Reviewer’s report

Title: Risk of mortality among children, adolescents and adults with autism spectrum disorder or attention deficit hyperactivity disorder and their first-degree relatives: a protocol for a systematic review and meta-analysis of observational studies

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Reviewer: Anna Van Metter

Reviewer's report:

The proposed protocol, "Risk of mortality among children, adolescents and adults with autism spectrum disorder or attention deficit hyperactivity disorder and their first-degree relatives: a protocol for a systematic review and meta-analysis of observational studies," describes the plan for conducting a meta-analysis of studies reporting on mortality among individuals with ADHD or Autism. Although the authors make a case for the importance of this study, I am concerned that the scope is too broad to yield meaningful results (particularly the inclusion of all ages and multiple diagnoses). I have some specific recommendations detailed below.

It isn't clear to me why the authors are combining ADHD and ASD. Although these disorders do co-occur, the majority of people with ADHD do not have ASD. Additionally, this approach will introduce a lot of heterogeneity that may be difficult to account for in the analyses: studies of ADHD will contribute more effect sizes; the patterns of comorbidity are different between the two groups, the sources of ascertainment are likely to be different, etc… If the authors are set on combining these two groups, I would strongly encourage them to calculate effect sizes separately (just ADHD, just ASD, people with comorbid ADHD/ASD, all studies)

It is not clear whether one of the inclusion criteria is that there is a comparator group. I suggest that it should be. The type of comparator group must be coded and included as a moderator; a medical or psychiatric comparator will likely give a more accurate depiction of the risk that can be attributed to these specific diagnoses (versus having a chronic illness in general).

The authors mention a number of effect sizes, "Effect measures will include the standardized mortality ratio (SMR), the relative risk (RR), the odds ratio (OR), the hazard ratio (HR)." It will be important to pick one and to determine the necessary information for calculating this effect size. It is likely that many articles will not include the necessary information, even if the topic is on point.

The authors may want to include PsycINFO as one of their search databases.

The authors will want to state the qualifications of the people coding the articles.
I would encourage the authors to also code for other medical and psychiatric comorbidities; mood disorders, overweight, asthma, etc are also associated with mortality. They could also consider a variable accounting for total number of comorbidities to account for cumulative effects.

Other moderators the authors should code for include method of diagnosis (e.g., structured interview, clinical diagnosis, etc…not all are equally valid), diagnostic criteria used (these have changed over time), IQ (not just disability), year of data collection/year of publication (these may be better than cumulative meta-analysis for accounting for shifts over time)

In regard to setting, medical settings (inpatient, outpatient) should also be accounted for, not just mental health settings.

Rather than this approach - "If primary studies report results separately for men and women or other 207 subgroups we will combine the subgroup specific estimates using a fixed effect model to 208 generate an estimate for both subgroups combined so that each study was represented only 209 once in the analyses" It is better to use a mixed model, so that multiple effect sizes from each study can be included and the nesting accounted for.

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