene expansion carriers in the molecular era. J Neurol 2021;268:4170–4177.

5. Pringsheim T, Wiltshire K, Day L, Dykeman J Steeves T, Jette N. The Incidence and Prevalence of Huntington's Disease: A Systematic Review and Meta-analysis. Mov Disord 2012;27:1083-1091.

6. García-González X, Cubo E, Simón-Vicente L, Mariscal N, Alcaraz R, Aguado L, Rivadeneyra-Posadas J, Sanz-Solas A, Saiz-Rodríguez M. Pharmacogenetics in the Treatment of Huntington's Disease: Review and Future Perspectives. J Pers Med. 2023;13(3):385.

7. Pereira CAS, Medaglia NC, Ureshino RP, Bincoletto C, Antonioli M, Fimia GM, Piacentini M, Pereira GJDS, Erustes AG, Smaili SS. NAADP-Evoked Ca2+ Signaling Leads to Mutant Huntingtin Aggregation and Autophagy Impairment in Murine Astrocytes. Int J Mol Sci. 2023;24(6):5593.

8. Geijtenbeek KW, Janzen J, Bury AE, Sanz-Sanz A, Hoebe RA, Bondulich MK, Bates GP, Reits EAJ, Schipper-Krom S. Reduction in PA28αβ activation in HD mouse brain correlates to increased mHTT aggregation in cell models. PLoS One. 2022;17(12):e0278130. d

9. Vuic B, Milos T, Tudor L, Konjevod M, Nikolac Perkovic M, Jazvinscak Jembrek M, Nedic Erjavec G, Svob Strac D. Cannabinoid CB2 Receptors in Neurodegenerative Proteinopathies: New Insights and Therapeutic Potential. Biomedicines. 2022;10(12):3000.

10. Borenstein M, Hedges LV, Higgins JPT, Rothstein R. Sub-Group Analyses. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein R. Eds. Introduction to Meta-Analysis. 2009; p166.

Region	Measure of heterogeneity				
	Incidence	Prevalence			
Africa	No meta-analysis reported	$l^2 = 91.4\%, Q = 11.6 (p < 0.0007)$			
Asia	No meta-analysis reported	$l^2 = 99.6\%, Q = 481.6 (p < 0.0001)$			
Europe	$l^2 = 91.8\%, Q = 110.2 (p < 0.0001)$	$l^2 = 98.3\%, Q = 801.3 (p < 0.0001)$			
North America	$l^2 = 97.3\%, Q = 37.3 (p < 0.0001)$	$l^2 = 99.6\%, Q = 495.1 (p < 0.0001)$			
South America	No meta-analysis reported	$l^2 = 99.4\%$ , $Q = 164.0$ ( $p < 0.0001$ )			
World-wide	$l^2 = 98.4\%, Q = 738.1 (p < 0.0001)$	$l^2 = 99.5\%$ , $Q = 4850.5$ ( $p < 0.0001$ )			

TABLE 1: Values of P and Q (p-value) for each meta-analysis reported in Medina et al [1].

Study	Cases	Population	P	revalence pe	r 100,000 popi	ulation	Events	95%-CI
Region = Europe								
Carrassi (2017)	15	354673	-+				4.23	[2.55; 7.02]
Evans (2013)	432	3515986					12.29 [	11.18; 13.50]
Gilling (2017)	329	5660000		*			5.81	[5.22; 6.48]
Kounidas (2021)	134	893440			•		15.00 [	12.66; 17.77]
Morrison (2011)	180	1698113					10.60	[ 9.16; 12.27]
Muroni (2020)	47	785785	-				5.98	[4.49; 7.96]
Ohlmeier (2019)	308	3325638					9.26	[ 8.28; 10.36]
Panas (2011)	278	10964020	*				2.54	[ 2.25; 2.85]
Roos Jamatland (2017)	28	126765					22.09 [	15.25; 31.99]
Roos Uppsala (2017)	17	348942	_	•			4.87	[ 3.03; 7.84]
Sackley (2011)	177	2964386					5.97	[5.15; 6.92]
Sipilia (2015)	114	5377358	+				2.12	[ 1.76; 2.55]
Sqitieri (2016)	34	313341			_		10.85	[ 7.75; 15.19]
Sveinsson (2016)	3	311114					0.96	[0.31; 2.99]
Vicente (2021)	32	647554		<u> </u>			4.94	[ 3.49; 6.99]
2	2		0	10	20	30		

Heterogeneity:  $I^2$  = 98.3%,  $\chi^2_{14}$  = 801.3 (p < 0.0001)