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ORIGINAL ARTICLE

Fetal growth and maternal glomerular filtration rate: a systematic review

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Abstract

Objective: Glomerular filtration rate (GFR) may influence concentrations of biomarkers of exposure and their etiologic significance in observational studies of associations between environmental contaminants and fetal growth. It is unknown whether the size of a developing fetus affects maternal GFR such that a small fetus leads to reduced plasma volume expansion (PVE), reduced GFR and subsequent higher concentrations of biomarkers in maternal serum. Our objective was to answer the question: ''Is there an association between fetal growth and maternal GFR in humans?''

Methods: We adapted and applied the Navigation Guide systematic review methodology to assess the evidence of an association between fetal growth and GFR, either directly or indirectly via reduction in PVE.

Results: We identified 35 relevant studies. We rated 31 human and two non-human observational studies as ''low'' quality and two experimental non-human studies as ''very low'' quality. We rated all three evidence streams as ''inadequate''. The association between fetal growth and GFR was ''not classifiable'' according to pre-specified definitions.

Conclusions: There is currently insufficient evidence to support the plausibility of a reverse causality hypothesis for associations between exposure to environmental chemicals during pregnancy and fetal growth. Further research would be needed to confirm or disprove this hypothesis.

Keywords

Fetal growth, glomerular filtration rate, perfluorooctanoic acid, plasma volume expansion, reproductive environmental health, reverse causality, the navigation guide

History

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Background

Impaired prenatal growth is an indicator for adverse developmental health impacts that can manifest across the human lifespan [1,2]. We conducted a systematic review that found greater levels of perfluorooctanoic acid (PFOA) that are associated with impaired fetal growth in humans [3]. However, there is some literature that suggests the possibility of ''reverse causality'' [4]; that is, smaller fetuses lead to greater concentrations of environmental chemicals measured in maternal serum via a reduction in plasma volume expansion (PVE) and reduced glomerular filtration rate (GFR; Figure 1). Pregnancy is associated with PVE to accommodate the growing fetus and an increase in kidney function, including GFR [5,6] (Supplementary Material 1); therefore, the reverse causality hypothesis posits that a smaller fetus leads to a reduction in GFR directly or indirectly through a lower PVE. In our review of PFOA we had robust experimental animal evidence that mirrored the human evidence and for which the reverse causality hypothesis would not apply [7]; however, experimental evidence may not always be available to augment the interpretation of observational human studies in environmental health. Thus, we assessed the strength of the evidence for the reverse causality hypothesis using the Navigation Guide systematic review method [8].

Methods

We adapted and applied the Navigation Guide systematic review methodology for environmental health [9] to assess the strength of evidence for a direct or indirect relationship between fetal growth and GFR. We conducted our systematic review as outlined beforehand in a protocol which is available online (http://prhe.ucsf.edu/prhe/) and summarized below.

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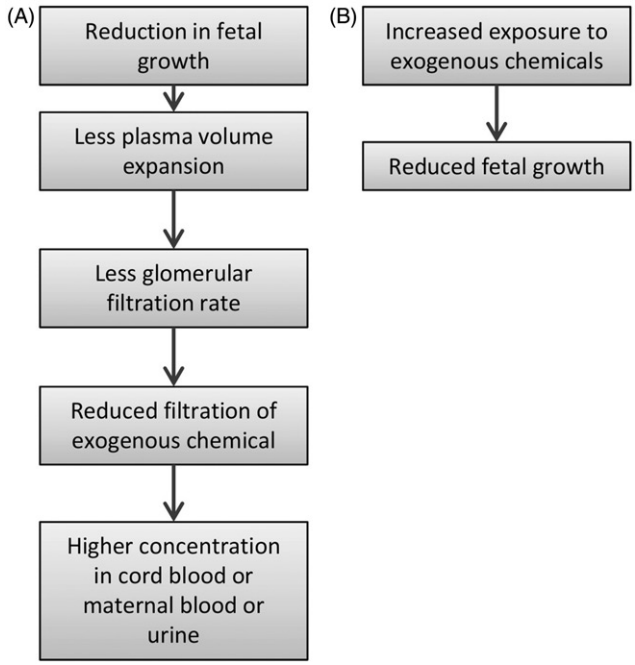

Figure 1. A flow diagram outlining two potential hypotheses for the relationship between exogenous chemicals and fetal growth. Changes in fetal growth may affect the concentration of measurable chemicals due to changes in the maternal plasma volume and subsequent changes in maternal GFR (A); or increased exposure to exogenous chemicals may cause changes in fetal growth (B). The Navigation Guide has previously evaluated the evidence in support of hypothesis B [7,8], whereas the present review evaluates the evidence in support of hypothesis A.

Step 1: Specify the study question

We used a ''PECO'' (Participants, Exposure, Comparator, Outcome) aid to outline the study question [modified from [10] (Supplementary Material 2)]. Our objective was to answer the question ''Is there an association between fetal growth and maternal GFR in humans?'' We considered the following potential direct and indirect relationships between fetal growth and GFR: (1) the direct relationship between fetal growth and GFR (Supplementary Figure 1A, arrow i); OR (2) between fetal growth and PVE (Supplementary Figure 1A, arrow ii); AND (3) between PVE and GFR (Supplementary Figure 1A, arrow iii). We evaluated both human and non-human mammalian models of the relationships described in Supplementary Figure 1.

Herein, we use the terms PVE or GFR as referring to any suitable measures of maternal PVE or GFR, respectively.

Step 2: Select the evidence

We conducted our online search, study selection criteria and data collection as described in the online protocol. Briefly, we searched four online databases (Biosis Previews, ISI Web of Science, Pubmed and Embase) on 15 August 2013 and selected relevant studies using pre-specified inclusion and exclusion criteria.

Step 3: Rate the quality and strength of the evidence

To rate the quality and strength of the evidence we: (1) assessed each included study for risk of bias; (2) rated the overall quality across all studies separately for the human and non-human evidence; and (3) rated the overall strength of the evidence across the combined body of all human and non-human studies. These steps are described in detail in the online protocol. Briefly, we rated the risk of bias across seven domains, five of which were the same across evidence streams. Next, we evaluated the data from each study. We conducted a quantitative analysis on studies which reported the study subjects, a mean score and variance (standard error (SE) or standard deviation (SD)) and either: dichotomized birth weight into average for gestational age and small for gestational age; or compared two groups with different mean birth weights.[1] Additionally, we conducted *post-hoc* analyses on raw data, when available, for the independent and dependent variable (individual participant data; IPD). For studies that dichotomized birth weight, we calculated the difference in mean effect sizes (see online protocol). For studies which reported individual participant data, we performed a *post-hoc* regression analysis using independent and dependent variables as described in Supplementary Figure 1 and using the beta-coefficient and 95% confidence intervals (CI) as our effect size estimate. Studies which did not report data suitable for a *post-hoc* analysis were assessed qualitatively.

Next, we rated the quality of the evidence across studies. Possible ratings for quality of a body of evidence were ''high'', ''moderate'' or ''low''. Ratings were determined beforehand by assigning an initial quality rating to each body of evidence, then considering factors that would lead us to downgrade and/or upgrade the rating, based on characteristics of the studies included in that body of evidence. We assigned initial ratings beforehand of ''moderate'' to observational human studies and ''high'' to experimental mammalian studies as described in detail previously [3,7]. Additionally, we considered the body of observational non-human studies identified in this review to be sufficiently similar in design to observational human studies and thus assigned beforehand an initial rating of ''moderate''. We rated the quality of human and non-human evidence separately according to five downgrade factors and three upgrade factors (see protocol).

Finally, we assigned one of the following possible ratings for the strength of evidence across studies: ''sufficient evidence of an association'', ''limited evidence of an association'', ''inadequate evidence of an association'' or ''evidence of lack of association''.

Integrating the strength of human and non-human evidence streams

We integrated the results of the strength of human and non-human evidence assessment as described previously [3,7] to achieve an overall statement on the evidence of an association between fetal growth and GFR: ''known to be associated'',

[1]For comparisons on which we were able to calculate a difference in means (Mdi) effect size, only four outcomes used sufficiently similar exposure groups (birth weight less than the 10th percentile for gestational age), comparator groups (birth weight above the 10th percentile for gestational age) and outcomes (absolute plasma volume); however, differences in the timing of assessment (gestational week) meant we were not able to combine these in a meta-analysis, and the small number of comparisons did not permit us to perform an analysis with time of assessment as a covariate, and thus no meta-analysis was conducted.

''probably associated'', ''possibly associated'', ''probably not associated'' or ''not classifiable''(Figure 3).

Results

Included studies

We identified 5261 publications in our literature search (Supplementary Figure 2 and Supplementary Material 3) of which 29 were considered relevant and an additional six were identified through hand searching. Thus, 35 studies (33 full publications and 2 human observational-study meeting abstracts) published between 1954 and 2012 (median 1992) were included in the systematic review as follows: 31 observational human studies, 2 observational mammalian studies (1 each in cows and dogs) and 2 experimental mammalian studies (1 each in rats and ewes) (full study details are available online at (http://prhe.ucsf.edu/prhe/).

Risk of bias of individual studies

We rated risk of bias across seven domains individually for the 33 full publications (Supplementary Figure 3). The majority of human studies were considered ''low'' or ''probably low'' risk of bias for blinding (83%), recruitment strategy (76%), confounding (66%), incomplete outcome data (62%), selective outcome reporting (97%) and other sources of bias (100%). For conflict of interest, we considered a large proportion of studies to be at ''probably high'' risk of bias (66%), because neither a funding source nor a conflict or interest statement was reported. Approximately, a third of studies were also considered ''probably high'' risk or ''high'' risk for confounding (34%) and ''probably high'' risk for incomplete outcome data (38%). For non-human observational studies, we rated both studies ''probably high'' risk for confounding: one study did not adjust for the age or weight of the animals [11] and the second study did not report the maternal or gestational age [12]. Additionally, we rated this second study as ''probably high'' risk for conflict of interest as no statement or funding source was reported. For allocation concealment, blinding and incomplete outcome data we rated both non-human experimental studies as ''probably high'' risk of bias and we rated one experimental mammalian study as ''probably high'' risk for randomization.

Summary of findings

We described the expected change in normal pregnancy for all of the outcome measures in Supplementary Material 1. The relationships assessed in each study and the graphical or qualitative results are presented in Figure 2, Supplementary Figures 4 to 7 and Supplementary Materials 4 to 7.

Quality of the body of evidence

We downgraded the overall quality of the human, observational mammalian and experimental mammalian studies according to the rationale reported in Supplementary Material 8.

- We downgraded the body of human studies ($N = 31$) from the initial rating of ''moderate'' to ''low'' due to inconsistency of findings among the studies (see ''Methods'' section for details). Specifically, while we found consistent evidence of an association among studies reporting the relationship between birth weight and PVE, studies of the relationship between GFR and birth weight were inconsistent and the majority of these studies were small (median sample size of 9, range 9 to 283). Additionally, although we considered there should be a dose-response relationship between hemoglobin levels and odds of SGA, there was no evidence of a dose-response relationship between fetal growth and GFR.
- We downgraded the body of observational mammalian studies ($N = 2$) from ''moderate'' to ''low'' because of imprecision as judged by wide confidence intervals. Specifically, we considered the two studies to be too small (total sample size of $n = 65$) to provide precise effect estimates.
- We downgraded the body of experimental mammalian studies ($N = 2$) from our initial rating of ''high'' to ''low'' based on a high risk of bias across studies, indirectness and imprecision. Both studies were ''probably high risk of bias'' for the allocation concealment, blinding and incomplete outcome data domains, and one study was also ''probably high risk of bias'' for randomization (Supplementary Figure 3). One study used an indirect measure of fetal growth (the product of estimated chest girth and estimated fetal weight to chest girth ratio using growth catheters), and we considered both studies to be too small ($n = 23$ in total) to provide precise effect estimates (Supplementary Figure 7).

Strength of the body of evidence

We assessed the strength of the evidence by considering the quality ratings described above with our assessment of the direction of effect and our confidence in the effect. We found the strength of the evidence of an association between fetal growth and GFR to be ''inadequate'' (see online Protocol for definitions) for both the human and non-human evidence streams (Supplementary Material 9).

- Our rationale for ''inadequate'' human studies was based on the ''low'' quality of evidence, the indeterminate direction of effect and a lack of confidence in the effect between fetal growth and GFR, either directly or via change in PVE. Although we were confident in the effect between fetal growth and PVE, based on data from the two largest studies [13,14], we had low confidence in the evidence on the association between fetal growth and GFR, or PVE and GFR. Thus, a new, well-designed and adequately powered study would be likely to change our certainty in the strength of the effect between fetal growth and GFR, or between PVE and GFR.
- Our rationale for ''inadequate'' evidence of an association from observational mammalian studies was based on the ''low'' quality of the evidence, the indeterminate direction of effect and a lack of confidence in the effect estimate because the data were limited to one small study each on the relationship between fetal growth and PVE and fetal growth and GFR. Thus, a new, well-designed and adequately powered study would be likely to change

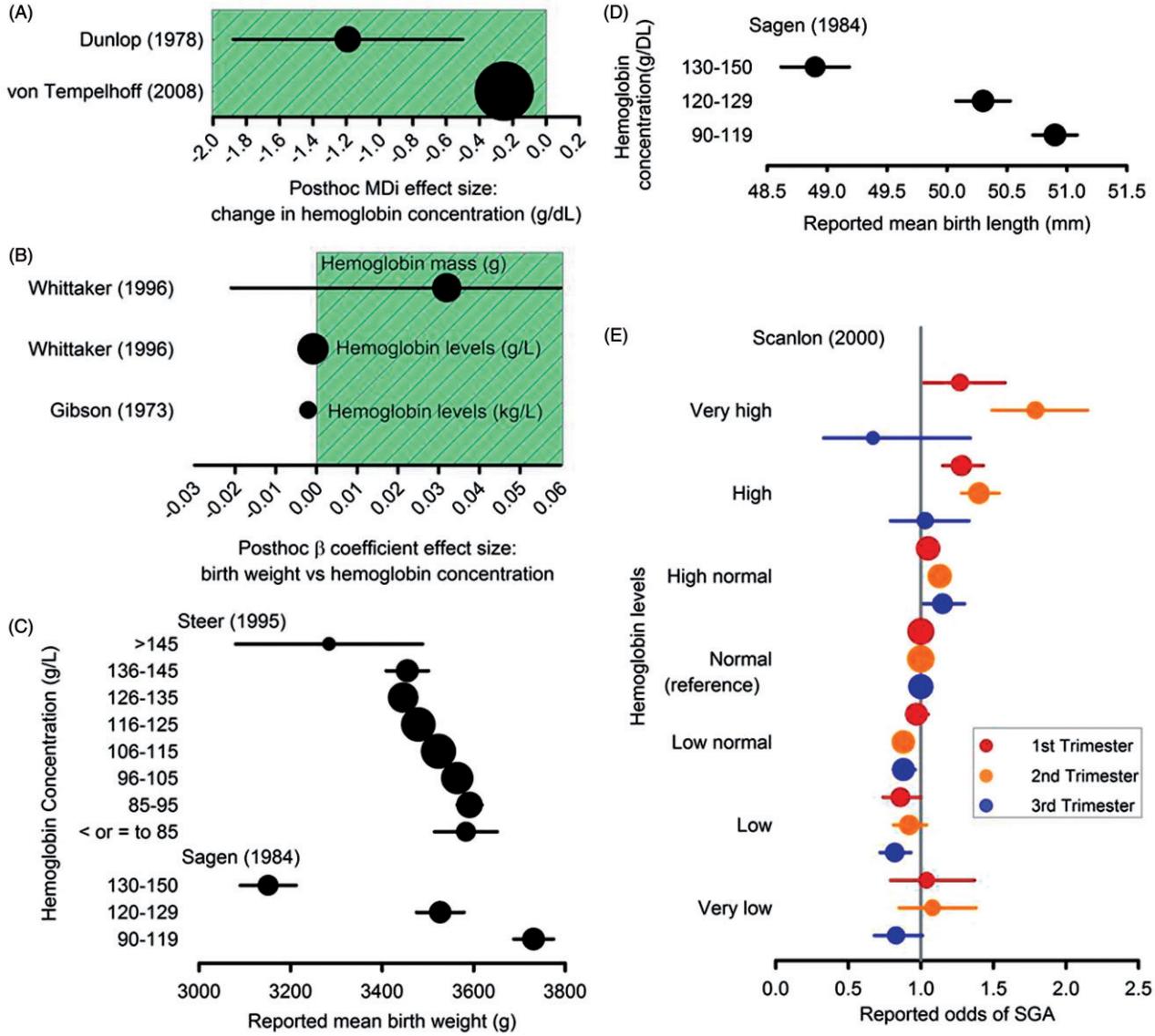

Figure 2. Association between fetal growth and hemoglobin levels. (A) *Post-hoc* mean difference effect sizes for the change in hemoglobin concentration in women gave birth to higher versus lower birth weight babies; (B) *post-hoc* beta-coefficients for the association between mean birth weight and hemoglobin levels; (C and D) reported data on the association between mean birth weight for various stratifications of hemoglobin; (E) reported odds of SGA for various stratifications of hemoglobin levels. Horizontal error bars represent 95% CI and symbol sizes represent the log of the number of study participants. For graphs of *post-hoc* calculated effect sizes, the shaded area represents the direction of effect (positive or negative in relation to zero (no effect)) which is consistent with the hypotheses for the change in normal pregnancy as outlined in Supplementary Material 1.

the certainty in the direction and strength of effect for all three relationships in the model.

- Our rationale for ''inadequate'' evidence of an association from experimental mammalian studies was based on the ''very low'' quality of evidence and a lack of confidence in the effect because the data were limited in both size and number. One study was designed to assess the direction of effect (causality) between fetal growth and PVE [15], with the results suggesting that fetal growth restriction preceded a decrease in plasma volume; however, this study was both small and of low quality. There was insufficient evidence on the other relationships in the model to assess the direction of effect between fetal growth and GFR, either directly or via change in PVE. Thus, a new, well-designed and adequately powered study would be likely to change the certainty in the direction and strength of the effect.

Integrating the evidence across evidence streams

The final step in our review was to integrate the strength ratings from the human and non-human evidence streams to determine the strength of the evidence over all. We found that the association between fetal growth and GFR was ''not classifiable'' (Figure 3) based on ''inadequate'' human evidence.

Discussion

To our knowledge this is the first systematic review on the strength of the evidence for a relationship between fetal growth and GFR. We found that the strength of the evidence for an association between fetal growth and GFR is ''not classifiable'' based on inadequate human and inadequate non-human evidence. Our findings systematically and transparently document that there is currently no empirical evidence

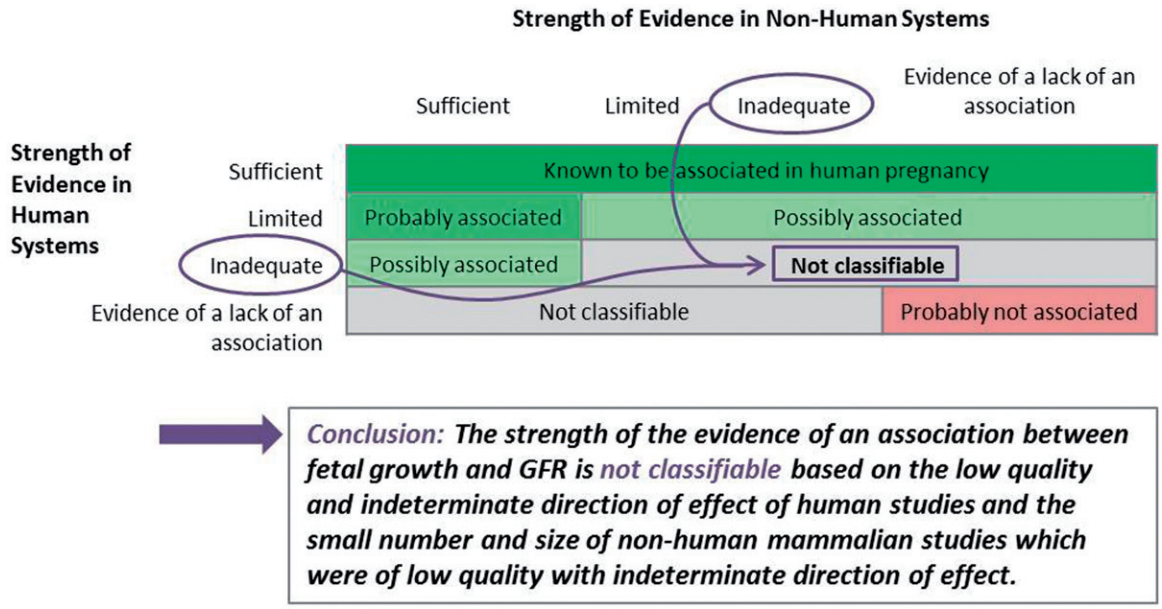

Figure 3. Overview of the framework to integrate strength of evidence from the human and non-human evidence streams to reach a conclusion on the strength of the association between fetal growth and GFR.

to support the hypothesis, but the findings do not disprove the reverse causality hypothesis. A well-conducted observational human study could increase our confidence in the strength of the association between the three variables (FG, PVE, GFR), and a well-conducted experimental mammalian study could increase our confidence in the direction of effect.

We found that the strength of the evidence differed among the various direct and indirect potential relationships considered. We found sufficient evidence of a relationship between birth weight and PVE from human studies (based on data from two large studies with low risk of bias [13,14] and reasonably consistent data from the small studies), an inconsistent effect between fetal growth and GFR, and insufficient data to assess the relationship between PVE and GFR. Moreover, for all three relationships examined, the direction of effect could not be determined. Despite one experimental study [15] suggesting that fetal growth could impact PVE, the size and quality of this study was insufficient to alter our conclusions. Assessing associations from observational studies is challenging; however, a high quality, well-designed and adequately-powered, experimental mammalian study using directly-relevant endpoints would give us greater confidence in both the strength and direction of the effect.

Limitations

Although we have used a systematic and transparent method to address our study question, there are a number of limitations to our approach. First, systematic reviews can only include studies which are available in the public domain, or which have been made available through, for example, contacting authors, which we did not do in this systematic review due to time constraints. Therefore, it cannot be ruled out that our review was missing studies that could have influenced the outcome. It should be noted that we were unable to locate one article despite a broad interlibrary loan search and attempts to contact the authors; however, we determined from the abstract that the article was on the relationship between fetal growth and PVE from 32 pregnant women [16], which we considered unlikely to alter our conclusions due to its small size.

Secondly, in our *post-hoc* findings we cannot rule out the possibility of spurious findings. Where we calculated difference in means effect sizes we took 95% CIs which did not cross zero as significant results at $p<0.05$ and thus we were unable to make adjustments for multiple comparisons as we did not formally calculate a p value [17].

Lastly, while the process that we have used is transparent, the conclusions on the quality and strength of the evidence involved judgments, which in turn can depend on the composition and interactions among study authors. It is possible that a different group of researchers at a different time might reach a different conclusion. The raw material used for our decision is available to the public so that any disagreement in our judgment can be openly discussed.

Summary and conclusions

We conducted a systematic review of the evidence of an association between fetal growth and GFR in order to assess the strength of the evidence of a ''reverse causality'' hypothesis, a potential alternate explanation for any body of observational studies that documents an inverse association between prenatal exposure to chemicals cleared renally and fetal growth. Using pre-specified factors, we found the quality of observational human and non-human studies to be ''low,'' and experimental non-human studies to be ''very low.'' We considered the overall strength of all three streams of evidence to be ''inadequate'' according to pre-specified and transparent definitions. We found evidence of an association between fetal growth and PVE; however, the small number, size and quality of the studies on GFR did not permit a conclusion on the association between fetal growth and GFR, either directly or via change in PVE. Moreover, we found insufficient data to perform a meta-analysis on any of the three relationships assessed. Finally, we used The Navigation

Guide methodology to integrate our strength ratings from human and non-human evidence streams and found the strength of the evidence on the association between fetal growth and GFR to be ''not classifiable''. At present, there is insufficient evidence to reliably assess whether the ''reverse causality'' hypothesis could explain the observed inverse association between exposure to chemicals and fetal growth. Further investigation of this hypothesis in high quality, well designed and adequately powered human and non-human studies are needed in order to reach a conclusion on the association between fetal growth and GFR.

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Declaration of interest

The authors have no conflicts of interest to declare.

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