Honghu,

Thanks. I will incorporate your comments and Mark's, send back a complete document. I will include all the tables at the end of the manuscript (see the instructions to the authors). The figures are supposed to be uploaded separately. Attached you will find an example of a meta-analysis published in Pediatrics. – 4 tables and 4 figures appear to be the standard. I was able to import all references into Mendeley Reference Manager.

I will send you the file with the 42 data points (non-endemic F areas). It looks like the steep decline is between 0.1 and 0.4.

Jay

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Sunday, March 27, 2022 7:43 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Meta-analysis

Hi Jay,
I have gone through the paper and made suggested edits/comments. You can cherry-pick/revise/ignore as you see fit/need to make it consistent with the overall theme and writing style of the paper. Here are some points for now:
(1) The SMD analyses in the abstract shows that on average, there is no difference in IQ between the low and normal doses; it will be helpful to also add the non-linear modeling results to show that there is no significant fluctuation in IQ scores across the differences in F doses. I added a little there to see if it fits, along with other edits/comments for the abstract.
(2) Although including Zhang Shun provides a slightly better curve in Figure 3 for SMD, it is easier to explain and avoid confusion with Zhang Shun excluded. I used the 8 studies without it and updated the Figure 3 (see attached combined Figures).
(3) I have updated the statistical methods section (page 9) regarding non-linear modeling with restricted cubic spline (the methods used for non-linear modeling and the Figure 3). Although due to limited number of studies, the Figure 3 is not curved much, it is better to show non-linear modeling and its results than linear approximation.
(4) I have updated the results section with the non-linear restricted cubic spline modeling (page 10-11). The Wald-test with p=0.77 was only for the non-linear part and the Wald test with p=0.21 is the overall test of the modeling (both linear and non-linear parts).
(5) I agree that the Supplemental Fig B is unfortunately not showing what we like to show due to limited quality of these studies we use; if we show Supplemental Fig B, we will need to do a

good job in explaining why it is missing leading and what causes it show the non-expected results. I would consider to use the LOESS Regression Scatterplot you created to replace the S Figure B, given we recognize that the Loess regression will again only focus on F <1.5mg/L, and we will not be able to display/discuss potential impact of high F dose value. In this case, the Loess regression basically re-ensures the results of Figure 3 which I think is fine as our focus is <1.5mg/L anyway. I was thinking about to only select the low F dose data points from Duan's and other studies to increase our sample size the for standardized IQ score analyses with F<1.5mg/L, but haven' got a chance to run that way. It seems that the Loess regression uses the similar idea to only pick the qualified dose data points with F <1.5mg/L which is fine.

If you can send me the 42 data points you used for the Loess regression (not clear how you pick the 42 data points), I can try it with parametric non-linear regression with cubic spline to see if we can get similar results (the shape of the curve looks good) since we have been using parametric modeling and for this, we use a different approach of non-parametric approach (Loess regression uses non-parametric approach) is a little bit inconsistent. Also, I can try to produce better Figure with higher resolution for this.

(6) Table 1 is mentioned in Page 4 (Lines 60 and 64) and in Page 6 (Line 109). But it seems the text for this two places refer to two different Table 1…

(7) Table 2-4 are mentioned in the paper, but I could not find the actual Tables 2-4 in the paper or in other files.

Let me know, if any question. We are getting closer.

Best,

Honghu

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Thursday, March 24, 2022 6:18 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Meta-analysis

Honghu and Mark,

Attached, please find a draft manuscript with tables and figures for your review and comment. I highlighted the statistical part for your special attention. The lines in red could be deleted to make room for other additions. The maximum word limit is 4000.

I think the reviewers will have many questions about Supplementary Figure B 3. Absolute IQ (restricted cubic spline) -- see StdIQ_N25.png because it appears to contradict other findings. I tried to limit the analysis to data <1.5 mg/L. I used the Flexplot in Jamovi to create a Loess regression for graphical presentation. This is consistent with our main question to limit the studies to F exposure <1.5. What do you think?

Because of the poor quality of the studies, the NAS committee commented on the NTP dose-response analysis.

"Much of the evidence presented in the report comes from studies that involve relatively high fluoride concentrations. Little or no conclusive information can be garnered from the revised monograph about the effects of fluoride at low exposure concentrations (less than 1.5 mg/mL). ***NTP therefore should make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations, including those typically associated with drinking-water fluoridation***. Drawing conclusions about the effects of low fluoride exposures (less than 1.5 mg/mL) would require a full dose–response assessment, which
would include at a minimum more detailed analyses of dose–response patterns, models, and model fit; full evaluations of the evidence for supporting or refuting threshold effects; assessment of the differences in exposure metrics and intake rates; more detailed analyses of statistical power and uncertainty; evaluation of differences in susceptibility; and detailed quantitative analyses of effects of bias and confounding of small effect sizes. Those analyses fall
outside the scope of the NTP monograph, which focuses on hazard identification and not dose–
response assessment. ***Given the substantial concern regarding health implications of various fluoride exposures, comments or inferences that are not based on rigorous analyses should be
avoided."***

Looking forward to your review and comments.

Jay
