Peer Review File

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Reviewer A

Comment 1: Is it allowed to publish the results before the review and the registration are finished in PROSPERO?

Reply 1: Thanks for your comments. We checked the PROSPERO website and found our registration had already finished with Registration ID CRD42023397185.

Changes in the text: We had modified our text "This study protocol was registered in PROSPERO with protocol number (CRD42023397185)." **(see Page 2, line 33-34)** and "This systematic review protocol was already registered with the online Prospero database (CRD42023397185)" **(see Page 4, line 82-83).**

Comment 2: Do the authors differentiate folic acid and folate? The former is synthetic acid while folate is found in natural products. The excess intake of the former is thought to have a risk.

Reply 2: Thanks for your comments, we do differentiate the folic acid and folate. In our review, we only included the research focused on folic acid supplementation during pregnancy (at any stage of gestation or periconceptional period), which involved dietary supplements containing folic acid, multivitamin tablets containing folic acid, and folic acid tablets. We have described the detail folic acid supplementation information in the Table 1 (**see Page 15**).

Comment 3: What does cystic kidney include? The authors use the term renal dysgenesis. When a dysgenetic kidney contain cysts, what would be the classification?

Reply 3: Thanks for your comments. According to the ICD-10 version: 2019 (see figure 1 below), cystic kidney disease includes congenital single renal cyst, polycystic kidney, autosomal recessive, polycystic kidney, autosomal dominant, polycystic kidney, unspecified, renal dysplasia, medullary cystic kidney and other cystic kidney diseases, cystic kidney disease, unspecified. Therefore, when a dysgenetic kidney contain cysts, it would be classified as cystic kidney.

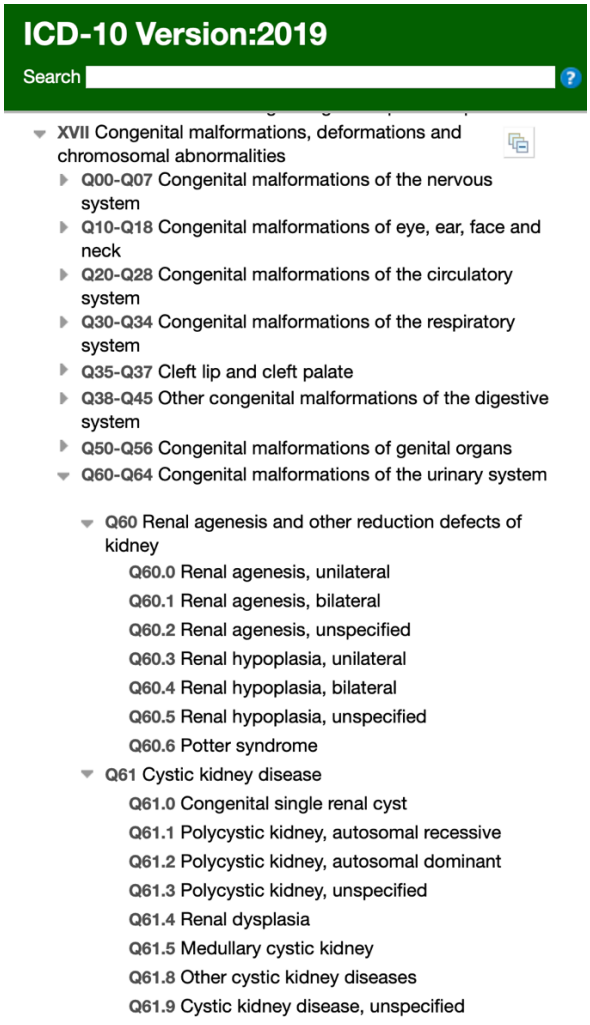

Figure 1: ICD-10 version: 2019
https://icd.who.int/browse10/2019/en#/N28.1

Comment 4: Authors' search strategy seems to have a problem since "with 1742 articles excluded following the title and "167 abstract review" (page 7) and" The study participants and study outcomes were not matched" (Figure 1). Only 8 papers ended up to be analyzed.

Reply 4: Thanks for your comments. We are apologized for the mathematical error in the manuscript and corrected the mistake in text and Figure 1. In fact, we initial literature screening **identified 1806 articles** after removing the duplicate papers (N = 1583), and **1773 articles were excluded** following the title and abstract review (1720 for study participants and study outcomes were not matched and 53 for animal study). Despite online inter-library searches, 3 records were unavailable of full texts, and studies in non-English for 14 records. The **final 16 full-text papers were retrieved**. The reasons for the removal of final full-text articles were outcomes not related to offspring renal outcomes (N = 2), without detailed clinical kidney outcomes (N = 3), and supplements were multivitamins that no detailed information on FA dosage was available (N = 3). The **remaining 8 articles were included in this current study,** concerned with maternal FA supplements and offspring renal outcomes.

Changes in the text: We had modified our text "The initial literature screening identified 1806 articles after removing duplicate papers (Figure 1), and 1773

articles were excluded following the title and abstract review." **(see Page 6, line 134-136)**" and also modified the Figure 1 **(see Page 16)**.

Comment 5: The title "effects of maternal folic acid supplementation and urinary development in human offspring" is not adequate. Not only urinary development but the kidney development should be mentioned. And the study is not about "urinary" development but about the development of CAKUT.
Reply 5: Thank you for your kind suggestion. CAKUT means the congenital anomalies of the kidney and urinary tract, which included the abnormal development of renal and urinary tract. So we considered to modified the "urinary development" to "renal urinary system development" in the title and the manuscript.
Changes in the text: We had modified our text of the title "Effects of maternal folic acid supplementation on renal urinary system development in human offspring - A meta-analysis" (**see Page 1, line 2-3 and Page 2, line 21-22**)". We carefully look through the manuscript and changed the "urinary" or "renal" to "renal urinary system" (see Page 2, line 29; Page 4, line 76, line 79; Page 5, line 126-127; Page 6, line 143, line 157, line 159; Page 8, line 196, line 199-200, line 204; Page 10, line 254, line 260, line 263).

Comment 6: Introduction is too long and contains discussion.
Reply 6: Thank you for your kind suggestion. We had shortened the introduction and added the relevant content to the discussion.
Changes in the text: We had modified our text, please see **Page 3-4, line 49-80, Page 8, line 207-215.**

Reviewer B
Comment 1: There is need for English grammar check.
Reply 1: Thank you for your kind suggestion. With your comments, our manuscript had been edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE (https://china.aje.com/cn) on 10th march 2023.

Comment 2: The introduction is too long, consider adding to discussion.
Reply 2: Thank you for your kind suggestion. We had shortened the introduction and added the relevant content to the discussion.
Changes in the text: We had modified our text, please see **Page 3-4, line 49-80, Page 8, line 207-215.**

Comment 3: This is a good effort but as was found there are many genes and many potential drug or medication interactions possibly related.
Reply 3: Thanks for your kind suggestion. Indeed, there are many genes and many potential drug or medication interactions possibly related to CAKUT incidence. We have reinforced in discussions as limitation.
Changes in the text: We had modified our text "Fourth, there are many genes and potential drug or medication interactions possibly related to CAKUT incidence, which were not considered in this study." **(see Page 11, line 277-279)**

Comment 4: The comment re caution for FH of kidney malformations needs to be

more focused as some will avoid FA and have other malformations such as NTD or CHD.
Reply 4: Thanks for your comments. This is indeed a matter of concern. Therefore, we are more conservative in our conclusions with limitation. At the same time, the clear protective effect of folic acid supplementation against NTD or CHD malformations has been repeatedly emphasized and mentioned in the manuscript.

Comment 5: The discussion could use a little more focused organization to help the reader as Fig 2-4 are very clear.
Reply 5: Thanks for your comments. In the first paragraph of the discussion, we added more focused organization to describe the Fig 2-4.
Changes in the text: We had modified our text "This meta-analysis clarified that maternal FA supplementation might increase the incidence of offspring's renal urinary malformations, mainly the incidence of cystic kidney. However, different doses of folic acid supplementation did not suggest a significant difference." **(see Page 8, line 195-198)**

Reviewer C

Comment 1. Abstract should be structured with the subheadings Background, Methods, Results, and Conclusions.

Comment 2. Reference #9 and #15 are the same. So do #6 and #14.

Comment 3. Please check if this number match Figure 3.

196 95% CI, 0.73-1.21; P = 0.64) showed nonstatistical significance. At the same time,
197 after CAKUT grouping, the heterogeneity of each group was still high (I^2 = 81.2%).

Comment 4. The numbers do not match Figure 4.

212 (OR = 0.78; 95% CI, 0.39-1.58; P = 0.49). When FA supplementation was ≤ 0.6
213 mg/day throughout pregnancy, the prevalence of CAKUT in offspring was
214 increased (OR = 1.11; 95% CI, 0.94-1.31; P = 0.22). At > 0.6 mg/day of FA

214 increased (OR = 1.11; 95% CI, 0.94-1.31; P = 0.22). At > 0.6 mg/day of FA
215 supplementation during pregnancy, the prevalence of CAKUT in offspring
216 decreased (OR = 0.48; 95% CI, 0.94-1.31; P = 0.22).

Comment 5. The author's name cited in text should be consistent with the reference.

174 detail; the study by Mark A. Canfield [15] and Lorenzo D. Botto [20] was performed

Comment 6. Please re-organize the article following the PRISMA guidelines. The PRISMA checklist should be provided as an additional file. In the checklist, please indicate the detailed Page Number, Line Number, Section and Paragraph. Do not

leave any blanks; If "N/A" is filled, please explain the reasons for not applicable items.

Comment 7. Please identify the report as a systematic review in the title.

Comment 8. Abbreviation should be spelled out the first time it is used in the Abstract/Body Text/Figure/Table. Please indicate the full name of the abbreviations that are marked in yellow in the attached manuscript.

Reply: Modifications were made to the manuscript in accordance with their recommendations. We hope that they meet with your approval. Please see the attached files.

Thank you and all the editors for the kind suggestions.