PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Physical health complications in children and young people with Avoidant Restrictive Food Intake Disorder (ARFID): A systematic review and meta-analysis
AUTHORS	James, Rachel O'Shea, Jonathan Micali, Nadia Russell, Dr Simon Hudson, Lee

VERSION 1 – REVIEW

REVIEWER	Dr. Daniel O'Reilly Rotunda Hospital Parnell square Dublin 1 Dublin 1 Dublin 1 County Dublin D01 P5W9 Ireland
REVIEW RETURNED	16-May-2024

GENERAL COMMENTS	Timely systematic review around an increasingly recognised diagnosis, would benefit from more clarity on why <25 years old was chosen as cut off beyond definition of adolescent/young adult. Age stratification was prespecified on prospero but no specific range suggested/offered. Limited experience of ARFID in general paediatrics to date has been in a largely younger cohort (<15yo)

VERSION 1 – AUTHOR RESPONSE

Thank you for your e-mail requesting a major revision. We are grateful for your consideration and encouragement with this systematic review, and for the important reviewers' comments. We have submitted a revised manuscript, and here provide responses to reviewer comments in order that they were provided.

Formatting Amendments

1) Reference citation format

References must be numbered sequentially as they appear in text. References numbers in the text must be inserted immediately after punctuation (with no word spacing)- for example,[6] not [6].
Where more than one reference is cited, separated by a comma- for example, [1, 4, 39].
For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen- for example, [22-25]. References provided in this format are translated during the production process to superscript type, which act as hyperlinks from the text to the quoted references in electronic format of the article.

Thank you, we have rectified this.

2) Table exceeds 3 pages or has more than 9 columns

Your Table 1 exceed 3 more pages. If the table is more than 2 pages long or has more than 9 columns, this has to be removed from the main document and designated as Supplementary table instead.

Thank you, we have rectified this.
3) Different Authors Name Format

The author's name format on the system and the main document file is different. "Lee Hudson" in the main document while "Hudson, Lee Duncan" in the system. The names indicated in the main text must match the name registered in the ScholarOne submission system.

Thank you, we have rectified this.

4) Supplementary File Format

Please be advised that supplemental materials and appendices included with the manuscript must be uploaded in PDF format. Kindly convert the supplemental file/s in the submission to PDF and re-upload. Kindly also rename your appendix to "Supplemental file 1" to avoid confusion.

Thank you, we have rectified this.

Associate Editor's reviewer comments.

1. I apologise for the delay in feedback - we asked many peer reviewers and only got back a response recently. To speed things up I am have reviewed myself. I would like to see this accepted but have a few points of action

We are really grateful for your input to speed things and for the helpful comments.

2. the meta-analysis concerns me. The heterogeneity is very high and the risk of bias problematic so I think you must be clear that no conclusions can be drawn - so not 'no difference' but no conclusions can be drawn on difference.

3. Discussing the unexplained cause for this heterogeneity is key for discussion and future research suggestions

Thank you for these important comments on heterogeneity – we have responded to number 2 and 3 points together here as they are linked. We agree that high levels of heterogeneity do add complexity to the interpretations of our meta-analysis. We discussed this in detail as a group before submission – and as we explained in the paper, we decided to use random effects models because of high heterogeneity. We acknowledge though that this approach does not deal with or account for the heterogeneity per se.
We do think however, that our sensitivity analyses are important in what we can say from the meta-analysis. In particular, the heart rate analysis (Figure 4.). In this meta-analysis, one particular study is an outlier on the forest plot [1]. This is also a smaller number study compared to others. When we removed this study from the meta-analysis, the I2 reduced to close to zero, and yet the overall (in both a random and fixed effect models: we can share the fixed effect if this is helpful) pooled outcome remained essentially the same (including confidence intervals). It would be incorrect to exclude that study just to address heterogeneity in our view given it meets a priori inclusion criteria, but the lack of difference with it in or out provides reassurance about a significant difference in heart rates. The finding is also plausible in terms of clinical experience, and the rest of evidence presented around heart rates – and moreover carries an important, plausible clinical message. We have elaborated on this in the discussion.
We tried where possible to examine for effects for consistently reported potential factors using meta-regression. It's possible that small numbers affected the power of such meta-regressions. Overall though, we aren't surprised about the high levels of heterogeneity. Ultimately, these studies are clinical samples, mostly retrospective and weren't designed with consistent protocols to measure the variables we retrieved from them. It's likely there was significant variation in how and when measures were taken – as suggested we have discussed the sources of heterogeneity in the manuscript with suggestions for future research.

4. what was the level of agreement, and do you have a statistical measure? Was extraction in duplicate - please clarify and also comment on agreement.

We didn't use a statistical measure to compare agreement and have not seen this used commonly in many published reviews. We will certainly consider this approach in future reviews. With regard to documented disagreement during abstract screen it was 2.45% and there was no disagreement on the full-text screen. We have added this to our paper.

5. I would put some time into supporting better utility and readability for the readership for what is now primarily narrative synthesis. I think a single infographic to fit a page of the journal summarising the findings in a clear and understandable way would really help this and the impact of the paper and would strongly encourage this or similar
Thank you for this helpful suggestion, we have created this and included in the resubmission.

Reviewer 1 comments

1. Timely systematic review around an increasingly recognised diagnosis, would benefit from more clarity on why <25 years old was chosen as cut off beyond definition of adolescent/young adult. Age stratification was prespecified on prospero but no specific range suggested/offered. Limited experience of ARFID in general paediatrics to date has been in a largely younger cohort (<15yo)

While we acknowledge that paediatric services are more likely to see ARFID <15, this is mostly because paediatric services frequently cease at 16 in many settings such as the UK and Ireland [2]. ARFID is however, a lifetime mental disorder and can be diagnosed at any age, and even when considering children and young people alone, they are likely to continue with that diagnosis through the life course. We originally planned a systematic review for all age groups (as per Prospero registration), but as explained in the methods have focused our findings to children and young people for this paper. Inclusion of up to 25-year-olds is in keeping with recent broader definitions and consideration of adolescence [3], and also includes "young adults" or "youth" as per the United Nations. Inclusion of up to 25 aligns with recent strategies for health policy for children and young people, in the UK – for example the NHS Long Term plan mental health strategy, NICE Disabled children and young people up to 25 with severe complex needs strategy[4], and the RCPCH and us strategy. For applicability of our review therefore we felt, and remain convinced, that it was important to include up to 25-year-olds as well as younger children in our inclusion criteria. We hope it will be of help to not just paediatricians, but clinicians looking after young adults and critically at the time of transition and transfer of care.

In addition to our changes and comments to the reviewers, it has come to our attention that a child died in the UK from ARFID with key learning from this sad case (https://www.judiciary.uk/prevention-of-future-death-reports/alfie-nicholls-prevention-of-future-deaths-report/). We wanted to qualify/contextualise the absence of mortality data in our searches accordingly. We have therefore edited this section further to signpost to this review. This very sad case is a potent reminder of why clinicians need to be alert to physical risk in CYP with ARFID which we reiterate as an important role of our review.

Thank you again for your time and consideration.