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

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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 ≥18 years and Evans *et al* [3], only for those ≥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 I^2. The values of *Q* and I^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 I^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 I^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.

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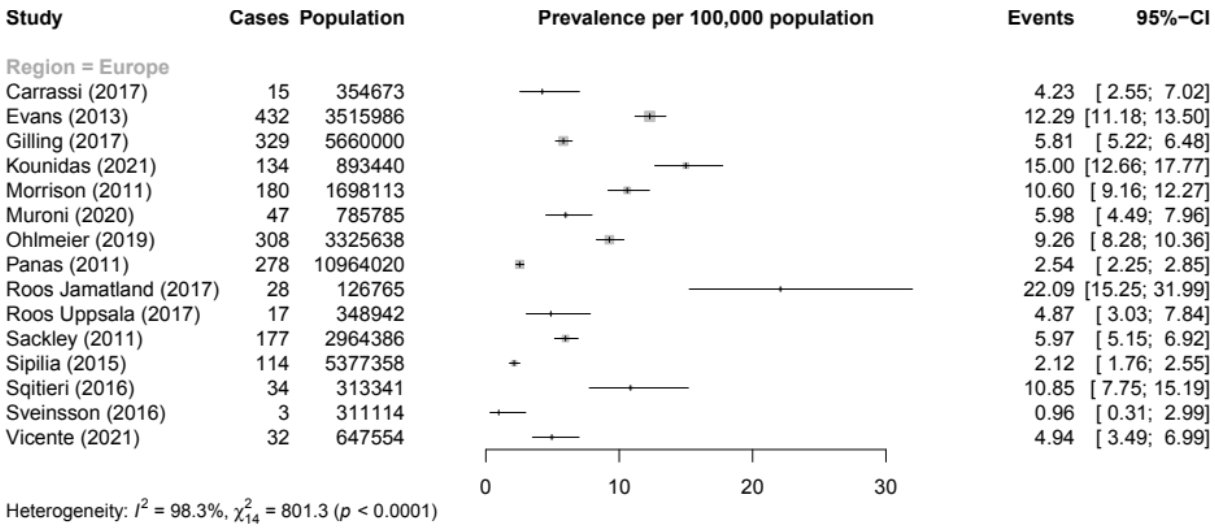
TABLE 1: Values of I^2 and Q (p-value) for each meta-analysis reported in Medina *et al* [1].

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



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