Author’s response to reviews

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

Authors:
Ferrán Catalá-López (ferran_catala@hotmail.com)
Brian Hutton (bhutton@ohri.ca)
Matthew Page (matthew.page@monash.edu)
Manuel Ridao (ridao_man@gva.es)
Jane Driver (jdriver@partners.org)
Adolfo Alonso-Arroyo (adolfo.alonso@uv.es)
Jaume Forés-Martos (fores.martos.jaume@gmail.com)
Diego Macías Saint-Gerons (dmacias.sg@gmail.com)
Eduard Vieta (evieta@clinic.ub.es)
Alfonso Valencia (alfonso.valencia@bsc.es)
Rafael Tabarés-Seisdedos (rafael.tabares@uv.es)

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Author’s response to reviews:
Valencia, 6 July 2017
Dr. Joseph L Mathew
Associate-Editor Systematic Reviews
Dear Dr. Mathew,

We thank you for having recently shared peer review on our protocol manuscript entitled: “(SYSR-D-17-00095) - 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, by Ferrán Catalá-López; Brian Hutton; Matthew J Page; Manuel Ridao; Jane A Driver; Adolfo Alonso-Arroyo; Jaume Forés-Martos; Diego Macías Saint-Gerons; Eduard Vieta; Alfonso Valencia; Rafael Tabarés-Seisdedos”, for publication in Systematic Reviews.

Along with this letter you will find a summary of our point-by-point responses to deal with reviewers’ comments. We have uploaded the revised manuscript and shown modifications using yellow highlighting to facilitate verification.

We thank you for your interest in our work and we look forward to hearing from you.

Sincerely yours,

Ferrán Catalá-López, on behalf of the rest of coauthors.
Specific requests:

Reviewer: 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.

Authors’ response:

Thank you for your comments. We have clarified and revised the manuscript following reviewers’ suggestions.

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)

Authors’ response:

Thank you for your comments. Neurodevelopmental disorders such as ADHD and autism, although most commonly considered in childhood, can be lifelong conditions. In our proposed systematic review, we will identify, assess, synthesize and discuss studies for both neurodevelopmental conditions. In the Introduction section, we acknowledge both distinction and grouping are helpful and that it is important to take into account the strong overlap across neurodevelopmental disorders (see also reference 1 by Thapar et al in Lancet Psychiatry 2017). To clarify, we are not proposing the combination of ADHD and ASD together in meta-analyses. We agree that approach will introduce a lot of heterogeneity. We have made minor/discretionary revisions to the manuscript following reviewers’ suggestions (Data synthesis section), as follows: “We will calculate summary effect estimates comparing the mortality in people with ADHD or ASD with mortality in the reference control group. Statistical combination of data from two or more observational studies in a meta-analysis will be conducted and reported separately for ADHD and ASD.”
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).

Authors’ response:

Thank you for your comments. We have made minor/discretionary revisions to the manuscript following reviewers’ comments, including a moderator analysis by setting or reference group (e.g. mixed, inpatient, outpatient or community/general population). To clarify: “Case-control studies, prospective cohort studies with a reference comparator, and retrospective cohort studies with a reference comparator (also known as historical cohort studies) will be included.”

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.

Authors’ response:

Thank you for your comments. It is unlikely that many articles/studies report crude results or data to calculate an effect size. As we discuss in methods, we will collect: “the number of cases and controls (in case-control studies) or the number of cases and population participants (in cohort studies) and/or the maximally adjusted effect measure (e.g. relative risk, hazard ratio or standardized mortality ratio) with 95% confidence intervals.” In random effects meta-analyses, we will synthetize maximally adjusted effect measures (reported at study level) where appropriate.

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

Authors’ response:

Thank you for your comment. We have included PsycINFO, as suggested.

The authors will want to state the qualifications of the people coding the articles.

Authors’ response:
Thank you for your suggestion. This is a protocol for a prospective systematic review. Coding of articles and data abstraction process have not been started yet. In our article, we have provided the qualifications of our review team: “FC-L is a PhD (Public Health) and MPH. BH is a PhD (Epidemiology and Biostatistics) and MSc. MJP is a PhD (Epidemiology) and BBSc Hons (Psychology). MR is a PhD (Medicine) and MSc (Economics). JAD is a MD (Oncology and Geriatrics) and MPH. AA-A is a PhD (Information and Documentation) and MA. DM-SG is a PhD (Pharmacology) and MPH. JF-M is a PhD candidate and MSc. EV is a MD (Psychiatry) and PhD. AV is a PhD (Molecular Biology) and MSc. RT-S is a MD (Psychiatry) and PhD.”

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.

Authors’ response:

Thank you for this suggestion. We acknowledge comorbidity is an important factor to consider. In our registered protocol, we have defined ‘a priori’: First, we will abstract “the general characteristics of participants (age, gender, ethnicity, social status, and comorbidities such as intellectual disability, substance abuse, epilepsy and other medical and neuropsychiatric conditions ),…”; second, if sufficient studies are identified, we will present subgroup analyses to attempt to explain any potential observed between-study heterogeneity. The potential moderators (covariates) considered will include medical or neuropsychiatric comorbidity (e.g. presence or absence of a comorbid disorder with ASD or ADHD), and number of comorbidities (e.g. 0, 1, 2, or >= 3).

We agree with the reviewer that obesity, asthma… are important comorbidities in childhood, but our (revised) general statement covers these medical conditions. To reiterate, if sufficient studies are identified reporting this information, we will explore the impact of comorbidity, including those mentioned by the reviewer.

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)

Authors’ response:

Thank you for these suggestions. We agree with the reviewer some of these covariates could be interesting to consider. In fact, year of data/publication is a moderator defined in our methods as
follows: “(…) year of publication as a proxy of changes in clinical practice over time (before 2000 or in 2000 and after), (…)”. Regarding diagnosis, we will use investigator-reported definitions of ASD or ADHD according to accepted diagnostic criteria (e.g., ninth or tenth revisions of the ICD coding system or the third, fourth or fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria): ASD (ICD-9: 299.0, 299.8; ICD-10: F84), ADHD (ICD-9: 314.00, 314.01; ICD-10: F90). We have included a moderator analysis of diagnostic criteria used, as suggested. Regarding IQ, please see our response on comorbidities. No further changes are suggested.

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

Authors’ response:

Thank you for your comment. To clarify, inpatient/outpatient refer to health services, not just to mental health setting. No changes are suggested.

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.

Authors’ response:

Thank you for your comment. Mixed linear models and meta-regressions are an extension to subgroup analyses that allows the effect of continuous, as well as categorical, characteristics to be investigated, and in principle allows the effects of multiple factors to be investigated simultaneously (although this is rarely possible due to inadequate numbers of studies). (…) For example, according to the Cochrane manual, meta-regression should generally not be considered when there are fewer than 10 studies in a meta-analysis.“

As we clearly stated in methods: “The random-effects model is selected a priori to synthesize the epidemiological data, as it considers both within-study and between-study variation by incorporating the heterogeneity of effects into the overall analyses.” We also report that, we will only conduct fixed effects models when a primary study reports two results separately, for example, for men and women to combine results at study level (same study) to generate an overall estimate for both subgroups (e.g. both sexes) so that each study is represented only once
in the analyses. We consider this a valid approach, and consistent with our recent protocols published in the Journal (references 38 and 39). No changes have been introduced on this regard.