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proposed modeling framework, but in the present study using six different outcome measures, we found it infeasible to model a 6×6 correlation structure based on the available sample size. Pooling samples from different cohorts could make this feasible.

iii. Homogeneity of progression may not be true. Assuming consistency of effects across subjects is a fundamental part of statistical modeling. However, as demonstrated in our study of the two major motor subtypes of MSA, one can use the proposed disease progression model to model differential disease progression in subgroups of patients.

iv. Death can contain additional information. We agree that the assumption of censoring due to death may bias results, and the joint modeling of the latent disease process and the risk of death as illustrated by Saulnier et al[4] is a welcome development. We look forward to more widespread future use.

This replication study based on the French MSA cohort underscores the importance of long-term follow-up data to accurately describe long-term disease progression in MSA. These findings are important not only for the design of observational studies but also for interventional studies of potentially disease-modifying therapies, where longer individual follow-up will enable a better understanding of how treatment changes the course of disease.

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Data Availability Statement

No Data Available

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Prevalence and Incidence of Huntington's Disease

We read with interest the updated review of the epidemiology of Huntington's disease (HD) by Medina et al.[1] In their article, 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. Worldwide pooled estimates are reported for prevalence and 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, whereas 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[1] 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 χ^2 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[1] suggest that heterogeneity is very small or absent. However, this is not actually the case.

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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 article. 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]

TABLE 1 *Values of* I^2 *and Q (P value) for each meta-analysis reported by 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	$I^2 = 99.4\%$, $Q = 164.0$ ($P < 0.0001$)
Worldwide	$I^2 = 98.4\%$, $Q = 738.1$ ($P < 0.0001$)	$I^2 = 99.5\%$, $Q = 4850.5$ ($P < 0.0001$)

We have calculated the correct values of Q and I^2, and in contrast with the values reported in the article, the results suggest a very high degree of heterogeneity (Table 1).

The high degree of heterogeneity can also be seen clearly in forest plots generated from the data presented in the article. 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[1] 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.

Data Availability Statement

The data that support the findings of this study are available in in Medina et al (2022) at DOI: 10.1002/mds.29228

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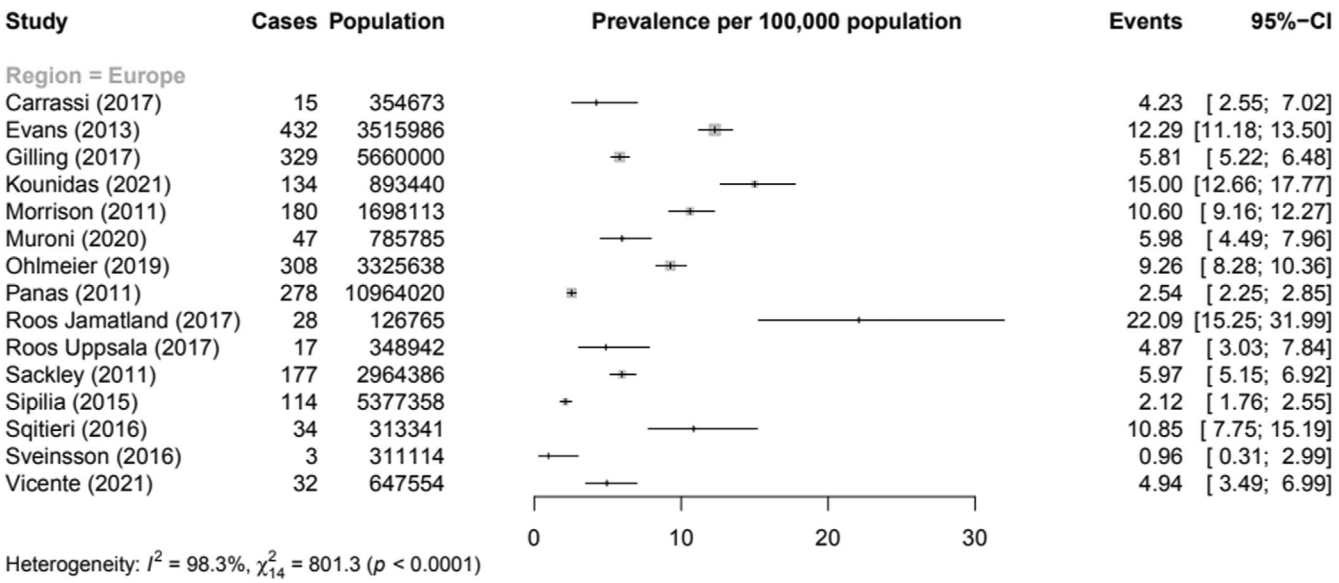

FIG. 1. European prevalence studies.

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Reply to Letter to the Editor: Prevalence and Incidence of Huntington's Disease Comment on Medina et al. (2022)

Drs. Quarrell and Strong caution against interpretation of the pooled estimates of prevalence and incidence of Huntington's disease (HD)[1] as meaningful for any population because of suggested high degrees of heterogeneity based on values of Q and I^2. The authors are correct that we reported the Q statistic and I^2 value for our random effects analysis, which are used for analysis of variance, rather than the Q statistic and I^2 computed from the fixed effects analysis, which assess between-studies dispersion. The numbers presented for Q and I^2 in table 1 of Quarrel and Strong are the same values we obtained with our data using a fixed effects analysis.

There has been debate in the literature regarding the appropriateness of meta-analysis within systematic reviews of prevalence, a view which Drs. Quarrell and Strong have previously expressed in their own systematic review of the prevalence of HD.[2] The debate centers on whether synthesizing across different populations is appropriate, as it is reasonable to expect disease prevalence to vary across different contexts. The Prevalence Estimates Reviews-Systematic Review Methodology Group (PERSyst) hold the view that meta-analysis can provide important information regarding burden of disease, identifying differences among populations and regions, changes over time, and can provide a summarized estimate that can be used for calculating baseline risk.[3] Indeed, the meta-analysis of HD incidence and prevalence provided in our manuscript does exactly this, identifying differences in prevalence by continent and over time.

Even greater debate surrounds the use of I^2 as a method of assessing heterogeneity in meta-analysis of prevalence studies. I^2 tells us what percentage of the variance in observed effects reflects variance in true effects rather than sampling error. It reflects the amount of overlap between confidence intervals of individual studies. Confidence intervals are related to sample size, with large studies leading to more precise, narrow confidence intervals. In a meta-analysis of prevalence studies, because of the very large sample sizes of individual studies and precise estimates, confidence intervals tend not to overlap, leading to high I^2 estimates. A recent meta-epidemiological study performed by PERSyst analyzed 235 systematic reviews of prevalence published between 2017 and 2018.[3] Of these, 65% conducted a meta-analysis with most using a random effects model, with heterogeneity assessed with I^2 in 95%. Of the 134 meta-analyses reporting I^2 for their main analyses, 104 (78%) presented I^2 higher than 90%, with a median of 96.9%.[4] Such high values for I^2 are not common in meta-analyses of other data types, with a median I^2 of 21% for 1011 Cochrane systematic reviews comparing the effect of interventions for binary health outcomes.[5] PerSyst cautioned that the decision on whether to report the results of a meta-analysis of prevalence should not be based on the value of I^2, and relying solely on I^2 to explore heterogeneity can be misleading especially for this type of data. They conclude that authors and readers should not be over concerned with high I^2 values in meta-analyses of prevalence. Other assessments of heterogeneity, including T^2 and prediction intervals, are likely more appropriate. Prediction intervals include the expected range of true effects in similar studies, a more conservative way to incorporate uncertainty in the analysis when true heterogeneity is expected. True heterogeneity is expected in prevalence because of differences in the time and place where included studies are conducted. However, only 2% of studies in their meta-epidemiological study reported prediction intervals.[3] Standards for reporting of meta-analysis of prevalence studies are currently evolving. We plan in our future work to report prediction intervals rather than I^2 to describe how widely effects vary.

Data Availability Statement

Not applicable

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